

## ENVIRONMENTAL PROTECTION AGENCY

### 40 CFR Part 50

[EPA-HQ-OAR-2013-0146; FRL-9965-28-OAR]

RIN 2060-AR57

### Review of the Primary National Ambient Air Quality Standards for Oxides of Nitrogen

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Proposed rule.

**SUMMARY:** Based on the Environmental Protection Agency's (EPA's) review of the air quality criteria addressing human health effects of oxides of nitrogen and the primary national ambient air quality standards (NAAQS) for nitrogen dioxide (NO<sub>2</sub>), the EPA is proposing to retain the current standards, without revision.

**DATES:** Comments must be received on or before September 25, 2017.

**Public Hearings:** If, by August 2, 2017, the EPA receives a request from a member of the public to speak at a public hearing concerning the proposed decision, we will hold a public hearing, with information about the hearing provided in a subsequent notice in the **Federal Register**.

To request a hearing, to register to speak at a hearing or to inquire if a hearing will be held, please contact Ms. Regina Chappell at (919) 541-3650 or by email at [chappell.regina@epa.gov](mailto:chappell.regina@epa.gov). The EPA will post all information regarding any public hearing on this proposed action, including whether a hearing will be held, its location, date, and time if applicable and any updates online at <https://www.epa.gov/naaqs/nitrogen-dioxide-no2-primary-air-quality-standards>.

**ADDRESSES:** Submit your comments, identified by Docket ID No. EPA-HQ-OAR-2013-0146 to the *Federal eRulemaking Portal*: <http://www.regulations.gov>. Follow the online instructions for submitting comments. Once submitted, comments cannot be edited or withdrawn. The EPA may publish any comment received to its public docket. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Multimedia submissions (audio, video, etc.) must be accompanied by a written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. The EPA will

generally not consider comments or comment contents located outside of the primary submission (*i.e.*, on the Web, Cloud, or other file sharing system). For additional submission methods, the full EPA public comment policy, information about CBI or multimedia submissions, and general guidance on making effective comments, please visit <http://www2.epa.gov/dockets/commenting-epa-dockets>.

**Docket:** All documents in the docket are listed on the [www.regulations.gov](http://www.regulations.gov) Web site. This includes documents in the docket for the proposed decision (Docket ID No. EPA-HQ-OAR-2013-0146) and a separate docket, established for the Integrated Science Assessment (ISA) for this review (Docket ID No. EPA-HQ-ORD-2013-0232) that has been incorporated by reference into the docket for this proposed decision. All documents in these dockets are listed on the [www.regulations.gov](http://www.regulations.gov) Web site. Although listed in the index, some information is not publicly available, *e.g.*, CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and may be viewed, with prior arrangement, at the EPA Docket Center. Publicly available docket materials are available either electronically in [www.regulations.gov](http://www.regulations.gov) or in hard copy at the Air and Radiation Docket Information Center, EPA/DC, WJC West Building, Room 3334, 1301 Constitution Ave. NW., Washington, DC. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744 and the telephone number for the Air and Radiation Docket Information Center is (202) 566-1742.

**FOR FURTHER INFORMATION CONTACT:** Ms. Breanna Alman, Health and Environmental Impacts Division, Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency, Mail Code C504-06, Research Triangle Park, NC 27711; telephone: (919) 541-2351; fax: (919) 541-0237; email: [alman.breanna@epa.gov](mailto:alman.breanna@epa.gov).

#### SUPPLEMENTARY INFORMATION:

#### General Information

##### Preparing Comments for the EPA

1. **Submitting CBI.** Do not submit this information to the EPA through [www.regulations.gov](http://www.regulations.gov) or email. Clearly mark the part or all of the information that you claim to be CBI. For CBI information in a disk or CD-ROM that you mail to the EPA, mark the outside of the disk or CD-ROM as CBI and then

identify electronically within the disk or CD-ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that includes information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket. Information so marked will not be disclosed except in accordance with procedures set forth in 40 Code of Federal Regulations (CFR) part 2.

2. **Tips for Preparing Your Comments.** When submitting comments, remember to:

- Identify the action by docket number and other identifying information (subject heading, **Federal Register** date and page number).
- Follow directions—the agency may ask you to respond to specific questions or organize comments by referencing a CFR part or section number.
- Explain why you agree or disagree, suggest alternatives, and substitute language for your requested changes.
- Describe any assumptions and provide any technical information and/or data that you used.
- Provide specific examples to illustrate your concerns, and suggest alternatives.
- Explain your views as clearly as possible, avoiding the use of profanity or personal threats.
- Make sure to submit your comments by the comment period deadline identified.

#### Availability of Information Related to This Action

A number of the documents that are relevant to this proposed decision are available through the EPA's Web site at <https://www.epa.gov/naaqs/nitrogen-dioxide-no2-primary-air-quality-standards>. These documents include the *Integrated Review Plan for the Primary National Ambient Air Quality Standards for Nitrogen Dioxide* (U.S. EPA, 2011a), available at [https://www3.epa.gov/ttn/naaqs/standards/nox/data/201406finalirp\\_primaryno2.pdf](https://www3.epa.gov/ttn/naaqs/standards/nox/data/201406finalirp_primaryno2.pdf), the *Integrated Science Assessment for Oxides of Nitrogen—Health Criteria* (U.S. EPA, 2016a), available at <https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310879>, and the *Policy Assessment for the Review of the Primary National Ambient Air Quality Standards for Oxides of Nitrogen* (U.S. EPA, 2017a), available at <https://www.epa.gov/naaqs/policy-assessment-review-primary-national-ambient-air-quality-standards-oxides-nitrogen>. These and other related documents are also available for

inspection and copying in the EPA docket identified above.

## Table of Contents

The following topics are discussed in this preamble:

### Executive Summary

#### I. Background

- A. Legislative Requirements
- B. Related NO<sub>2</sub> Control Programs
- C. Review of the Air Quality Criteria and Standards for Oxides of Nitrogen

#### II. Rationale for Proposed Decisions on the Primary NO<sub>2</sub> Standards

##### A. General Approach

1. Approach in the Last Review
2. Approach for the Current Review

##### B. Characterization of NO<sub>2</sub> Air Quality

1. Atmospheric Chemistry
2. National Trends in NO<sub>x</sub> Emissions and Ambient NO<sub>2</sub> Concentrations
3. Near-Road NO<sub>2</sub> Air Quality
4. Relationships Between Hourly and Annual NO<sub>2</sub> Concentrations

##### C. Health Effects Information

1. Health Effects With Short-Term Exposure to NO<sub>2</sub>
2. Health Effects With Long-Term Exposure to NO<sub>2</sub>
3. Potential Public Health Implications

##### D. Human Exposure and Health Risk Characterization

1. Overview of Approach To Estimating Potential NO<sub>2</sub> Exposures
2. Results of Updated Analyses
3. Uncertainties
4. Conclusions

##### E. Summary of CASAC Advice

##### F. Proposed Conclusions on the Adequacy of the Current Primary NO<sub>2</sub> Standards

1. Evidence-Based Considerations
2. Exposure and Risk-Based Considerations
3. CASAC Advice
4. Administrator's Proposed Conclusions Regarding the Adequacy of the Current Primary NO<sub>2</sub> Standards

#### III. Statutory and Executive Order Reviews

##### A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review

##### B. Paperwork Reduction Act (PRA)

##### C. Regulatory Flexibility Act (RFA)

##### D. Unfunded Mandates Reform Act (UMRA)

##### E. Executive Order 13132: Federalism

##### F. Executive Order 13175: Consultation and Coordination With Indian Tribal Governments

##### G. Executive Order 13045: Protection of Children From Environmental Health and Safety Risks

##### H. Executive Order 13211: Actions That Significantly Affect Energy Supply, Distribution or Use

##### I. National Technology Transfer and Advancement Act (NTTAA)

##### J. Executive Order 12898: Federal Actions To Address Environmental Justice in Minority Populations and Low-Income Populations

##### K. Determination Under Section 307(d)

#### References

## Executive Summary

This section summarizes background information about this proposed action and the Administrator's proposed decision to retain the current primary NO<sub>2</sub> standards.

### Summary of Background Information

There are currently two primary standards for oxides of nitrogen. NO<sub>2</sub> is the component of oxides of nitrogen of greatest concern for health and is the indicator for the primary NAAQS. The two primary NO<sub>2</sub> standards are: A 1-hour standard established in 2010 at a level of 100 parts per billion (ppb) and based on the 98th percentile of the annual distribution of daily maximum 1-hour NO<sub>2</sub> concentrations, averaged over 3 years; and an annual standard, originally set in 1971, at a level of 53 ppb and based on annual average NO<sub>2</sub> concentrations.

Sections 108 and 109 of the Clean Air Act (CAA) govern the establishment, review, and revision, as appropriate, of the NAAQS to protect public health and welfare. The CAA requires the EPA to periodically review the air quality criteria—the science upon which the standards are based—and the standards themselves. This review of the primary (health-based) NO<sub>2</sub> NAAQS is being conducted pursuant to these statutory requirements. The schedule for completing this review is established by a federal court order, which requires signature of a proposed determination by July 14, 2017, and a final determination by April 6, 2018.

The last review of the primary NO<sub>2</sub> NAAQS was completed in 2010. In that review, the EPA supplemented the existing primary annual NO<sub>2</sub> standard by establishing a new short-term 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 (75 FR 6474, February 9, 2010). Revisions to the NAAQS were accompanied by revisions to the data handling procedures and the ambient air monitoring and reporting requirements, including the establishment of requirements for states to locate monitors near heavily trafficked roadways in large urban areas and in other locations where maximum NO<sub>2</sub> concentrations can occur.

Consistent with the review completed in 2010, this review is focused on the health effects associated with gaseous oxides of nitrogen and on the protection afforded by the primary NO<sub>2</sub> standards. The gaseous oxides of nitrogen include NO<sub>2</sub> 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). The EPA is separately considering the health and non-ecological welfare effects of particulate species in the review of the NAAQS for particulate matter (PM) (U.S. EPA, 2016b). In addition, the EPA is separately reviewing the ecological welfare effects associated with oxides of nitrogen, oxides of sulfur, and PM, and the protection provided by the secondary NO<sub>2</sub>, SO<sub>2</sub> and PM standards. (U.S. EPA, 2017b).

### Summary of Proposed Decision

In this notice, the EPA is proposing to retain the current primary NO<sub>2</sub> standards, without revision. This proposed decision has been informed by a careful consideration of the full body of scientific evidence and information available in this review, giving particular weight to the assessment of the evidence in the ISA; analyses and considerations in the Policy Assessment (PA); and the advice and recommendations of the Clean Air Scientific Advisory Committee (CASAC).

As in the last review, the strongest evidence continues to come from studies examining respiratory effects following short-term NO<sub>2</sub> exposures (e.g., typically minutes to hours). In particular, the ISA concludes that “[a] causal relationship exists between short-term NO<sub>2</sub> exposure and respiratory effects based on evidence for asthma exacerbation” (U.S. EPA, 2016a, pp. 1–17). The strongest support for this conclusion comes from controlled human exposure studies examining the potential for NO<sub>2</sub>-induced increases in airway responsiveness (AR) (which is a hallmark of asthma) in individuals with asthma. Most of these studies were available in the last review and, consistent with the evidence in that review, an updated meta-analysis indicates increased AR in some people with asthma following resting exposures to NO<sub>2</sub> concentrations from 100 to 530 ppb. However, there is not an apparent dose-response relationship between NO<sub>2</sub> exposure and increased AR and there is uncertainty regarding the potential adversity of reported responses. In addition, these studies are largely focused on adults with mild asthma, rather than adults or children with more severe cases of the disease.

Evidence supporting the ISA conclusion also comes from epidemiologic studies reporting associations between short-term NO<sub>2</sub> exposures and an array of respiratory outcomes related to asthma exacerbation. Such studies consistently

report associations with several asthma-related outcomes, including asthma-related hospital admissions and emergency department visits in children and adults. The epidemiologic evidence that is newly available in the current review is consistent with evidence from the last review and does not fundamentally alter our understanding of respiratory effects related to short-term NO<sub>2</sub> exposures. While our fundamental understanding of such effects has not changed, recent epidemiologic studies do reduce some uncertainty from the last review by reporting health effect associations with short-term NO<sub>2</sub> exposures in copollutant models and by their use of improved exposure metrics.

In addition to the effects of short-term exposures, the ISA concludes that there is “likely to be a causal relationship” between long-term NO<sub>2</sub> exposures and respiratory effects, based on the evidence for asthma development in children. The strongest evidence supporting this conclusion comes from recent epidemiologic studies demonstrating associations between long-term NO<sub>2</sub> exposures and asthma incidence. While these studies strengthen the evidence for effects of long-term exposures, compared to the last review, they are subject to uncertainties resulting from the methods used to assign NO<sub>2</sub> exposures, the high correlations between NO<sub>2</sub> and other traffic-related pollutants, and the lack of information regarding the extent to which reported effects are independently associated with NO<sub>2</sub> rather than the overall mixture of traffic-related pollutants. Additional support comes from experimental studies supporting the biological plausibility of a potential mode of action by which NO<sub>2</sub> exposures could cause asthma development. These include studies that support a potential role for repeated short-term NO<sub>2</sub> exposures in the development of asthma.

While the evidence supports the occurrence of adverse NO<sub>2</sub>-related respiratory effects at ambient NO<sub>2</sub> concentrations likely to have been above those allowed by the current primary NO<sub>2</sub> NAAQS, available studies do not call into question the adequacy of the public health protection provided by the current standards. In particular, compared to the last review when the 1-hour standard was set, evidence from controlled human exposure studies has not altered our understanding of the NO<sub>2</sub> exposure concentrations that cause increased AR. In addition, while epidemiologic studies report relatively precise associations with serious NO<sub>2</sub>-related health outcomes (*i.e.*, emergency

department visits, hospital admissions, asthma incidence) in locations likely to have violated the current 1-hour and/or annual standards during portions of study periods, studies do not indicate such associations in locations with NO<sub>2</sub> concentrations that would have clearly met those standards.

Beyond the scientific evidence, the EPA also considers the extent to which quantitative analyses can inform conclusions on the adequacy of the public health protection provided by the current primary NO<sub>2</sub> standards. In particular, the EPA considers analyses estimating the potential for NO<sub>2</sub> exposures of public health concern that could be allowed by the current standards. Overall, these analyses indicate that the current 1-hour standard provides substantial protection against exposures to ambient NO<sub>2</sub> concentrations that have consistently been shown to increase AR in people with asthma, even under worst-case conditions across a variety of study areas in the U.S. Such NO<sub>2</sub> concentrations were not estimated to occur, even at monitoring sites adjacent to some of the most heavily trafficked roads. In addition, the analyses indicate that meeting the current 1-hour standard limits the potential for exposure to 1-hour NO<sub>2</sub> concentrations that have the potential to exacerbate symptoms in some people with asthma, but for which uncertainties in the evidence become increasingly important.

When taken together, the Administrator reaches the proposed conclusion that the current body of scientific evidence and the results of quantitative analyses support the degree of public health protection provided by the current 1-hour and annual primary NO<sub>2</sub> standards and do not call into question any of the elements of those standards. He additionally reaches the proposed conclusion that the current 1-hour and annual NO<sub>2</sub> primary standards, together, are requisite to protect public health with an adequate margin of safety.

These proposed conclusions are consistent with CASAC recommendations. In its advice to the Administrator, “the CASAC recommends retaining, and not changing the existing suite of standards” (Diez Roux and Sheppard, 2017). The CASAC further stated that “it is the suite of the current 1-hour and annual standards, together, that provide protection against adverse effects” (Diez Roux and Sheppard, 2017, p. 9).

Therefore, in this review, the Administrator proposes to retain the current primary NO<sub>2</sub> standards, without revision. The Administrator solicits

comment on his proposed conclusions regarding the public health protection provided by the current primary NO<sub>2</sub> standards and on his proposal to retain those standards in this review. He invites comment on all aspects of these proposed conclusions and their underlying rationales, as discussed in detail in section II below.

## I. Background

### A. Legislative Requirements

Two sections of the Clean Air Act (CAA or the Act) govern the establishment 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 his “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 . . . [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. 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.”<sup>1</sup> 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.”<sup>2</sup>

<sup>1</sup> The legislative history of section 109 indicates that a primary standard is to be set at “the maximum permissible ambient air level . . . which will protect the health of any [sensitive] group of the population,” and that for this purpose “reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group.” See S. Rep. No. 91-1196, 91st Cong., 2d Sess. 10 (1970).

<sup>2</sup> As specified in section 302(h) (42 U.S.C. 7602(h)) effects on welfare include, but are not limited to, “effects on soils, water, crops,

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. *See Lead Industries Association v. EPA*, 647 F.2d 1130, 1154 (DC Cir 1980), *cert. denied*, 449 U.S. 1042 (1980); *American Petroleum Institute v. Costle*, 665 F.2d 1176, 1186 (D.C. Cir. 1981), *cert. denied*, 455 U.S. 1034 (1982); *American Farm Bureau Federation v. EPA*, 559 F. 3d 512, 533 (D.C. Cir. 2009); *Association of Battery Recyclers v. EPA*, 604 F. 3d 613, 617–18 (D.C. Cir. 2010). 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, *see Lead Industries v. EPA*, 647 F.2d at 1156 n.51, but rather at a level that reduces risk sufficiently so as to protect public health with an adequate margin of safety.

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 sensitive population(s) at risk,<sup>3</sup> and the kind and degree of the uncertainties that must be addressed. The selection of any particular approach to providing an adequate margin of safety is a policy choice left specifically to the Administrator's judgment. *See Lead Industries Association v. EPA*, 647 F.2d at 1161–62.

In setting primary and secondary standards that are “ requisite ” to protect

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.”

<sup>3</sup> As used here and similarly throughout this notice, the term population (or group) refers to persons having a quality or characteristic in common, such as a specific pre-existing illness or a specific age or life stage. As discussed more fully in section II.C.3 below, the identification of sensitive groups (called at-risk groups or at-risk populations) involves consideration of susceptibility and vulnerability.

public health and welfare, respectively, 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. *See generally, Whitman v. American Trucking Associations*, 531 U.S. 457, 465–472, 475–76 (2001). Likewise, “[a]ttainability and technological feasibility are not relevant considerations in the promulgation of national ambient air quality standards.” *American Petroleum Institute v. Costle*, 665 F. 2d at 1185.

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).<sup>4</sup>

#### B. Related NO<sub>2</sub> Control Programs

States are primarily responsible for ensuring attainment and maintenance of ambient air quality standards once EPA has established them. Under section 110 of the Act, 42 U.S.C. 7410, and related provisions, states are to submit, for EPA approval, state implementation plans (SIPs) that provide for the attainment and maintenance of such standards through control programs directed to sources of the pollutants involved. The states, in conjunction with EPA, also administer the prevention of significant deterioration program that covers these pollutants. *See* 42 U.S.C. 7470–7479. In addition, federal programs provide for nationwide reductions in emissions of these and other air pollutants under Title II of the Act, 42 U.S.C. 7521–7574, which involves controls for automobile, truck, bus, motorcycle, nonroad engine and equipment, and aircraft emissions;

<sup>4</sup> Lists of CASAC members and members of the NO<sub>2</sub> Review Panel are available at: <http://yosemite.epa.gov/sab/sabproduct.nsf/WebCASAC/CommitteesandMembership?OpenDocument>.

the new source performance standards (NSPS) under section 111 of the Act, 42 U.S.C. 7411; and the national emission standards for hazardous air pollutants under section 112 of the Act, 42 U.S.C. 7412.

Currently there are no areas in the United States that are designated as nonattainment of the NO<sub>2</sub> NAAQS (*see* 77 FR 9532 (February 17, 2012)). In addition, there are currently no monitors where there are design values (DVs)<sup>5</sup> above either the 1-hour or annual standard (U.S. EPA, 2017 Figure 2–5), with the maximum DVs in 2015 being 30 ppb (annual) and 72 ppb (hourly) (U.S. EPA, 2017 Section 2.3.1).<sup>6</sup>

While NO<sub>x</sub> (the sum of NO and NO<sub>2</sub>) is emitted from a wide variety of source types, the top three categories of sources of NO<sub>x</sub> emissions are highway vehicles, off-highway vehicles, and stationary fuel combustion sources.<sup>7</sup> The EPA anticipates that NO<sub>x</sub> emissions will continue to decrease over the next 20 years as a result of the ongoing implementation of mobile source emissions standards.<sup>8</sup> In particular, Tier 2 and Tier 3 emission standards for new light-duty vehicles, combined with the reduction of gasoline sulfur content, will significantly reduce motor vehicle emissions of NO<sub>x</sub>, with Tier 3 standards phasing in from model year 2017 to model year 2025. For heavy-duty engines, new NO<sub>x</sub> standards were phased in between the 2007 and 2010 model years, following the introduction of ultra-low sulfur diesel fuel. More stringent NO<sub>x</sub> standards for nonroad diesel engines, locomotives, and certain marine engines are becoming effective throughout the next decade. In future decades, these vehicles and engines

<sup>5</sup> The metric used to determine whether areas meet or exceed the NAAQS is called a design value (DV). In the case of the primary NO<sub>2</sub> NAAQS, there are 2 types of DVs: the annual DV and the hourly DV. The annual DV for a particular year is the average of all hourly values within that calendar year. The hourly DV is the three-year average of the 98th percentiles of the annual distributions of daily maximum 1-hour NO<sub>2</sub> concentrations. These DVs are considered to be valid if the monitoring data used to calculate them meet completeness criteria described in 40 CFR 50.11 and Appendix S to Part 50.

<sup>6</sup> For more information on estimated DVs, *see* Section 2.3 of the NO<sub>2</sub> PA.

<sup>7</sup> Highway vehicles include all on-road vehicles, including light duty as well as heavy duty vehicles, both gasoline- and diesel-powered. Off-highway vehicles and engines include aircraft, commercial marine vessels, locomotives and non-road equipment. Fuel combustion sources includes electric power generating units (EGUs), which derive their power generation from all types of fuels.

<sup>8</sup> Reductions in ambient NO<sub>2</sub> concentrations could also result from the implementation of NAAQS for other pollutants (e.g., ozone, PM), to the extent NO<sub>x</sub> emissions are reduced as part of the implementation of those standards.

meeting more stringent NO<sub>x</sub> standards will become an increasingly large fraction of in-use mobile sources, leading to large NO<sub>x</sub> emission reductions.

NO<sub>x</sub> emissions from stationary fuel combustion sources are primarily from electric utility sources, both coal and gas-fired. NO<sub>x</sub> emissions from these sources, as well as for some large industrial combustion sources, are also expected to continue to decrease over the next decade as newer replacement units come on-line which will have to meet NSPS and SIP compliance limits, and as additional existing sources opt-in to NO<sub>x</sub> trading programs to maintain state emissions budget programs.

### C. Review of the Air Quality Criteria and Standards for Oxides of Nitrogen

In 1971, the EPA added oxides of nitrogen 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).<sup>9</sup> Based on these air quality criteria, the EPA promulgated the NO<sub>2</sub> NAAQS (36 FR 8186, April 30, 1971). Both primary and secondary standards were set at 53 ppb,<sup>10</sup> annual average. Since then, the Agency has completed multiple reviews of the air quality criteria and primary NO<sub>2</sub> standards. In the last review, the EPA made revisions to the primary NO<sub>2</sub> NAAQS in order to provide requisite protection of public health. Specifically, the EPA supplemented the existing primary annual NO<sub>2</sub> standard by establishing a new short-term 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 (75 FR 6474, February 9, 2010). In addition, revisions to the NAAQS were accompanied by revisions to the data handling procedures and the ambient air monitoring and reporting requirements, including requirements for states to locate monitors near heavily trafficked roadways in large urban areas and in other locations where maximum NO<sub>2</sub> concentrations can occur.

Industry groups filed petitions for judicial review of the 2010 rule in the U.S. Court of Appeals for the District of Columbia Circuit. *API v. EPA*, 684 F.3d 1342 (D.C. Cir. 2012). The court upheld the 2010 rule, denying the petitions' challenges to the adoption of the 1-hour NO<sub>2</sub> NAAQS and dismissing, for lack of jurisdiction, the challenges to

statements regarding permitting in the preamble of the 2010 rule. *Id.* at 1354.

Subsequent to the 2010 rulemaking, the Agency revised the deadlines by which the near-road monitors were to be operational in order to implement a phased deployment approach (78 FR 16184, March 14, 2013), with a majority of the network becoming operational by 2015. In 2016, after analyzing available monitoring data, the Agency revised the size requirements of the near-road network, reducing the network to only operate in Core Based Statistical Areas (CBSAs) with populations of 1 million or more (81 FR 96381, December 30, 2016).

In February 2012, the EPA announced the initiation of the current periodic review of the air quality criteria for oxides of nitrogen and of the primary NO<sub>2</sub> NAAQS and issued a call for information in the **Federal Register** (77 FR 7149, February 10, 2012). A wide range of external experts as well as EPA staff representing a variety of areas of expertise (e.g., epidemiology, human and animal toxicology, statistics, risk/exposure analysis, atmospheric science, and biology) participated in a workshop held by the EPA on February 29 to March 1, 2012 in Research Triangle Park, NC. The workshop provided an opportunity for a public discussion of the key policy-relevant issues around which the Agency would structure this primary NO<sub>2</sub> NAAQS review and the most meaningful new science that would be available to inform the EPA's understanding of these issues.

Based in part on the workshop discussions, the EPA developed a draft plan for the ISA and a draft Integrated Review Plan (IRP) outlining the schedule, process, and key policy-relevant questions that would guide the evaluation of the health-related air quality criteria for NO<sub>2</sub> and the review of the primary NO<sub>2</sub> NAAQS. The draft plan for the ISA was released in May 2013 (78 FR 26026) and was the subject of a consultation with the CASAC on June 5, 2013 (78 FR 27234). Comments from the CASAC and the public were considered in the preparation of the first draft ISA and the draft IRP. In addition, preliminary draft materials for the ISA were reviewed by subject matter experts at a public workshop hosted by the EPA's National Center for Environmental Assessment (NCEA) in May 2013 (78 FR 27374). The first draft ISA was released in November 2013 (78 FR 70040). During this time, the draft IRP was also in preparation and was released in February 2014 (79 FR 7184). Both the draft IRP and first draft ISA were reviewed by the CASAC at a public meeting held in March 2014 (79

FR 8701), and the first draft ISA was further discussed at an additional teleconference held in May 2014 (79 FR 17538). The CASAC finalized its recommendations on the first draft ISA and the draft IRP in letters dated June 10, 2014 (Frey, 2014a; Frey, 2014b), and the final IRP was released in June 2014 (79 FR 36801).

The EPA released the second draft ISA in January 2015 (80 FR 5110) and the Risk and Exposure Assessment (REA) Planning document in May 2015 (80 FR 27304). These documents were reviewed by the CASAC at a public meeting held in June 2015 (80 FR 22993). A follow-up teleconference with the CASAC was held in August 2015 (80 FR 43085) to finalize recommendations on the second draft ISA. The final ISA was released in January 2016 (81 FR 4910). The CASAC's recommendations on the second draft ISA and the draft REA Plan were provided to the EPA in letters dated September 9, 2015 (Diez Roux and Frey, 2015a; Diez Roux and Frey 2015b), and the final ISA was released in January, 2016 (81 FR 4910).

After considering CASAC's advice and public comments, the EPA prepared a draft Policy Assessment (PA), which was released on September 23, 2016 (81 FR 65353). The draft PA was reviewed by the CASAC on November 9–10, 2016 (81 FR 68414), and a follow-up teleconference was held on January 24, 2017 (81 FR 95137). The CASAC's recommendations, based on its review of the draft PA, were provided in a letter to the EPA Administrator dated March 7, 2017 (Diez Roux and Sheppard, 2017). The EPA staff took into account these recommendations, as well as public comments provided on the draft PA, when developing the final PA, which was released in April 2017.<sup>11</sup>

In addition, in July 2016, a lawsuit was filed against the EPA and included a claim that EPA had failed to complete its review of the primary NO<sub>2</sub> NAAQS within five years, as required by the CAA. *Center for Biological Diversity et al. v. McCarthy*, (No. 4:16-cv-03796-VC, N.D. Cal., July 7, 2016). Consistent with CAA section 113(g), a notice of a proposed consent decree to resolve this litigation was published in the **Federal Register** on January 17, 2017 (82 FR 4866). The EPA received two public comments on the proposed consent decree, neither of which disclosed facts or considerations indicating that the Department of Justice or EPA should withhold consent. The parties to the

<sup>9</sup>In the 1971 proposal, the EPA used the term nitrogen oxides.

<sup>10</sup>In 1971, primary and secondary NO<sub>2</sub> NAAQS were set at levels of 100 micrograms per cubic meter (µg/m<sup>3</sup>), which equals 0.053 parts per million (ppm) or 53 ppb.

<sup>11</sup>This document may be found at: <https://www.epa.gov/naaqs/policy-assessment-review-primary-national-ambient-air-quality-standards-oxides-nitrogen>.

litigation filed a joint motion asking the court to enter the consent decree, and the court entered the consent decree as a consent judgment on April 28, 2017. The consent judgment established July 14, 2017, as the deadline for signature of a notice setting forth the proposed decision in this review, and April 6, 2018, as the deadline for signature of a notice setting forth the final decision.

Consistent with the review completed in 2010, this review is focused on health effects associated with gaseous oxides of nitrogen and the protection afforded by the primary NO<sub>2</sub> standards. The gaseous oxides of nitrogen include NO<sub>2</sub> and NO as well as their gaseous reaction products. Total oxides of nitrogen include these gaseous species as well as particulate species (e.g., nitrates). Health effects and non-ecological welfare effects associated with the particulate species are addressed in the review of the NAAQS for PM (U.S. EPA, 2016b).<sup>12</sup> The EPA is separately reviewing the ecological welfare effects associated with oxides of nitrogen, oxides of sulfur, and PM, and the protection provided by the secondary NO<sub>2</sub>, SO<sub>2</sub> and PM standards. (U.S. EPA, 2017a).<sup>13</sup>

## II. Rationale for Proposed Decisions on the Primary NO<sub>2</sub> Standards

This section presents the rationale for the Administrator's proposed decision to retain the existing NO<sub>2</sub> primary standards. This rationale is based on a thorough review of the latest scientific information generally published through August 2014,<sup>14</sup> as presented in the ISA, on human health effects associated with NO<sub>2</sub> and pertaining to the presence of NO<sub>2</sub> in the ambient air. The Administrator's rationale also takes into account: (1) The EPA staff's consideration of the scientific evidence and technical information and staff's conclusions based on that evidence and information, presented in the PA; (2) the CASAC's advice and recommendations, as reflected in discussions at public meetings of drafts of the various

documents that were prepared for this review, including the ISA and PA, and in the CASAC's letters to the Administrator; and (3) public input received during the development of these documents, either in connection with CASAC meetings or separately.<sup>15</sup>

In presenting the rationale for the Administrator's proposed decision and its foundations, Section II.A provides background on the general approach for review of the primary NO<sub>2</sub> NAAQS, including a summary of the approach used in the last review (Section II.A.1) and the general approach taken in the PA for the current review (Section II.A.2). Section II.B characterizes ambient NO<sub>2</sub> concentrations throughout the United States. Section II.C summarizes the body of available scientific evidence, focusing on consideration of key policy-relevant questions, and Section II.D summarizes the available information from quantitative analyses evaluating the potential for NO<sub>2</sub> exposures that could be of public health concern. Section II.E summarizes CASAC advice. Section II.F presents the Administrator's proposed conclusions on adequacy of the current standard, drawing on both evidence-based and exposure-/risk-based considerations (Sections II.F.1 and II.F.2, respectively), and advice from CASAC (Section II.F.3).

### A. General Approach

The past and current approaches described below are both based, most fundamentally, on using the EPA's assessment of the current scientific evidence and associated quantitative analyses to inform the Administrator's judgment regarding primary NO<sub>2</sub> standards that protect public health with an adequate margin of safety. As noted in the PA (U.S. EPA, 2017a, section 1.4), in drawing conclusions with regard to the primary standards, the final decision on the adequacy of the current standards is largely a public health policy judgment to be made by the Administrator. The Administrator's decisions 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. The PA's approach to informing these judgments, discussed more fully below, is based on the recognition that the available health effects evidence

generally reflects a continuum, consisting of higher 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 sections 108 and 109 of the Act and with how the EPA and the courts have historically interpreted the Act. These provisions require the establishment of primary standards that, in the judgment of the Administrator, are requisite to protect public health with an adequate margin of safety. In fulfilling this responsibility, the Administrator seeks to establish standards that are neither more nor less stringent than necessary for this purpose. The Act 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 including the health of sensitive groups. The four basic elements of the NAAQS (indicator, averaging time, level, and form) are considered collectively in evaluating the health protection afforded by the current standards.

### 1. Approach in the Last Review

The last review of the primary NO<sub>2</sub> NAAQS was completed in 2010 (75 FR 6474, February 9, 2010). In that review, the EPA established a new 1-hour standard to provide increased public health protection, including for people with asthma and other at-risk populations,<sup>16</sup> against an array of adverse respiratory health effects that had been linked to short-term NO<sub>2</sub> 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 annual distribution of daily maximum 1-hour NO<sub>2</sub> concentrations, with a level of 100 ppb. In addition to setting the new 1-hour standard, the EPA retained the existing annual standard with its level of 53 ppb (75 FR 6502, February 9, 2010). The Administrator in that review concluded that, together, the two standards provide protection against adverse respiratory health effects associated with short-term exposures to NO<sub>2</sub> and effects potentially associated with long-term exposures. In conjunction with the revised primary NO<sub>2</sub> NAAQS, the EPA also established a multi-tiered monitoring network composed of (1) near-road monitors which would be placed near heavily trafficked roads in urban areas; (2) monitors located to characterize areas with the highest expected NO<sub>2</sub> concentrations at the neighborhood and

<sup>12</sup> Additional information on the PM NAAQS is available at: <https://www.epa.gov/naaqs/particulate-matter-pm-air-quality-standards>.

<sup>13</sup> Additional information on the ongoing and previous review of the secondary NO<sub>2</sub> and SO<sub>2</sub> NAAQS is available at: <https://www.epa.gov/naaqs/nitrogen-dioxide-no2-and-sulfur-dioxide-so2-secondary-air-quality-standards>.

<sup>14</sup> In addition to the review's opening "call for information" (77 FR 7149, February 10, 2012), "the U.S. EPA routinely conducted literature searches to identify relevant peer-reviewed studies published since the previous ISA (i.e., from January 2008 through August 2014)" (U.S. EPA, 2016a p. 1–3). References that are cited in the ISA, the references that were considered for inclusion but not cited, and electronic links to bibliographic information and abstracts can be found at: <http://hero.epa.gov/oxides-of-nitrogen>.

<sup>15</sup> Public input during the review process, including on drafts of the ISA and PA, and CASAC's advice in light of that public input, were considered by the EPA staff in developing final documents.

larger spatial scales (also referred to as “area-wide” monitors); and (3) forty NO<sub>2</sub> monitors to characterize air quality for susceptible and vulnerable communities, nationwide (75 FR 6505 to 6511). Subsequent to the 2010 rulemaking, the Agency adopted a phased implementation schedule for the near-road monitoring network and removed the requirement for near-road NO<sub>2</sub> monitoring in CBSAs with population of less than 1 million (78 FR 16184, March 14, 2013; 81 FR 96381, December 30, 2016). Key aspects of the Administrator’s approach in the last review to reaching these decisions are described below.

a. Approach to Considering the Need for Revision in the Last Review

The 2010 decision to revise the existing primary NO<sub>2</sub> standard was based largely on the body of scientific evidence published through early 2008 and assessed in the 2008 ISA (U.S. EPA, 2008a); the quantitative exposure and risk analyses and the assessment of the policy-relevant aspects of the evidence presented in the REA (U.S. EPA, 2008b);<sup>17</sup> the advice and recommendations of the CASAC (Samet, 2008); and public comments on the proposal.

As an initial consideration in reaching that decision, the Administrator noted that the evidence relating short-term (minutes to weeks) NO<sub>2</sub> exposures to respiratory morbidity was judged in the ISA to be “sufficient to infer a likely causal relationship” (75 FR 6489, February 9, 2010; U.S. EPA, 2008a, Sections 3.1.7 and 5.3.2.1).<sup>18</sup> The scientific evidence included controlled human exposure studies providing evidence of increases in airway responsiveness in people with asthma following short-term exposures to NO<sub>2</sub> concentrations as low as 100 ppb<sup>19</sup> and epidemiologic studies reporting associations between short-term NO<sub>2</sub> exposures and respiratory effects in

<sup>17</sup> As discussed in the IRP for this review (U.S. EPA, 2014, Section 1.3), due to changes in the NAAQS process, the last review of the NO<sub>2</sub> NAAQS did not include a separate PA document. Rather, the REA for that review included a policy assessment chapter.

<sup>18</sup> In contrast, the evidence relating long-term (weeks to years) NO<sub>2</sub> exposures to health effects was judged to be either “suggestive of 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, February 9, 2010). The causal framework used in the ISA for the current review is discussed in Chapter 3 of the PA (U.S. EPA, 2017a).

<sup>19</sup> Transient increases in airway responsiveness have the potential to increase asthma symptoms and worsen asthma control (74 FR 34415, July 15, 2009; U.S. EPA, 2008a, sections 5.3.2.1 and 5.4).

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. 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 associated with adjusting air quality in such analyses (75 FR 6489, February 9, 2010). 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<sub>2</sub> exposures; most people with asthma in Atlanta could be exposed on multiple days per year to NO<sub>2</sub> concentrations at or above 300 ppb; and most locations evaluated could experience on-/near-road NO<sub>2</sub> concentrations above 100 ppb on more than half of the days in a given year” (75 FR 6489, February 9, 2010; U.S. EPA, 2008b, Section 10.3.2).

In reaching the conclusion on adequacy of the annual standard alone, the Administrator also considered advice received from the CASAC. In its advice, the CASAC agreed that the primary concern in the review was to protect against health effects that have been associated with short-term NO<sub>2</sub> exposures. The 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, “[The] CASAC concurs with EPA’s judgment that the current NAAQS does not protect the public’s health and that it should be revised” (Samet, 2008, p. 2).

Based on the considerations summarized above, the Administrator concluded that the annual NO<sub>2</sub> NAAQS alone 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 people with asthma, children, and older adults (75 FR 6490, February 9, 2010). Upon consideration of approaches to revising the standard, the Administrator concluded that it was appropriate to set a new short-term standard, in addition

to the existing annual standard with its level of 53 ppb, as described below.

b. Approach to Considering the Elements of a Revised Standard in the Last Review

In considering appropriate revisions in the last review, each of the four basic elements of the NAAQS (indicator, averaging time, level, and form) were evaluated. The sections below summarize the approaches used by the Administrator, and her final decisions, on each of those elements.

i. Indicator

In the review completed in 2010, as well as in previous reviews, the EPA focused on NO<sub>2</sub> as the most appropriate indicator for oxides of nitrogen because the available scientific information regarding health effects was largely indexed by NO<sub>2</sub>. Controlled human exposure studies and animal toxicological studies provided specific evidence for health effects following exposures to NO<sub>2</sub>. In addition, epidemiologic studies typically reported effects associated with NO<sub>2</sub> concentrations<sup>20</sup> (75 FR 6490, February 9, 2010; U.S. EPA 2008a, Section 2.2.3). Based on the information available in the last review, and consistent with the views of the CASAC (Samet, 2008, p. 2; Samet, 2009, p. 2), the EPA concluded it was appropriate to continue to use NO<sub>2</sub> as the indicator for a standard that was intended to address effects associated with exposure to NO<sub>2</sub>, 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<sub>2</sub> will also reduce exposures to other oxides of nitrogen (75 FR 6490, February 9, 2010).

ii. Averaging Time

In considering the most appropriate averaging time(s) for the primary NO<sub>2</sub> 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, and recommendations from the CASAC.<sup>21</sup> Her key considerations are summarized below.

When considering averaging time, the Administrator first noted that the evidence relating short-term (minutes to weeks) NO<sub>2</sub> exposures to respiratory

<sup>20</sup> The degree to which monitored NO<sub>2</sub> reflected actual NO<sub>2</sub> concentrations, as opposed to NO<sub>2</sub> 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).

<sup>21</sup> She also considered public comments received on the proposal (75 FR 6490, February 9, 2010).

morbidity was judged in the ISA to be “sufficient to infer a likely causal relationship” (U.S. EPA, 2008a, section 5.3.2.1). The Administrator concluded that this strength of evidence most directly supported consideration of an averaging time that focused protection on effects associated with short-term exposures to NO<sub>2</sub>. In 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 epidemiologic studies. Controlled human exposure studies and animal toxicological studies provided evidence that NO<sub>2</sub> exposures from less than 1 hour up to 3 hours can result in respiratory effects such as increased AR and inflammation (U.S. EPA, 2008a, Section 5.3.2.7). The Administrator specifically noted the ISA conclusion that exposures of adults with asthma to 100 ppb NO<sub>2</sub> for 1-hour (or 200 to 300 ppb for 30 minutes) can result in small but statistically significant increases in nonspecific AR (U.S. EPA, 2008a, Section 5.3.2.1). In addition, the epidemiologic 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<sub>2</sub> concentrations. Based on REA analyses of ratios between 1-hour and 24-hour NO<sub>2</sub> concentrations (U.S. EPA, 2008b, Section 10.4.2), she further concluded that a standard based on 1-hour daily maximum NO<sub>2</sub> concentrations could also be effective at protecting against effects associated with 24-hour NO<sub>2</sub> exposures (75 FR 6490).

Based on the above, the Administrator judged that it was appropriate to set a new NO<sub>2</sub> standard with a 1-hour averaging time. She concluded that such a standard would be expected to effectively limit short-term (*e.g.*, 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 against effects potentially associated with long-term exposures to oxides of nitrogen (75 FR 6502, February 9, 2010). These decisions were consistent with CASAC advice to establish a short-term primary standard for oxides of nitrogen based on using 1-hour maximum NO<sub>2</sub> concentrations and to retain the current annual standard (Samet, 2008, p. 2; Samet, 2009, p. 2).

### iii. Level

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<sub>2</sub> standard at 100 ppb. This standard was focused on limiting the *maximum* 1-hour NO<sub>2</sub> concentrations in ambient air (75 FR 6474, February 9, 2010).<sup>22</sup> In establishing this new standard, the Administrator emphasized the importance of protecting against short-term exposures to peak concentrations of NO<sub>2</sub>, 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<sub>2</sub> concentrations and, therefore, are important contributors to NO<sub>2</sub>-associated public health risks (U.S. EPA, 2008b, Figures 8–17 and 8–18).

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 largely 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<sub>2</sub>-induced increase in AR at or above 100 ppb presented a potential risk of adverse effects for some people with asthma, especially those with more serious (*i.e.*, more than mild) asthma. The Administrator noted that the risks associated with increased AR could not be fully characterized based on available controlled human exposure studies. However, the Administrator concluded that people with asthma, particularly those suffering from more severe asthma, warrant protection from the risk of adverse effects associated with the NO<sub>2</sub>-induced increase in AR. Therefore, the Administrator concluded that the 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

<sup>22</sup> In conjunction with this new standard, the Administrator established a multi-tiered monitoring network that included monitors sited to measure the maximum NO<sub>2</sub> concentrations near major roadways, as well as monitors sited to measure maximum area-wide NO<sub>2</sub> concentrations and for the characterization of NO<sub>2</sub> exposure for susceptible and vulnerable populations.

conclude that this evidence did not support setting a standard level lower than 100 ppb (75 FR 6500–6501, February 9, 2010).

The Administrator also considered the more serious health effects reported in NO<sub>2</sub> epidemiologic studies. She noted that a new standard focused on protecting against maximum 1-hour NO<sub>2</sub> 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<sup>23</sup> NO<sub>2</sub> concentrations to below 85 ppb, which was the lowest 98th percentile 1-hour daily maximum NO<sub>2</sub> concentration in the cluster of five key epidemiologic studies which reported associations with respiratory-related hospital admissions or emergency department visits and which the Administrator gave substantial weight. The Administrator also concluded that such a 1-hour standard would be consistent with the REA conclusions based on the NO<sub>2</sub> exposure and risk information (75 FR 6501, February 9, 2010).

Given the above considerations and the comments received on the proposal, and considering the entire body of evidence and information before her, as well as the related uncertainties, the Administrator judged it appropriate to set a 1-hour standard with a level of 100 ppb. Specifically, she concluded that such a standard, with an appropriate form as discussed below, would provide a substantial 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<sub>2</sub> exposures in both controlled human exposure and epidemiologic studies. This includes limiting exposures at and above 100 ppb for the vast majority of people, including those in at-risk groups, and maintaining maximum area-wide NO<sub>2</sub> concentrations below those in locations where key U.S. epidemiologic studies had reported that ambient NO<sub>2</sub> 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 the CASAC. (75 FR 6501, February 9, 2010).

In setting the standard level at 100 ppb rather than at a lower level, the Administrator also acknowledged the

<sup>23</sup> Area-wide concentrations refer to those measured by monitors that have been sited to characterize ambient concentrations at the neighborhood and larger spatial scales.



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<sub>2</sub> concentrations below 100 ppb and/or associated with area-wide NO<sub>2</sub> concentrations well below those in locations where key U.S. epidemiologic studies had reported associations with respiratory-related emergency department visits and hospital admissions. Based on the available 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 observed 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. (75 FR 6501–02, February 9, 2010).

#### iv. Form

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 Administrator recognized that for short-term standards, concentration-based forms that 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.<sup>24</sup> In addition, she recognized that it is desirable from a public health perspective to have a form that is reasonably stable and insulated from the impacts of extreme meteorological events, and concluded that when averaged over three years, these concentration-based forms provide an appropriate balance between limiting peak pollutant concentrations and

<sup>24</sup> 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.

providing a stable regulatory target (75 FR 6492, February 9, 2010).

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<sub>2</sub> standard. The focus on the upper percentiles of the distribution was based, in part, on evidence of health effects associated with short-term NO<sub>2</sub> exposures from experimental studies which provided information on specific exposure concentrations that were linked to respiratory effects. In a letter to the Administrator following issuance of the Agency’s proposed rule, the CASAC recommended a form based on the 3-year average of the 98th percentile of the distribution of 1-hour daily maximum NO<sub>2</sub> concentrations (Samet, 2009, p. 2). In making this recommendation, the CASAC noted the potential for instability in the higher percentile concentrations and the absence of data from the near-road monitoring network, which at that time had been proposed but was not yet established.

Given the limited available information on the variability in peak NO<sub>2</sub> concentrations near important sources of NO<sub>2</sub>, primarily near major roadways, and given the recommendation from the CASAC regarding 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<sub>2</sub> concentrations. In addition, consistent with the CASAC’s advice (Samet, 2008, p. 2; Samet, 2009, p. 2), the EPA retained the form of the annual standard (75 FR 6502, February 9, 2010).

#### c. Areas of Uncertainty in Last Review

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<sub>2</sub> in the complex ambient mixture which includes a range of co-occurring pollutants (*e.g.*, fine particulate matter (PM<sub>2.5</sub>),<sup>25</sup> carbon monoxide (CO), and

<sup>25</sup> In general terms, particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm; a measurement of fine particles. In regulatory terms, particles with an upper 50% cut -point of 2.5 μm aerodynamic diameter (the 50% cut point diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) and a penetration curve as measured by a reference method based on

other traffic-related pollutants; ozone (O<sub>3</sub>); and sulfur dioxide (SO<sub>2</sub>)) (*e.g.*, 75 FR 6485 February 9, 2010); (2) understanding the extent to which monitored ambient NO<sub>2</sub> concentrations used in epidemiologic studies reflect exposures in study populations and the range of ambient concentrations over which the evidence indicates confidence in the health effects observed in the epidemiologic studies (*e.g.*, 75 FR 6501, February 9, 2010); (3) understanding the magnitude and potential adversity of NO<sub>2</sub>-induced respiratory effects reported in controlled human exposure studies (*e.g.*, 75 FR 6500, February 9, 2010); and (4) understanding the NO<sub>2</sub> concentration gradients around important sources, such as major roads, and relating those gradients to broader ambient monitoring concentrations (*e.g.*, 75 FR 6479, February 9, 2010).

#### 2. Approach for the Current Review

The approach in this review of the primary NO<sub>2</sub> NAAQS takes into consideration the approach used in the last review, and addresses key policy-relevant questions in light of the currently available scientific and technical information. To evaluate whether it is appropriate to consider retaining the current primary NO<sub>2</sub> standards, or whether consideration of revision is appropriate, the EPA has adopted an approach that builds upon the general approach used in the last review and reflects the body of evidence and information now available. As summarized above, the decisions in the last review were based on the integration of NO<sub>2</sub> health effects information with judgments on the adversity and public health significance of key health effects, policy judgments as to when the standard is requisite to protect public health with an adequate margin of safety, consideration of CASAC advice, and consideration of public comments.

In the current review, the EPA’s approach recognizes that the available health effects evidence reflects a continuum from relatively higher NO<sub>2</sub> concentrations, at which scientists generally agree that health effects are likely to occur, through lower concentrations, at which the likelihood and magnitude of a response become increasingly uncertain. In reaching a final decision on the current primary NO<sub>2</sub> standards, the Administrator will draw upon the available scientific

Appendix L of 40 CFR part 50 and designated in accordance with 40 CFR part 53, by an equivalent method designated in accordance with 40 CFR part 53, or by an approved regional method designated in accordance with Appendix C of 40 CFR part 58.

evidence for NO<sub>2</sub>-attributable health effects and upon information from available quantitative analyses, including judgments about the appropriate weight to assign the range of uncertainties inherent in the evidence and analyses. The Administrator will also consider advice from CASAC and public comments received in response to this proposed decision.

The final decision on the primary NO<sub>2</sub> standards is largely a public health policy judgment to be made by the EPA Administrator. The weight to be given to various elements of the evidence and the available quantitative analyses is part of the public health policy judgments that the Administrator will make in reaching decisions on the standards.

To inform the Administrator's judgments and decisions, the PA presents evidence-based and exposure/risk-based considerations. Evidence-based considerations focus on the findings of epidemiologic studies, controlled human exposure studies, and experimental animal studies evaluating health effects related to NO<sub>2</sub> exposures. The PA's consideration of such studies draws from the assessment of the evidence presented in the ISA (U.S. EPA, 2016a). Exposure/risk-based considerations draw upon the results of the PA's quantitative analyses of potential NO<sub>2</sub> exposures. The PA's consideration of the evidence and quantitative information is framed by a series of key policy-relevant questions (U.S. EPA, 2017a, Figure 1–1). These questions focus on the strength of the evidence for various NO<sub>2</sub>-related health effects and for potential at-risk populations, the NO<sub>2</sub> exposure concentrations at which adverse effects occur, the potential for NO<sub>2</sub> exposures and health effects of public health concern with NO<sub>2</sub> concentrations that meet the current standards, and uncertainties in the available evidence and information. The PA's consideration of these issues is intended to inform the Administrator's decisions as to whether, and if so how, to revise the current NO<sub>2</sub> standards. These considerations are discussed below (II.C to II.F).

### B. Characterization of NO<sub>2</sub> Air Quality

This section presents information on NO<sub>2</sub> atmospheric chemistry and ambient concentrations, with a focus on information that is most relevant for the review of the primary NO<sub>2</sub> standards. This section is drawn from the more detailed discussion of NO<sub>2</sub> air quality in the PA (U.S. EPA, 2017a, Chapter 2) and

the ISA (U.S. EPA, 2016a, Chapter 2).<sup>26</sup> It presents a summary of NO<sub>2</sub> atmospheric chemistry (II.B.1), trends in ambient NO<sub>2</sub> concentrations (II.B.2), ambient NO<sub>2</sub> concentrations measured at monitors near roads (II.B.3), the relationships between hourly and annual ambient NO<sub>2</sub> concentrations (II.B.4), and background concentrations of NO<sub>2</sub> (II.B.5).

#### 1. Atmospheric Chemistry

Ambient concentrations of NO<sub>2</sub> are influenced by both direct NO<sub>2</sub> emissions and by emissions of nitric oxide (NO), with the subsequent conversion of NO to NO<sub>2</sub> primarily through reaction with ozone (O<sub>3</sub>). The initial reaction between NO and O<sub>3</sub> to form NO<sub>2</sub> occurs fairly quickly during the daytime, with reaction times on the order of minutes. However, NO<sub>2</sub> can also be photolyzed to regenerate NO, creating new O<sub>3</sub> in the process (U.S. EPA, 2016a, Section 2.2). A large number of oxidized nitrogen species in the atmosphere are formed from the oxidation of NO and NO<sub>2</sub>. These include nitrate radicals (NO<sub>3</sub>), nitrous acid (HONO), nitric acid (HNO<sub>3</sub>), dinitrogen pentoxide (N<sub>2</sub>O<sub>5</sub>), nitryl chloride (ClNO<sub>2</sub>), peroxyxynitric acid (HNO<sub>4</sub>), peroxyacetyl nitrate and its homologues (PANs), other organic nitrates, such as alkyl nitrates (including isoprene nitrates), and pNO<sub>3</sub>. The sum of these reactive oxidation products and NO plus NO<sub>2</sub> comprise the oxides of nitrogen.<sup>27 28</sup>

Due to the close relationship between NO and NO<sub>2</sub>, and their ready interconversion, these species are often grouped together and referred to as NO<sub>x</sub>. The majority of NO<sub>x</sub> emissions are in the form of NO. For example, 90% or more of tail-pipe NO<sub>x</sub> emissions are in the form of NO, with only about 2% to 10% emitted as NO<sub>2</sub> (Itano et al., 2014; Kota et al., 2013; Jimenez et al., 2000; Richmond-Bryant et al., 2016). NO<sub>x</sub> emissions require time and sufficient O<sub>3</sub> concentrations for the conversion of NO to NO<sub>2</sub>. Higher temperatures and concentrations of reactants result in

<sup>26</sup> The focus is on NO<sub>2</sub> in this notice, as this is the indicator for the current standards and is most relevant to the evaluation of health evidence. Characterization of air quality for the broader category of oxides of nitrogen is provided in the ISA (U.S. EPA, 2016a, Chapter 2).

<sup>27</sup> This follows usages in the Clean Air Act Section 108(c): "Such criteria [for oxides of nitrogen] shall include a discussion of nitric and nitrous acids, nitrites, nitrates, nitrosamines, and other carcinogenic and potentially carcinogenic derivatives of oxides of nitrogen." By contrast, within air pollution research and control communities, the terms "nitrogen oxides" and NO<sub>x</sub> are often restricted to refer only to the sum of NO and NO<sub>2</sub>.

<sup>28</sup> See Figure 2–1 of the NO<sub>2</sub> PA for additional information (U.S. EPA, 2017a).

shorter conversion times (e.g., less than one minute under some conditions), while dispersion and depletion of reactants result in longer conversion times. The time required to transport emissions away from a roadway can vary from less than one minute (e.g., under open conditions) to about one hour (e.g., for certain urban street canyons) (Düring et al., 2011; Richmond-Bryant and Reff, 2012). These factors can affect the locations where the highest NO<sub>2</sub> concentrations occur. In particular, while ambient NO<sub>2</sub> concentrations are often elevated near important sources of NO<sub>x</sub> emissions, such as major roadways, the highest measured ambient concentrations in a given urban area may not always occur immediately adjacent to those sources.<sup>29</sup>

#### 2. National Trends in NO<sub>x</sub> Emissions and Ambient NO<sub>2</sub> Concentrations

Ambient concentrations of NO<sub>2</sub> in the U.S. are due largely to NO<sub>x</sub> emissions from anthropogenic sources. Background NO<sub>2</sub> is estimated to make up only a small fraction of current ambient concentrations (U.S. EPA, 2016a, Section 2.5.6; U.S. EPA, 2017, Section 2.3.4).<sup>30</sup> Nationwide estimates indicate that there has been a 61% reduction in total NO<sub>x</sub> emissions from 1980 to 2016 (U.S. EPA, 2017a, Section 2.1.2, Figure 2–2). These reductions have been driven primarily by decreases in emissions from mobile sources and fuel combustion (U.S. EPA, 2017, Section 2.1.2, Figure 2–3).

Long-term trends in NO<sub>2</sub> DVs across the U.S. show that ambient concentrations of NO<sub>2</sub> have been declining, on average, since 1980 (U.S. EPA, 2017a, Figure 2–4). Data have been collected for at least some part of the period since 1980 at 2099 sites in the U.S., with individual sites having a wide range in duration and continuity of operations across multiple decades. Overall, the majority of sampling sites have observed statistically significant downward trends in ambient NO<sub>2</sub> concentrations (U.S. EPA, 2017a, Figure 2–5).<sup>31</sup> The annual and hourly DVs

<sup>29</sup> Ambient NO<sub>2</sub> concentrations around stationary sources of NO<sub>x</sub> emissions are similarly impacted by the availability of O<sub>3</sub> and by meteorological conditions, although surface-level NO<sub>2</sub> concentrations can be less impacted in cases where stationary source NO<sub>x</sub> emissions are emitted from locations elevated substantially above ground level.

<sup>30</sup> Background concentrations of a pollutant can be defined in various ways, depending on context and circumstances. Background concentrations of NO<sub>2</sub> are discussed in the ISA (U.S. EPA, 2016a, Section 2.5.6) and the PA (U.S. EPA, 2017, Section 2.3.4).

<sup>31</sup> Based on an analysis of data from sampling sites with sufficient data to produce at least five valid DVs.

trended upward in less than 4% of the sites.<sup>32</sup> Even considering the fact that there are a handful of sites where upward trends in NO<sub>2</sub> concentrations have occurred, the maximum DVs in 2015 across the whole monitoring network were well-below the NAAQS, with the highest values being 30 ppb (annual) and 72 ppb (hourly) (U.S. EPA, 2017a, Section 2.3.1).

### 3. Near-Road NO<sub>2</sub> Air Quality

The largest single source of NO<sub>x</sub> emissions is on-road vehicles, and emissions are primarily in the form of NO, with NO<sub>2</sub> formation requiring both time and sufficient O<sub>3</sub> concentrations. Depending on local meteorological conditions and O<sub>3</sub> concentrations, ambient NO<sub>2</sub> concentrations can be higher near roadways than at sites in the same area but farther removed from the road (and from other sources of NO<sub>x</sub> emissions).

When considering the historical relationships between NO<sub>2</sub> concentrations at monitors near roadways, and monitors further away from roads, NO<sub>2</sub> DVs are generally highest at sampling sites nearest to the road (less than 50 meters) and decrease as distance from the road increases (U.S. EPA, 2017a, Section 2.3.2, Figure 2–6). This relationship is more pronounced for annual DVs than for hourly DVs. The general pattern of decreasing DVs with increasing distance from the road has persisted over time, though the absolute difference (in terms of ppb) between NO<sub>2</sub> concentrations close to roads and those farther from roads has generally decreased over time (U.S. EPA, 2017a, Section 2.3.2, Figure 2–6).

In addition, data from the recently deployed network<sup>33</sup> of dedicated near-road NO<sub>2</sub> monitors indicate that daily maximum 1-hour NO<sub>2</sub> concentrations are generally higher at near-road monitors than at non-near-road monitors in the same CBSA (U.S. EPA, 2017a, Figures 2–7 to 2–10). The 98th percentiles of 1-hour daily maximum concentrations (the statistic most relevant to the 2010 standard) were highest at near-road monitors (*i.e.*, higher than all non-near-road monitors

<sup>32</sup> It is not clear whether specific sources may be responsible for these upward trends in ambient NO<sub>2</sub> concentrations. As discussed in the PA (U.S. EPA, 2017a, Section 2.1.2), since 1980 increases in NO<sub>x</sub> emissions have been observed for several types of sources, including oil and gas production, agricultural field burning, prescribed fires and mining. Though relatively small contributors nationally, emissions from these sources can be substantial in some areas (*e.g.*, see U.S. EPA, 2016a, Section 2.3.5).

<sup>33</sup> Prior to the 2010 rulemaking, monitors were “not sited to measure peak roadway-associated NO<sub>2</sub> concentrations. . . .” (75 FR 6479).

in the same CBSA) in 58% to 77% of the CBSAs evaluated, depending on the year (U.S. EPA, 2017a, Section 2.3.2, Figures 2–7 to 2–10).<sup>34</sup>

### 4. Relationships Between Hourly and Annual NO<sub>2</sub> Concentrations

Control programs have resulted in substantial reductions in NO<sub>x</sub> emissions since the 1980s. These reductions in NO<sub>x</sub> emissions have decreased both short-term peak NO<sub>2</sub> concentrations and annual average concentrations (U.S. EPA, 2017a, Section 2.3.1). When considering the change in NO<sub>2</sub> DVs since the 1980s, the median annual DV has decreased by about 65% and the median 1-hour DV has decreased by about 50% (U.S. EPA, 2017a, Section 2.3.3, Figure 2–10). These DVs were measured predominantly by NO<sub>2</sub> monitors located at area-wide monitoring sites and data from the new near-road monitoring network were not included in the analysis due to the limited amount of data available.<sup>35</sup> At various times in the past, a number of these area-wide sites would have violated the 1-hour standard without violating the annual standard; however, no sites would have violated the annual standard without also violating the 1-hour standard (U.S. EPA, 2017a p.2–21). Furthermore, examination of historical data indicate that 1-hour DVs at or below 100 ppb generally correspond to annual DVs below 35 ppb (U.S. EPA, 2017a p.2–21). Based on this, meeting the 1-hour standard with its level of 100 ppb would be expected to maintain annual average NO<sub>2</sub> concentrations well-below the 53 ppb level of the annual standard (U.S. EPA, 2017a, Figure 2–11). It will be important to reevaluate this relationship as more data become available from recently deployed near-road monitors.

### C. Health Effects Information

This section summarizes the available scientific evidence on the health effects of NO<sub>2</sub> exposures. These summaries are based primarily on the assessment of the evidence in the ISA (U.S. EPA, 2016a) and on the PA’s consideration of that evidence in evaluating the public health protection provided by the current primary NO<sub>2</sub> standards (U.S. EPA, 2017a).

<sup>34</sup> The upper end of this range (*i.e.*, 77%) reflects more recent years during which most near-road monitors were in operation. The lower end of this range (*i.e.*, 58%) reflects the smaller number of near-road monitors in operation during the early years of the deployment of the near-road network.

<sup>35</sup> As noted above (II.A.1), area-wide sites are intended to characterize ambient NO<sub>2</sub> concentrations at the neighborhood and larger spatial scales.

In the current review of the primary NO<sub>2</sub> NAAQS, the ISA uses frameworks to characterize the strength of the available scientific evidence for health effects attributable to NO<sub>2</sub> exposures and to classify the evidence for factors that may increase risk in some populations<sup>36</sup> or lifestages (U.S. EPA, 2015, Preamble, Section 6). These frameworks provide the basis for robust, consistent, and transparent evaluation of the scientific evidence, including uncertainties in the evidence, and for drawing conclusions on air pollution-related health effects and at-risk populations.

With regard to characterization of the health effects evidence, the ISA uses a five-level hierarchy to classify the overall weight of evidence into one of the following categories: causal relationship; likely to be a causal relationship; suggestive of, but not sufficient to infer, a causal relationship; inadequate to infer a causal relationship; and not likely to be a causal relationship (U.S. EPA, 2015, Preamble Table II). The PA considers the full body of health evidence addressed in the ISA, placing the greatest emphasis on the effects for which the evidence has been judged in the ISA to demonstrate a “causal” or a “likely to be a causal” relationship with NO<sub>2</sub> exposures (U.S. EPA, 2017a).<sup>37</sup> In the ISA, a “causal” relationship is supported when, “the consistency and coherence of evidence integrated across scientific disciplines and related health outcomes are sufficient to rule out chance, confounding, and other biases with reasonable confidence” (U.S. EPA, 2016a, p. 1–5). A “likely to be a causal” relationship is supported when “there are studies where results are not explained by chance, confounding, or other biases, but uncertainties remain in the evidence overall. For example, the influence of other pollutants is difficult to address, or evidence among scientific disciplines may be limited or inconsistent” (U.S. EPA, 2016a, p. 1–5). Many of the health effects evaluated in the ISA, have complex etiologies. For instance, diseases such as asthma are typically initiated by multiple agents. For example, outcomes depend on a variety of factors such as age, genetic background, nutritional status, immune competence, and social factors (U.S.

<sup>36</sup> The term “population” refers to people having a quality or characteristic in common, including a specific pre-existing illness or a specific age or lifestage.

<sup>37</sup> In this review, as in past reviews, there were causal determination changes for different endpoint categories. For more information on changes in causal determinations from the previous review, see below and Table 1–1 of the ISA (U.S. EPA, 2016a).

EPA, 2017a Preamble, Section 5.b). Thus, exposure to NO<sub>2</sub> is likely one of several contributors to the health effects evaluated in the ISA.

With regard to identifying specific populations or lifestages that may be at increased risk of health effects related to NO<sub>2</sub> exposures, the ISA characterizes the evidence for a number of “factors”, including both intrinsic (*i.e.*, biologic, such as pre-existing disease or lifestage) and extrinsic (*i.e.*, non-biologic, such as diet or socioeconomic status) factors. The categories considered in classifying the evidence for these potential at-risk factors are “adequate evidence,” “suggestive evidence,” “inadequate evidence,” and “evidence of no effect” (U.S. EPA, 2016a, Section 5.c, Table II). Within the PA, the focus is on the consideration of potential at-risk populations and lifestages for which the ISA judges there is “adequate” evidence (U.S. EPA, 2016a, Table 7–27).

Section II.C.1 summarizes the evidence for effects related to short-term NO<sub>2</sub> exposures (*e.g.*, minutes to weeks). Section II.C.2 summarizes the evidence for effects related to long-term NO<sub>2</sub> exposures (*e.g.*, months to years). Section II.C.3 discusses the potential public health implications of NO<sub>2</sub> exposures, based on the evidence for populations and lifestages at increased risk of NO<sub>2</sub>-related effects.

#### 1. Health Effects With Short-Term Exposure to NO<sub>2</sub>

This section discusses the evidence for health effects following short-term NO<sub>2</sub> exposures. Section II.C.1.a discusses the nature of the health effects that have been shown to occur following short-term NO<sub>2</sub> exposures and the strength of the evidence supporting various effects, based on the assessment of that evidence in the ISA. Section II.C.1.b discusses the NO<sub>2</sub> concentrations at which health effects have been demonstrated to occur, based on the considerations and analyses included in the PA.<sup>38</sup>

##### a. Nature of Effects

Across previous reviews of the primary NO<sub>2</sub> NAAQS (U.S. EPA, 1993; U.S. EPA, 2008a), evidence has consistently demonstrated respiratory effects attributable to short-term NO<sub>2</sub> exposures. In the last review, the 2008 ISA concluded that evidence was “sufficient to infer a likely causal relationship between short-term NO<sub>2</sub>

exposure and adverse effects on the respiratory system” based on the large body of epidemiologic evidence demonstrating positive associations with respiratory symptoms and hospitalization or emergency department (ED) visits as well as supporting evidence from controlled human exposure and animal studies (U.S. EPA, 2008a, p. 5–6). Evidence for cardiovascular effects and mortality attributable to short-term NO<sub>2</sub> exposures was weaker and was judged “inadequate to infer the presence or absence of a causal relationship” and “suggestive of, but not sufficient to infer, a causal relationship,” respectively. The 2008 ISA noted an overarching uncertainty in determining the extent to which NO<sub>2</sub> is independently associated with effects or if NO<sub>2</sub> is a marker for the effects of another traffic-related pollutant or mix of pollutants (U.S. EPA, 2008a, Section 5.3.2.2 to 5.3.2.6).

For the current review, there is newly available evidence for both respiratory effects and other health effects critically evaluated in the ISA as part of the full body of evidence informing the nature of the relationship between health effects and short-term exposures to NO<sub>2</sub> (U.S. EPA, 2016a).<sup>39</sup> In considering the available evidence and the causal determinations presented in the ISA, consistent with the PA (U.S. EPA, 2017a), this proposal focuses on respiratory effects (II.C.1.a.i), cardiovascular effects (II.C.1.a.ii), and mortality (II.C.1.a.iii).

##### i. Respiratory Effects

The ISA concludes that evidence supports a causal relationship between respiratory effects and short-term NO<sub>2</sub> exposures, primarily based on evidence for asthma exacerbation. In reaching this conclusion, the ISA notes that “epidemiologic, controlled human exposure, and animal toxicological evidence together can be linked in a coherent and biologically plausible pathway to explain how NO<sub>2</sub> exposure can trigger an asthma exacerbation” (U.S. EPA, 2016a, p. 1–17). In the last review, the 2008 ISA described much of the same evidence and determined it was “sufficient to infer a likely causal relationship” with respiratory effects, citing uncertainty as to whether the epidemiologic results for NO<sub>2</sub> could be disentangled from effects related to other traffic-related pollutants. In contrast to the current review, the 2008 ISA evaluated evidence for the broad

category of respiratory effects and did not explicitly evaluate the extent to which various lines of evidence supported effects on more specific endpoints such as asthma exacerbation (*i.e.*, asthma attacks). In the current review, the ISA states that “the determination of a causal relationship is not based on new evidence as much as it is on the integrated findings for asthma attacks with due weight given to experimental studies” (U.S. EPA, 2016a, p. 1xxxiii).<sup>40</sup>

Strong evidence supporting this causal determination in the ISA comes from a meta-analysis of controlled human exposure studies that evaluate the potential for increased AR<sup>41</sup> following 20-minute to 1-hour NO<sub>2</sub> exposures (Brown, 2015).<sup>42</sup> While individual controlled human exposure studies can lack statistical power to identify effects, the meta-analysis of individual-level data combined from multiple studies has greater statistical power due to increased sample size.<sup>43</sup> AR has been the key respiratory outcome from controlled human exposures in the previous and current reviews of the primary NO<sub>2</sub> NAAQS, and the ISA specifically notes that “airway hyperresponsiveness can lead to poorer control of symptoms and is a hallmark of asthma” (U.S. EPA, 2016a, p. 1–18). Brown (2015) examined the relationship between AR and NO<sub>2</sub> exposures in subjects with asthma across the large body of controlled human exposure studies,<sup>44</sup> most of which were available in the last review (U.S. EPA, 2017a, Tables 3–2 and 3–3). More specifically, the meta-analysis

<sup>40</sup> Experimental studies, such as controlled human exposure studies, provide support for effects of exposures to NO<sub>2</sub> itself, and generally do not reflect the complex atmospheres to which people are exposed. Thus, unlike epidemiologic studies, experimental studies that evaluate exposures to NO<sub>2</sub> itself are not subject to uncertainties related to the potential for copollutant confounding.

<sup>41</sup> The ISA states that airway responsiveness is “inherent responsiveness of the airways to challenge by bronchoconstricting agents” (U.S. EPA, 2016a, p. 5–9). More specifically, airway hyperresponsiveness refers to increased sensitivity of the airways to an inhaled bronchoconstricting agent. This is often quantified as the dose of challenge agent that results in a 20% reduction in forced expiratory volume for 1 second (FEV<sub>1</sub>), but some studies report the change in FEV<sub>1</sub> for a specified dose of challenge agent. The change in specific airways resistance (sRaw) is also used to quantify AR.

<sup>42</sup> These studies evaluate the effect of inhaled NO<sub>2</sub> on the inherent responsiveness of the airways to challenge by bronchoconstricting agents.

<sup>43</sup> A meta-analysis synthesizes data from multiple studies using statistical analyses.

<sup>44</sup> These controlled human exposure studies were conducted in people with asthma, a group at increased risk for NO<sub>2</sub>-related effects. The severity of asthma varied across studies, ranging from inactive asthma up to severe asthma. (Brown, 2015).

<sup>38</sup> When considering the NO<sub>2</sub> concentrations at which health effects have been demonstrated to occur, the EPA places the greatest emphasis on evidence supporting health endpoints that the ISA has determined to have a “causal” or “likely to be a causal” relationship with NO<sub>2</sub> exposure.

<sup>39</sup> A list of the causal determinations from the ISA for the current review, and those from the previous review, for respiratory effects, cardiovascular effects, and mortality is presented in Table 3–1 of the NO<sub>2</sub> PA (U.S. EPA, 2017a).

identified the fraction of individuals having an increase in AR following NO<sub>2</sub> exposure, compared to the fraction having a decrease, across studies.<sup>45</sup> The meta-analysis also stratified the data to consider the influence of factors that may affect results including exercise versus rest and non-specific versus specific challenge agents.<sup>46</sup>

The results from the meta-analysis demonstrate that the majority of study volunteers with asthma experienced increased AR following resting exposure to NO<sub>2</sub> concentrations ranging from 100 to 530 ppb, relative to filtered air. Limitations in this evidence result from the lack of an apparent dose-response relationship, uncertainty in the potential adversity of responses, and the general focus of available studies on people with mild asthma, rather than more severe cases of the disease. These controlled human exposure studies, the meta-analysis, and uncertainties in this body of evidence are discussed in greater detail below (II.C.1.b.i).

The ISA further characterizes the clinical relevance of these increases in AR, using an approach that is based on guidelines from the American Thoracic Society (ATS) and the European Respiratory Society (ERS) for the assessment of therapeutic agents (Reddel et al., 2009). Specifically, based on individual-level responses reported in a subset of studies, the ISA considered a halving of the provocative dose (PD) to indicate responses that may be clinically relevant.<sup>47</sup> <sup>48</sup> With regard to this approach, the ISA notes that “in a

joint statement of the [ATS] and [ERS], one doubling dose change in PD is recognized as a potential indicator, although not a validated estimate, of clinically relevant changes in AR (Reddel et al., 2009)” (U.S. EPA, 2016a, p. 5–12).

Based on a subset of the controlled human exposure studies considered in the ISA, Brown (2015) shows that NO<sub>2</sub> exposures from 100 to 530 ppb resulted in a halving of the dose of a challenge agent required to increase AR (*i.e.*, a halving of the PD) for about a quarter of study volunteers. While these results support the potential for clinically relevant increases in AR in some individuals with asthma following NO<sub>2</sub> exposures within the range of 100 to 530 ppb, uncertainty remains given that this analysis is limited to a small subset of the studies included in the broader Brown et al. (2015) meta-analysis and given the lack of an apparent dose-response relationship.<sup>49</sup> In addition, compared to conclusions based on the entire range of NO<sub>2</sub> exposure concentrations evaluated (*i.e.*, 100 to 530 ppb), there is greater uncertainty in reaching conclusions about the potential for clinically relevant effects at any particular NO<sub>2</sub> exposure concentration within this range.

Controlled human exposure studies discussed in the ISA also evaluated a range of other respiratory effects, including lung function decrements, respiratory symptoms, and pulmonary inflammation. The evidence does not consistently demonstrate these effects following exposures to NO<sub>2</sub> concentrations at or near those found in the ambient air in the U.S. However, a subset of studies using NO<sub>2</sub> exposures to 260 ppb for 15–30 min or 400 ppb for up to 6 hours provide evidence that study volunteers with asthma and allergy can experience increased inflammatory responses following allergen challenge. Evidence for pulmonary inflammation was more mixed across studies that did not use an allergen challenge following NO<sub>2</sub> exposures ranging from 300–1,000 ppb (U.S. EPA, 2016a, Section 5.2.2.5).

In addition to this evidence for NO<sub>2</sub>-induced increases in AR and allergic inflammation in controlled human exposure studies, the ISA also describes consistent evidence from epidemiologic studies for positive associations between short-term NO<sub>2</sub> exposures and an array of respiratory outcomes related to asthma. Thus, coherence and biological plausibility is demonstrated

in the evidence integrated between controlled human exposure studies and the various asthma-related outcomes examined in epidemiologic studies. The ISA indicates that epidemiologic studies consistently demonstrate NO<sub>2</sub>-health effect associations with asthma hospital admissions and ED visits among subjects of all ages and children, and with asthma symptoms in children (U.S. EPA, 2016a, Sections 5.2.2.4 and 5.2.2.3). The robustness of the evidence is demonstrated by associations found in studies conducted in diverse locations in the U.S., Canada, and Asia, including several multicity studies. The evidence for asthma exacerbation is substantiated by several recent studies with strong exposure assessment characterized by measuring NO<sub>2</sub> concentrations in subjects' location(s). Epidemiologic studies also demonstrated associations between short-term NO<sub>2</sub> exposures and respiratory symptoms, lung function decrements, and pulmonary inflammation, particularly for measures of personal total and ambient NO<sub>2</sub> exposures and NO<sub>2</sub> measured outside schools. This is important because there is considerable spatial variability in NO<sub>2</sub> concentrations, and measurements in subjects' locations may better represent variability in ambient NO<sub>2</sub> exposures, compared to measurements at central site monitors (U.S. EPA, 2016a, Sections 2.5.3 and 3.4.4). Epidemiologic studies also consistently indicate ambient or personal NO<sub>2</sub>-associated increases in exhaled nitric oxide (eNO, a marker of airway inflammation), which is coherent with experimental findings for allergic inflammation (U.S. EPA, 2016a, Section 5.2.2.6).

In assessing the evidence from epidemiologic studies, the ISA not only considers the consistency of effects across studies, but also evaluates other study attributes that affect study quality, including potential confounding and exposure assignment. Regarding potential confounding, the ISA notes that NO<sub>2</sub> associations with asthma-related effects persist with adjustment for temperature; humidity; season; long-term time trends; and PM<sub>10</sub>, SO<sub>2</sub>, or O<sub>3</sub>. Recent studies also add findings for NO<sub>2</sub> associations that generally persist with adjustment for a key copollutant, including PM<sub>2.5</sub> and traffic-related copollutants such as elemental carbon (EC) or black carbon (BC), ultra-fine particles (UFPs), or carbon monoxide (CO) (U.S. EPA, 2016a, Figures 5–16 and 5–17, Table 5–38). Confounding by organic carbon (OC), PM metal species, or volatile organic compounds (VOCs) is poorly studied, but NO<sub>2</sub> associations

<sup>45</sup> More information on the distribution of study subjects across NO<sub>2</sub> concentrations can be found below (II.C.1.b.i). Information on the fraction of individuals who experienced an increase versus a decrease stratified by concentration can also be found in this section.

<sup>46</sup> “Bronchial challenge agents can be classified as nonspecific (*e.g.*, histamine; SO<sub>2</sub>; cold air) or specific (*i.e.*, an allergen). Nonspecific agents can be differentiated between ‘direct’ stimuli (*e.g.*, histamine, carbachol, and methacholine) which act on airway smooth muscle receptors and ‘indirect’ stimuli (*e.g.*, exercise, cold air) which act on smooth muscle through intermediate pathways, especially via inflammatory mediators. Specific allergen challenges (*e.g.*, house dust mite, cat allergen) also act ‘indirectly’ via inflammatory mediators to initiate smooth muscle contraction and bronchoconstriction” (U.S. EPA, 2016a, p. 5–8).

<sup>47</sup> PD is the dose of challenge agent required to elicit a specified change in a measure of lung function, typically a 20% decrease in FEV<sub>1</sub> or a 100% increase in specific airway resistance (sRaw).

<sup>48</sup> The ISA's characterization of a clinically relevant response is based on evidence from controlled human exposure studies evaluating the efficacy of inhaled corticosteroids that are used to prevent bronchoconstriction and airway responsiveness as described by Reddel et al. (2009). Generally, a change of at least one doubling dose is considered to be an indication of clinical relevance. Based on this, a halving of the PD is taken in the ISA to represent an increase in AR that indicates a clinically relevant response.

<sup>49</sup> Section 3.2.2.1 of the PA (U.S. EPA, 2017a) includes additional discussion of these uncertainties.

with asthma exacerbation tend to persist in the few available copollutant models. The ISA recognizes, however, that copollutant models have inherent limitations and cannot conclusively rule out confounding (U.S. EPA, 2015, Preamble, Section 4.b).

The ISA also notes that results based on personal exposures or pollutants measured at people's locations provide support for NO<sub>2</sub> associations that are independent of PM<sub>2.5</sub>, EC/BC, organic carbon (OC), or UFPs. Compared to ambient NO<sub>2</sub> concentrations measured at central-site monitors, personal NO<sub>2</sub> exposure concentrations and indoor NO<sub>2</sub> concentrations exhibit lower correlations with many traffic-related copollutants (e.g.,  $r = -0.37$  to  $0.31$ ). Thus, these health effect associations with personal and indoor NO<sub>2</sub> may be less prone to confounding by these traffic-related copollutants (U.S. EPA, 2016a, Section 1.4.3).

Overall, the strongest evidence supporting the conclusion of the causal relationship determined in the ISA comes from controlled human exposure studies demonstrating NO<sub>2</sub>-induced increases in AR in individuals with asthma, with supporting evidence for a range of respiratory effects from epidemiologic studies. The conclusion of a causal relationship in the ISA is based on this evidence, and its explicit integration within the context of effects related to asthma exacerbation. Most of the controlled human exposure studies assessed in the ISA were available in the last review, particularly studies of non-specific AR, and thus, do not themselves provide substantively new information. However, by pooling data from a subset of studies, the newly available meta-analysis (Brown, 2015) has partially addressed an uncertainty from the last review by demonstrating the potential for clinically relevant increases in AR following exposures to NO<sub>2</sub> concentrations in the range of 100 to 530 ppb. Similarly, the epidemiologic evidence that is newly available in the current review is consistent with evidence from the last review and does not alter the understanding of respiratory effects related to ambient NO<sub>2</sub> exposures. New epidemiologic evidence does, however, reduce some uncertainty from the last review regarding the extent to which effects may be independently related to NO<sub>2</sub> as there is more evidence from studies using measures that may better capture personal exposure as well as a more robust evidence base examining copollutant confounding. Some uncertainty remains in the epidemiologic evidence regarding confounding by the most relevant

copollutants as it can be difficult to disentangle the independent effects of highly correlated pollutants (i.e., NO<sub>2</sub> and traffic-related pollutants).

#### ii. Cardiovascular Effects

The evidence for cardiovascular health effects and short-term NO<sub>2</sub> exposures in the 2016 ISA was judged "suggestive of, but not sufficient to infer, a causal relationship" (U.S. EPA, 2016a, Section 5.3.11), which is stronger than the conclusion in the last review that the evidence was "inadequate to infer the presence or absence of a causal relationship." The more recent causal determination was primarily supported by consistent epidemiologic evidence from multiple new studies indicating associations for triggering of a myocardial infarction. However, further evaluation and integration of evidence points to uncertainty related to exposure measurement error and potential confounding by traffic-related pollutants. There is consistent evidence demonstrating NO<sub>2</sub>-associated hospital admissions and ED visits for ischemic heart disease, myocardial infarction, and angina as well as all cardiovascular diseases combined, which is coherent with evidence from other studies indicating NO<sub>2</sub>-associated repolarization abnormalities and cardiovascular mortality. There are experimental studies that provide some evidence for effects on key events in the proposed mode of action (e.g., systemic inflammation), but these studies do not provide evidence that is sufficiently coherent with the epidemiologic studies to help rule out chance, confounding, and other biases. In particular, the ISA concludes that "[t]here continues to be a lack of experimental evidence that is coherent with the epidemiologic studies to strengthen the inference of causality for NO<sub>2</sub>-related cardiovascular effects, including [myocardial infarction]" (U.S. EPA, 2016a, p. 5–335). Beyond evidence for myocardial infarction, there were studies examining other cardiovascular health effects, but results across these outcomes are inconsistent. Thus, while the evidence is stronger in the current review than in the last review, important uncertainties remain regarding the independent effects of NO<sub>2</sub>.

#### iii. Mortality

The ISA concludes that the evidence for short-term NO<sub>2</sub> exposures and total mortality is "suggestive of, but not sufficient to infer, a causal relationship" (U.S. EPA, 2016a, Section 5.4.8), which is the same conclusion reached in the last review (U.S. EPA, 2008a). Several recent multicity studies add to the

evidence base for the current review and demonstrate associations that are robust in copollutant models with PM<sub>10</sub>, O<sub>3</sub>, or SO<sub>2</sub>. However, confounding by traffic-related copollutants, which is of greatest concern, is not examined in the available copollutant models for NO<sub>2</sub>-associated mortality. Overall, the recent evidence assessed in the ISA builds upon and supports conclusions in the last review, but key limitations across the evidence include a lack of biological plausibility as experimental studies and epidemiologic studies on cardiovascular morbidity, a major cause of mortality, do not clearly provide a mechanism by which NO<sub>2</sub>-related effects could lead to mortality. In addition, important uncertainties remain regarding the independent effect of NO<sub>2</sub> (i.e., independent of other traffic-related pollutants).

#### b. Short-Term NO<sub>2</sub> Concentrations in Health Studies

In evaluating what the available health evidence indicates with regard to the degree of public health protection provided by the current standards, it is appropriate to consider the short-term NO<sub>2</sub> concentrations that have been associated with various effects. The PA explicitly considers these NO<sub>2</sub> concentrations within the context of evaluating the public health protection provided by the current standards (U.S. EPA, 2017a, Section 3.2). This section summarizes those considerations from the PA.

In evaluating the NO<sub>2</sub> exposure concentrations associated with health effects within the context of considering the adequacy of the current standards, the PA focuses on the evidence for asthma-related effects (i.e., the strongest evidence supporting a causal relationship, as discussed above). The PA specifically considers to what extent the evidence indicates adverse asthma-related effects attributable to short-term exposures to NO<sub>2</sub> concentrations lower than previously identified or below the existing standards (U.S. EPA, 2017a p. 3–11). In addressing this issue, the PA considers the extent to which NO<sub>2</sub>-induced adverse effects have been reported over the ranges of NO<sub>2</sub> exposure concentrations evaluated in controlled human exposure studies and the extent to which NO<sub>2</sub>-associated effects have been reported for distributions of ambient NO<sub>2</sub> concentrations in epidemiologic study locations meeting existing standards. These considerations are discussed below for controlled human exposure studies (II.C.1.b.i) and epidemiologic studies (II.C.1.b.ii).

#### i. NO<sub>2</sub> Concentrations in Controlled Human Exposure Studies

Controlled human exposure studies, most of which were available and considered in the last review, have evaluated various respiratory effects following short-term NO<sub>2</sub> exposures. These include AR, inflammation and oxidative stress, respiratory symptoms, and lung function decrements. Generally, when considering respiratory effects from controlled human exposure studies in healthy adults without asthma, evidence does not indicate respiratory symptoms or lung function decrements following NO<sub>2</sub> exposures below 4,000 ppb and limited evidence indicates airway inflammation following exposures below 1,500 ppb (U.S. EPA, 2016a, Section 5.2.7).<sup>50</sup> There is a substantial body of evidence demonstrating increased AR in healthy adults with exposures in the range of 1,500–3,000 ppb.

Evidence for respiratory effects following exposures to NO<sub>2</sub> concentrations at or near those found in the ambient air is strongest for AR in individuals with asthma (U.S. EPA, 2016a, Section 5.2.2 p. 5–7). As discussed above, increased AR has been reported in people with asthma following exposures to NO<sub>2</sub> concentrations as low as 100 ppb. In contrast, controlled human exposure studies evaluated in the ISA do not provide consistent evidence for respiratory symptoms, lung function decrements, or pulmonary inflammation in adults with asthma following exposures to NO<sub>2</sub> concentrations at or near those in ambient air (*i.e.*, <1,000 ppb; U.S. EPA, 2016a, Section 5.2.2). There is some indication of allergic inflammation in adults with allergy and asthma following exposures to 260–1,000 ppb. However, the generally high exposure concentrations make it difficult to interpret the likelihood that these effects could potentially occur following NO<sub>2</sub> exposures at or below the level of the current standard.

Thus, in considering the exposure concentrations evaluated in controlled human exposure studies, the PA focuses on the body of evidence for NO<sub>2</sub>-induced increases AR in adults with asthma. In evaluating the NO<sub>2</sub> exposure concentrations at which increased AR is observed, the PA considers both the group mean results reported in individual studies and the results evaluated across studies in the meta-analysis by Brown (2015; U.S. EPA,

2016a, Section 5.2.2.1). Group mean responses in individual studies, and the variability in those responses, can provide insight into the extent to which observed changes in AR are due to NO<sub>2</sub> exposures, rather than to chance alone, and have the advantage of being based on the same exposure conditions. The meta-analysis by Brown (2015) aids in identifying trends in individual-level responses across studies and has the advantage of increased power to detect effects, even in the absence of statistically significant effects in individual studies.<sup>51</sup>

#### Consideration of Group Mean Results From Individual Studies

In first considering controlled human exposure studies conducted at rest, the PA notes that the lowest NO<sub>2</sub> concentration to which individuals with asthma have been exposed is 100 ppb, with an exposure duration of 60 minutes in all studies. Of the five studies conducted at 100 ppb, a statistically significant increase in AR following exposure to NO<sub>2</sub> was only observed in the study by Orehek et al. (1976) (N=20). Of the four studies that did not report statistically significant increases in AR following exposures to 100 ppb NO<sub>2</sub>, three reported weak trends towards decreased AR (n = 20, Ahmed et al., 1983b; n=15, Hazucha et al., 1983; n=8, Tunnicliffe et al., 1994), and one reported a trend towards increased AR (n=20, Ahmed et al., 1983a). Resting exposures to 140 ppb NO<sub>2</sub> resulted in increases in AR that reached marginal statistical significance (n=20; Bylin et al., 1988). In addition, the one study conducted at 200 ppb demonstrated a trend towards increased AR, but this study was small and results were not statistically significant (n=4; Orehek et al., 1976). Thus, individual controlled human exposure studies have generally not reported statistically significant increases in AR following resting exposures to NO<sub>2</sub> concentrations from 100 to 200 ppb. Group mean responses in these studies suggest a trend towards increased AR following exposures to 140 and 200 ppb NO<sub>2</sub>, while trends in the direction of group

mean responses were inconsistent following exposures to 100 ppb NO<sub>2</sub>.

In next considering studies in individuals with asthma conducted with exercise, the PA notes that three studies evaluated NO<sub>2</sub> exposure concentrations between 150 and 200 ppb (n=19, Roger et al., 1990; n=31, Kleinman et al., 1983; n=11, Jenkins et al., 1999). Of these studies, only Kleinman et al. (1983) reported a statistically significant increase in AR following NO<sub>2</sub> exposure (*i.e.*, at 200 ppb). Roger et al. (1990) and Jenkins et al. (1999) did not report statistically significant increases, but showed weak trends for increases in AR following exposures to 150 ppb and 200 ppb NO<sub>2</sub>, respectively. Thus, as with studies of resting exposures, studies that evaluated exposures to 150 to 200 ppb NO<sub>2</sub> with exercise report trends toward increased AR, though results are generally not statistically significant.

Several studies evaluated exposures of individuals with asthma to NO<sub>2</sub> concentrations above 200 ppb. Of the five studies that evaluated 30-minute resting exposures to NO<sub>2</sub> concentrations from 250 to 270 ppb, NO<sub>2</sub>-induced increases in AR were statistically significant in three (n=14, Jörres et al., 1990; n=18, Strand et al., 1988; n=20, Bylin et al., 1988). Statistically significant increases in AR are also more consistently reported across studies that evaluated resting exposures to 400–530 ppb NO<sub>2</sub>, with three of four studies reporting a statistically significant increase in AR following such exposures. However, studies conducted with exercise do not indicate consistent increases in AR following exposures to NO<sub>2</sub> concentrations from 300 to 600 ppb (U.S. EPA, 2017a, Table 3–3).<sup>52</sup>

#### Consideration of Results From the Meta-Analysis

As discussed above, the ISA assessment of the evidence for AR in individuals with asthma also focuses on a recently published meta-analysis (Brown, 2015) investigating individual-level data from controlled human exposure studies. While individual controlled human exposure studies can lack statistical power to identify effects, the meta-analysis of individual-level data combined from multiple studies (Brown, 2015) has greater statistical

<sup>51</sup> Tables 3–2 and 3–3 in the NO<sub>2</sub> PA (adapted from the ISA; U.S. EPA, 2016a, Tables 5–1 and 5–2) provide details for the studies examining AR in individuals with asthma at rest and with exercise, respectively. These tables note various study details including the exposure concentration, duration of exposure, type of challenge (nonspecific or specific), number of study subjects, number of subjects having an increase or decrease in AR following NO<sub>2</sub> exposure, average provocative dose (PD; dose of challenge agent required to elicit a particular magnitude of change in FEV<sub>1</sub> or other measure of lung function) across subjects, and the statistical significance of the change in AR following NO<sub>2</sub> exposures.

<sup>52</sup> There are eight additional studies with exercising exposures to 300–350 ppb NO<sub>2</sub> as presented in Table 3-3 of the NO<sub>2</sub> PA, with exposure durations ranging from 30–240 minutes. Results across these studies are inconsistent, with only two of eight reporting significant results. Only one of four studies with exercising exposures of 400 or 600 ppb reported statistically significant increases in airway responsiveness.

<sup>50</sup> Exposure durations were from one to three hours in studies evaluating AR and respiratory symptoms, and up to five hours in studies evaluating lung function decrements.

power due to increased sample size. The meta-analysis considered individual-level responses, specifically whether individual study subjects experienced an increase or decrease in AR following NO<sub>2</sub> exposure compared to air exposure.<sup>53</sup> Evidence was evaluated together across all studies and also stratified for exposures conducted with exercise and at rest, and for measures of specific and non-specific AR. The ISA notes that these methodological differences may have important implications with regard to results (U.S. EPA, 2016a (discussing Brown, 2015; Goodman et al., 2009)), contributing to the ISA's emphasis on studies of resting exposures and non-specific challenge agents. Overall, the meta-analysis presents the fraction of individuals having an increase in AR following exposure to various NO<sub>2</sub> concentrations (*i.e.*, 100 ppb, 100 ppb to <200 ppb, 200 ppb up to and including 300 ppb, and above 300 ppb) (U.S. EPA, 2016a, Section 5.2.2.1).<sup>54 55</sup>

When evaluating results from the meta-analysis, first the PA considers results across all exposure conditions (*i.e.*, resting, exercising, non-specific challenge, and specific challenge). For 100 ppb NO<sub>2</sub> exposures, Brown (2015) reported that, of the study participants who experienced either an increase or decrease in AR following NO<sub>2</sub> exposures, 61% experienced an increase ( $p=0.08$ ). For 100 to <200 ppb NO<sub>2</sub> exposures, 62% of study subjects experienced an increase in AR following NO<sub>2</sub> exposures ( $p=0.014$ ). For 200 to 300 ppb NO<sub>2</sub> exposures, 58% of study subjects experienced an increase in AR following NO<sub>2</sub> exposures ( $p=0.008$ ). For exposures above 300 ppb NO<sub>2</sub>, 57% of study subjects experienced an increase in AR following NO<sub>2</sub> exposures, though this fraction was not statistically different than the fraction experiencing a decrease.

The PA also considers the results of Brown (2015) for various subsets of the available studies, based on the exposure conditions evaluated (*i.e.*, resting, exercising) and the type of challenge agent used (specific, non-specific). For exposures conducted at rest, across all exposure concentrations (*i.e.*, 100–530

ppb NO<sub>2</sub>,  $n=139$ ; U.S. EPA, 2017a, Table 3–2), Brown (2015) reported that a statistically significant fraction of study participants (71%,  $p<0.001$ ) experienced an increase in AR following NO<sub>2</sub> exposures, compared to the fraction that experienced a decrease in AR. The meta-analysis also presented results for various concentrations or ranges of concentrations. Following resting exposure to 100 ppb NO<sub>2</sub>, 66% of study participants experienced increased non-specific AR. For exposures to concentrations of 100 ppb to <200 ppb, 200 ppb up to and including 300 ppb, and above 300 ppb, increased non-specific AR was reported in 67%, 78%, and 73% of study participants, respectively.<sup>56</sup> For non-specific challenge agents, the differences between the fractions of individuals who experienced increased AR following resting NO<sub>2</sub> exposures and the fraction who experienced decreased AR reached statistical significance for all of the ranges of exposures concentrations evaluated ( $p<0.05$ ).

In contrast to the results from studies conducted at rest, the fraction of individuals having an increase in AR following NO<sub>2</sub> exposures with exercise was not consistently greater than 50%, and none of the results were statistically significant (Brown, 2015). Across all NO<sub>2</sub> exposures with exercise, measures of non-specific AR were available for 241 individuals, 54% of whom experienced an increase in AR following NO<sub>2</sub> exposures relative to air controls. There were no studies in this group conducted at 100 ppb, and for exercising exposures to 150–200 ppb, 250–300 ppb, and 350–600 ppb, the fraction of individuals with increased AR was 59%, 55%, and 49%, respectively.

In addition to examining results from studies of non-specific AR, the meta-analysis also considered results from studies that evaluated changes in specific AR (*i.e.*, AR following an allergen challenge;  $n=130$ ; U.S. EPA, 2017a, Table 3–3) following NO<sub>2</sub> exposures. The results do not indicate statistically significant fractions of individuals having an increase in specific AR following exposure to NO<sub>2</sub> at concentrations below 400 ppb, even when considering resting and exercising exposures separately (Brown, 2015). Of the three studies that evaluated specific AR at concentrations of 400 ppb, one was conducted at rest (Tunnicliffe et al., 1994). This study reported that all

individuals experienced increased AR following 400 ppb NO<sub>2</sub> exposures (Brown, 2015, Table 4). In contrast, for exposures during exercise, most study subjects did not experience NO<sub>2</sub>-induced increases in specific AR.<sup>57</sup> Overall, results across studies are less consistent for increases in specific AR following NO<sub>2</sub> exposures.

#### Uncertainties in Evidence for AR

When considering the evidence for NO<sub>2</sub>-induced increases in AR in individuals with asthma, there are important uncertainties that should be considered. One uncertainty is that available studies of NO<sub>2</sub> and AR have generally evaluated adults with mild asthma, while people with more severe cases could experience more serious effects and/or effects following exposures to lower NO<sub>2</sub> concentrations.<sup>58</sup> Additional uncertainties include the lack of an apparent dose-response relationship and uncertainty in the potential adversity of the reported effects. Each of these is discussed below.

Both the meta-analysis by Brown (2015) and an additional meta-analysis and meta-regression by Goodman et al. (2009) conclude that there is no indication of a dose-response relationship for exposures between 100 and 500 ppb NO<sub>2</sub> and increased AR in individuals with asthma. A dose-response relationship generally increases confidence that observed effects are due to pollutant exposures rather than to chance; however, the lack of a dose-response relationship does not necessarily indicate that there is no relationship between the exposure and effect, particularly in these analyses based on between-subject comparisons (*i.e.*, as opposed to comparisons within the same subject exposed to multiple concentrations). As discussed in the ISA, there are a number of methodological differences across studies that could contribute to between-subject differences and that could obscure a dose-response relationship between NO<sub>2</sub> and AR. These include subject activity level (rest versus exercise) during NO<sub>2</sub> exposure, asthma medication usage, choice of airway challenge agent, method of administering the bronchoconstricting agents, and physiological endpoint used to assess AR. Such methodological

<sup>53</sup> The meta-analysis combined information from the studies presented in Tables 3–2 and 3–3 of the PA.

<sup>54</sup> Brown et al. (2015) compared the number of study participants who experienced an increase in AR following NO<sub>2</sub> exposures to the number who experienced a decrease in AR. Study participants who experienced no change in AR were not included in comparisons. *P*-value refers to the significance level of a two-tailed sign test.

<sup>55</sup> The number of participants in each study and the number having an increase or decrease in AR is indicated in Tables 3–2 and 3–3 of the NO<sub>2</sub> PA.

<sup>56</sup> For the exposure category of “above 300 ppb”, exposures included 400, 480, 500, and 530 ppb. No studies conducted at rest used concentrations between 300 and 400 ppb.

<sup>57</sup> Forty-eight percent experienced increased AR and 52% experienced decreased AR, based on individual-level data for study participants exposed to 350 ppb (Riedl et al., 2012) or 400 ppb (Jenkins et al., 1999; Witten et al., 2005) NO<sub>2</sub>.

<sup>58</sup> Brown (2015) notes, however, that disease status varied, ranging from “inactive asthma up to severe asthma in a few studies.”



differences across studies likely contribute to the variability and uncertainty in results across studies and complicate interpretation of the overall body of evidence for NO<sub>2</sub>-induced AR. Thus, while the lack of an apparent dose-response relationship adds uncertainty to the interpretation of controlled human exposure studies of AR, it does not necessarily indicate the lack of an NO<sub>2</sub> effect.

An additional uncertainty in interpreting these studies within the context of considering the adequacy of the protection provided by the NO<sub>2</sub> NAAQS is the potential adversity of the reported NO<sub>2</sub>-induced increases in AR. As discussed above, the meta-analysis by Brown (2015) used an approach that is consistent with guidelines from the ATS and the ERS for the assessment of therapeutic agents (Reddel et al., 2009) to assess the potential for clinical relevance of these responses. Specifically, based on individual-level responses reported in a subset of studies, Brown (2015) considered a halving of the PD to indicate responses that may be clinically relevant. With regard to this approach, the ISA notes that “one doubling dose change in PD is recognized as a potential indicator, although not a validated estimate, of clinically relevant changes in AR (Reddel et al., 2009)” (U.S. EPA, 2016a, p. 5–12). While there is uncertainty in using this approach to characterize whether a particular response in an individual is “adverse,” it can provide insight into the potential for adversity, particularly when applied to a population of exposed individuals.<sup>59</sup>

Five studies provided data for each individual’s provocative dose. These five studies provided individual-level data for a total of 72 study participants (116 AR measurements) and eight NO<sub>2</sub> exposure concentrations, for resting exposures and non-specific bronchial challenge agents. Across exposures to 100, 140, 200, 250, 270, 480, 500, and 530 ppb NO<sub>2</sub>, 24% of study participants experienced a halving of the provocative dose (indicating increased AR) while 8% showed a doubling of the provocative dose (indicating decreased AR). The relative distributions of the provocative doses at different concentrations were similar, with no dose-response relationship indicated (Brown, 2015). While these results support the potential for clinically relevant increases in AR in some individuals with asthma following NO<sub>2</sub>

exposures within the range of 100 to 530 ppb, uncertainty remains given that this analysis is limited to a small subset of studies and given the lack of an apparent dose-response relationship. In addition, compared to conclusions based on the entire range of NO<sub>2</sub> exposure concentrations evaluated (*i.e.*, 100 to 530 ppb), there is greater uncertainty in reaching conclusions about the potential for clinically relevant effects at any particular NO<sub>2</sub> exposure concentration within this range.

#### PA Conclusions on Short-Term NO<sub>2</sub> Concentrations in Controlled Human Exposure Studies

As in the last review, a meta-analysis of individual-level data supports the potential for increased AR in individuals with generally mild asthma following 30 minute to 1 hour exposures to NO<sub>2</sub> concentrations from 100 to 530 ppb, particularly for resting exposures and measures of non-specific AR (N = 33 to 70 for various ranges of NO<sub>2</sub> exposure concentrations). In about a quarter of these individuals, increases were large enough to be of potential clinical relevance. Individual studies most consistently report statistically significant NO<sub>2</sub>-induced increases in AR following exposures to NO<sub>2</sub> concentrations at or above 250 ppb. Individual studies (N = 4 to 20) generally do not report statistically significant increases in AR following exposures to NO<sub>2</sub> concentrations at or below 200 ppb, though the evidence suggests a trend toward increased AR following NO<sub>2</sub> exposures from 140 to 200 ppb. In contrast, individual studies do not indicate a consistent trend towards increased AR following 1-hour exposures to 100 ppb NO<sub>2</sub>. Important limitations in this evidence include the lack of a dose-response relationship between NO<sub>2</sub> and AR and uncertainty in the adversity of the reported increases in AR. These limitations become increasingly important at the lower NO<sub>2</sub> exposure concentrations (*i.e.*, at or near 100 ppb), where the evidence for NO<sub>2</sub>-induced increases in AR is not consistent across studies.

#### ii. Consideration of NO<sub>2</sub> Concentrations in Locations of Epidemiologic Studies

In addition to considering the exposure concentrations evaluated in the controlled human exposure studies, the PA also considers distributions of ambient NO<sub>2</sub> concentrations in locations where epidemiologic studies have examined NO<sub>2</sub> associations with asthma-related hospital admissions or ED visits. These outcomes are clearly adverse and study results comprise a

key line of epidemiologic evidence in the determination of a causal relationship in the ISA (U.S. EPA, 2016a, Section 5.2.9). As in other NAAQS reviews (U.S. EPA, 2014; U.S. EPA, 2011), when considering epidemiologic studies within the context of evaluating the adequacy of the current standard, the PA emphasizes those studies conducted in the U.S. and Canada.<sup>60</sup> For short-term exposures to NO<sub>2</sub>, the PA emphasizes studies reporting associations with effects judged in the ISA to be robust to confounding by other factors, including exposure to co-occurring air pollutants. In addition, the PA considers the statistical precision of study results, and the inclusion of at-risk populations for which the NO<sub>2</sub>-health effect associations may be larger. These considerations help inform the range of ambient NO<sub>2</sub> concentrations over which the evidence indicates the most confidence in NO<sub>2</sub>-associated health effects and the range of concentrations over which confidence in such effects is appreciably lower. In consideration of these issues, the PA specifically focuses on the following question: To what extent have U.S. and Canadian epidemiologic studies reported associations between asthma-related hospital admissions or ED visits and short-term NO<sub>2</sub> concentrations in study areas that would have met the current 1-hour NO<sub>2</sub> standard during the study period?

Addressing this question can provide important insights into the extent to which NO<sub>2</sub>-associated health effect associations are present for distributions of ambient NO<sub>2</sub> concentrations that would be allowed by the current primary standards. The presence of such associations would support the potential for the current standards to allow the NO<sub>2</sub>-associated effects indicated by epidemiologic studies. To the degree studies have not reported associations in locations meeting the current NO<sub>2</sub> standards, there is greater uncertainty regarding the potential for the reported effects to occur following the NO<sub>2</sub> exposures associated with air quality meeting those standards.

In addressing the question above, the PA places the greatest emphasis on studies reporting positive, and relatively precise (*i.e.*, relatively narrow 95% confidence intervals), health effect

<sup>59</sup> As noted above, the degree to which populations in U.S. urban areas have the potential for such NO<sub>2</sub> exposures is evaluated in Chapter 4 of the PA and described in Section II.D below.

<sup>60</sup> Such studies are likely to reflect air quality and exposure patterns that are generally applicable to the U.S. In addition, air quality data corresponding to study locations and study time periods is often readily available for studies conducted in the U.S. and Canada. Nonetheless, the PA recognizes the importance of all studies, including other international studies, in the ISA’s assessment of the weight of the evidence that informs the causal determinations.

associations. In evaluating whether such associations are likely to reflect NO<sub>2</sub> concentrations meeting the existing 1-hour standard, the PA considers the 1-hour ambient NO<sub>2</sub> concentrations measured at monitors in study locations during study periods. The PA also considers what additional information is available regarding the ambient NO<sub>2</sub> concentrations that could have been present in the study locations during the study periods (e.g., around major roads). When considered together, this information can provide important insights into the extent to which NO<sub>2</sub> health effect associations have been reported for NO<sub>2</sub> air quality concentrations that likely would have met the current 1-hour NO<sub>2</sub> standard.

The PA evaluates U.S. and Canadian studies of respiratory-related hospital admissions and ED visits, with a focus on studies of asthma-related effects (studies identified from Table 5–10 in U.S. EPA, 2016a).<sup>61</sup> For each NO<sub>2</sub> monitor in the locations included in these studies, and for the ranges of years encompassed by studies, the PA identifies the 3-year averages of the 98th percentiles of the annual distributions of daily maximum 1-hour NO<sub>2</sub> concentrations.<sup>62</sup> These concentrations approximate the DVs that are used when determining whether an area meets the primary NO<sub>2</sub> NAAQS.<sup>63</sup> Thus, these estimated DVs can provide perspective on whether study areas would likely have met or exceeded the primary 1-hour NO<sub>2</sub> NAAQS during the study periods. Based on this approach, study locations would likely have met the current 1-hour standard over the entire study period if all of the hourly DV estimates were at or below 100 ppb.

A key limitation in these analyses of NO<sub>2</sub> DV estimates is that currently

required near-road NO<sub>2</sub> monitors were not in place during study periods. The studies evaluated were based on air quality from 1980–2006, with most studies spanning the 1990s to early 2000s. There were no specific near-road monitoring network requirements during these years, and most areas did not have monitors sited to measure NO<sub>2</sub> concentrations near the most heavily-trafficked roadways. In addition, mobile source NO<sub>x</sub> emissions were considerably higher during the time periods of the available epidemiologic studies than in more recent years (U.S. EPA, 2017a, section 2.1.2), suggesting that the NO<sub>2</sub> concentration gradients around major roads could have been more pronounced than indicated by data from recently deployed near-road monitors.<sup>64</sup> This information suggests that if the current near-road monitoring network had been in operation during study periods, NO<sub>2</sub> concentrations measured at near-road monitors would likely have been higher than those identified in the PA (U.S. EPA, 2017a, Figure 3–1). This uncertainty particularly limits the degree to which strong conclusions can be reached based on study areas with DV estimates that are at or just below 100 ppb.<sup>65</sup>

With this key limitation in mind, the PA considers what the available epidemiologic evidence indicates with regard to the adequacy of the public health protection provided by the current 1-hour standard against short-term NO<sub>2</sub> exposures. To this end, the PA highlights the epidemiologic studies examining associations between asthma hospitalizations or ED visits and short-term exposures to ambient NO<sub>2</sub> that were conducted in the U.S. and Canada (U.S. EPA, 2017a, Figure 3–1). These studies were identified and evaluated in the ISA and include both the few recently published studies and the studies that were available in the previous review.

In considering the epidemiologic information presented in the U.S. and Canadian studies, the PA notes that multi-city studies tend to have greater power to detect associations. The one multi-city study that has become available since the last review (Stieb et al., 2009) reported a null association with asthma ED visits, based on study locations with maximum estimated DVs ranging from 67–242 ppb (six of seven

study cities had maximum estimated DVs at or above 85 ppb). Of the single city studies identified, those reporting positive and relatively precise associations were conducted in locations with maximum, and often mean, estimated DVs at or above 100 ppb (i.e., Linn et al., 2000; Peel et al., 2005; Ito et al., 2007; Villeneuve et al., 2007; Burnett et al., 1999; Strickland et al., 2010). Maximum estimated DVs from these study locations ranged from 100 to 242 ppb (U.S. EPA, Figure 3–1). For the other single city studies, two reported more mixed results in locations with maximum estimated DVs around 90 ppb (Jaffe et al., 2003; ATSDR, 2006).<sup>66</sup> Associations in these studies were generally not statistically significant, were less precise (i.e., wider 95% confidence intervals), and included a negative association (Manhattan, NY). One single city study was conducted in a location with 1-hour estimated DVs well-below 100 ppb (Li et al., 2011), though the reported associations were not statistically significant and were relatively imprecise. Thus, of the U.S. and Canadian studies that can most clearly inform consideration of the adequacy of the current NO<sub>2</sub> standards, the lone multicity study did not report a positive health effect association and the single-city studies reporting positive, and relatively precise, associations were generally conducted in locations with maximum 1-hour estimated DVs at or above 100 ppb (i.e., up to 242 ppb). The evidence for associations in locations with maximum estimated DVs below 100 ppb is more mixed, and reported associations are generally less precise.

An uncertainty in this body of evidence is the potential for copollutant confounding. Copollutant (two-pollutant) models can be used in epidemiologic studies in an effort to disentangle the independent pollutant effects, though there can be limitations in these models due to differential exposure measurement error and high correlations with traffic-related copollutants. For NO<sub>2</sub>, the copollutants that are most relevant to consider are those from traffic sources such as CO, EC/BC, UFP, and VOCs such as benzene as well as PM<sub>2.5</sub> and PM<sub>10</sub> (U.S. EPA, 2016a, Section 3.5). Of the studies

<sup>61</sup> Strong support was also provided by epidemiologic studies for respiratory symptoms, but the majority of studies on respiratory symptoms were only conducted over part of a year, complicating the evaluation of a DV based on data from 3 years of monitoring data relative to the respective health effect estimates. For more information on these studies and the estimated DVs in the study locations, see Appendix A of the PA (U.S. EPA, 2017a).

<sup>62</sup> All study locations had maximum annual DVs below 53 ppb (U.S. EPA, 2017a, Appendix A).

<sup>63</sup> As described in I.B.2., a DV is a statistic that describes the air quality status of a given area relative to the NAAQS and that is typically used to classify nonattainment areas, assess progress towards meeting the NAAQS, and develop control strategies. For the 1-hour NO<sub>2</sub> standard, the DV is calculated at individual monitors and based on 3 consecutive years of data collected from that site. In the case of the 1-hour NO<sub>2</sub> standard, the design value for a monitor is based on the 3-year average of the 98th percentile of the annual distribution of daily maximum 1-hour NO<sub>2</sub> concentrations. For more information on these studies and the calculation of the study area DVs estimates see Appendix A of the NO<sub>2</sub> PA (U.S. EPA, 2017a).

<sup>64</sup> Recent data indicate that, for most near-road monitors, measured 1-hour NO<sub>2</sub> concentrations are higher than those measured at all of the non-near-road monitors in the same CBSA (Section II.B.3).

<sup>65</sup> Epidemiologic studies that evaluate potential NO<sub>2</sub> health effect associations during time periods when near-road monitors are operational could reduce this uncertainty in future reviews.

<sup>66</sup> The study by the U.S. Agency for Toxic Substances and Disease Registry (ATSDR) was not published in a peer-review journal. Rather, it was a report prepared by New York State Department of Health's Center for Environmental Health, the New York State Department of Environmental Conservation and Columbia University in the course of performing work contracted for and sponsored by the New York State Energy Research and Development Authority and the ATSDR.

examining asthma-related hospital admissions and ED visits in the U.S. and Canada, three examined copollutant models (Ito et al., 2007; Villeneuve et al., 2007; Strickland et al., 2010). Ito et al. (2007) found that in copollutant models with PM<sub>2.5</sub>, SO<sub>2</sub>, CO, or O<sub>3</sub>, NO<sub>2</sub> consistently had the strongest effect estimates that were robust to the inclusion of other pollutants. Villeneuve et al. (2007) utilized a model including NO<sub>2</sub> and CO (r = 0.74) for ED visits in the warm season and reported that associations for NO<sub>2</sub> were robust to CO. Strickland et al. (2010) found that the relationship between ambient NO<sub>2</sub> and asthma ED visits in Atlanta, GA was robust in models including O<sub>3</sub>, but copollutant models were not analyzed for other pollutants and the correlations between NO<sub>2</sub> and other pollutants were not reported. Taken together, these studies provide some evidence for independent effects of NO<sub>2</sub> for asthma ED visits, but some important traffic-related copollutants (e.g. EC/BC, VOCs) have not been examined in this body of evidence and the limitations of copollutant models in demonstrating an independent association are noted (U.S. EPA, 2016a).

Considering this evidence together, the PA notes the following observations. First, the only recent multicity study evaluated, which had maximum estimated DVs ranging from 67 to 242 ppb, did not report a positive association between NO<sub>2</sub> and ED visits (Stieb et al., 2009). In addition, of the single-city studies reporting positive and relatively precise associations between NO<sub>2</sub> and asthma hospital admissions and ED visits, most locations likely had NO<sub>2</sub> concentrations above the current 1-hour NO<sub>2</sub> standard over at least part of the study period. Although maximum estimated DVs for the studies conducted in Atlanta were 100 ppb, it is likely that those DVs would have been higher than 100 ppb if currently required near-road monitors had been in place. For the study locations with maximum estimated DVs below 100 ppb, mixed results are reported with associations that are generally not statistically significant and imprecise, indicating that associations between NO<sub>2</sub> concentrations and asthma-related ED visits are more uncertain in locations that could have met the current standards. Given that near-road monitors were not in operation during study periods, it is not clear that these DVs below 100 ppb indicate study areas that would have met the current 1-hour standard.

Thus, while epidemiologic studies provide support for NO<sub>2</sub>-associated hospital admissions and ED visits at

ambient NO<sub>2</sub> concentrations likely to have been above those allowed by the current 1-hour standard, the PA reaches the conclusion that available U.S. and Canadian epidemiologic studies do not provide support for such NO<sub>2</sub>-associated outcomes in locations with NO<sub>2</sub> concentrations that would have clearly met that standard.

## 2. Health Effects With Long-Term Exposure to NO<sub>2</sub>

This section discusses the evidence for health effects associated with long-term NO<sub>2</sub> exposures. Section II.C.2.a discusses the nature of the health effects that have been shown to be associated with long-term NO<sub>2</sub> exposures and the strength of the evidence supporting various effects, based on the assessment of that evidence in the ISA. Section II.C.2.b discusses the NO<sub>2</sub> concentrations at which health effects have been demonstrated to occur, based on the considerations and analyses included in the PA.

### a. Nature of Effects

In the last review of the primary NO<sub>2</sub> NAAQS, evidence for health effects related to long-term ambient NO<sub>2</sub> exposure was judged “suggestive of, but not sufficient to infer a causal relationship” for respiratory effects and “inadequate to infer the presence or absence of a causal relationship” for several other health effect categories. These included cardiovascular, and reproductive and developmental effects as well as cancer and total mortality. In the current review, new epidemiologic evidence, in conjunction with explicit integration of evidence across related outcomes, has resulted in strengthening of some of the causal determinations. Though the evidence of health effects associated with long-term exposure to NO<sub>2</sub> is more robust than in previous reviews, there are still a number of uncertainties limiting understanding of the role of long-term NO<sub>2</sub> exposures in causing health effects.

Chapter 6 of the ISA presents a detailed assessment of the evidence for health effects associated with long-term NO<sub>2</sub> exposures (U.S. EPA, 2016a). This evidence is summarized briefly below for respiratory effects (II.C.2.a.i), cardiovascular effects and diabetes (II.C.2.a.ii), reproductive and developmental effects (II.C.2.a.iii), premature mortality (II.C.2.a.iv), and cancer (II.C.2.a.v).

#### i. Respiratory Effects

The 2016 ISA concluded that there is “likely to be a causal relationship” between long-term NO<sub>2</sub> exposure and respiratory effects, based primarily on

evidence integrated across disciplines for a relationship with asthma development in children.<sup>67</sup> Evidence for other respiratory outcomes integrated across epidemiologic and experimental studies, including decrements in lung function and partially irreversible decrements in lung development, respiratory disease severity, chronic bronchitis/asthma incidence in adults, chronic obstructive pulmonary disease (COPD) hospital admissions, and respiratory infections, is less consistent and has larger uncertainty as to whether there is an independent effect of long-term NO<sub>2</sub> exposure (U.S. EPA, 2016a, Section 6.2.9). As noted above, NO<sub>2</sub> is only one of many etiologic agents that may contribute to respiratory health effects such as the development of asthma in children.

The conclusion of a “likely to be a causal relationship” in the current review represents a change from 2008 ISA conclusion that the evidence was “suggestive of, but not sufficient to infer, a causal relationship” (U.S. EPA, 2008a, Section 5.3.2.4). This strengthening of the causal determination is due to the epidemiologic evidence base, which has expanded since the last review and biological plausibility from some experimental studies (U.S. EPA, 2016 Table 1–1). This expanded evidence includes several recently published longitudinal studies that indicate positive associations between asthma incidence in children and long-term NO<sub>2</sub> exposures, with improved exposure assessment in some studies based on NO<sub>2</sub> modeled estimates for children’s homes or NO<sub>2</sub> measured near children’s homes or schools. Associations were observed across various periods of exposure, including first year of life, year prior to asthma diagnosis, and cumulative exposure. In addition, the ISA notes several other strengths of the evidence base including the general timing of asthma diagnosis and relative confidence that the NO<sub>2</sub> exposure preceded asthma development in longitudinal studies, more reliable estimates of asthma incidence based on physician-diagnosis in children older than 5 years of age from parental report or clinical assessment, as well as residential NO<sub>2</sub> concentrations estimated from land use regression (LUR) models with good NO<sub>2</sub> prediction in some studies.

While the causal determination has been strengthened in this review,

<sup>67</sup> Asthma development is also referred to as “asthma incidence” in this notice and elsewhere. Both asthma development and asthma incidence refer to the onset of the disease rather than the exacerbation of existing disease.

important uncertainties remain. For example, the ISA notes that as in the last review, a “key uncertainty that remains when examining the epidemiologic evidence alone is the inability to determine whether NO<sub>2</sub> exposure has an independent effect from that of other pollutants in the ambient mixture” (U.S. EPA, 2016a, Section 6.2.2.1, p. 6–21). While a few studies have included copollutant models for respiratory effects other than asthma development, the ISA states that “[e]pidemiologic studies of asthma development in children have not clearly characterized potential confounding by PM<sub>2.5</sub> or traffic-related pollutants [e.g., CO, BC/EC, volatile organic compounds (VOCs)]” (U.S. EPA, 2016a, p. 6–64). The ISA further notes that “[i]n the longitudinal studies, correlations with PM<sub>2.5</sub> and BC were often high (e.g.,  $r = 0.7$ – $0.96$ ), and no studies of asthma incidence evaluated models to address copollutant confounding, making it difficult to evaluate the independent effect of NO<sub>2</sub>” (U.S. EPA, 2016a, p. 6–64). High correlations between NO<sub>2</sub> and other traffic-related pollutants were based on modeling, and studies of asthma incidence that used monitored NO<sub>2</sub> concentrations as an exposure surrogate did not report such correlations (U.S. EPA, 2016a, Table 6–1). This uncertainty is important to consider when interpreting the epidemiologic evidence regarding the extent to which NO<sub>2</sub> is independently related to asthma development.

The ISA also evaluated copollutant confounding in long-term exposure studies beyond asthma incidence to examine whether studies of other respiratory effects could provide information on the potential for confounding by traffic-related copollutants. Several studies examined correlations between NO<sub>2</sub> and traffic-related copollutants and found them to be relatively high in many cases, ranging from 0.54–0.95 for PM<sub>2.5</sub>, 0.54–0.93 for BC/EC, 0.2–0.95 for PM<sub>10</sub>, and 0.64–0.86 for OC (U.S. EPA, 2016a, Tables 6–1 and 6–3). While these correlations are often based on model estimates, some are based on monitored pollutant concentrations (*i.e.*, McConnell et al. (2003) reported correlations of 0.54 with PM<sub>2.5</sub> and EC) (U.S. EPA, 2016a, Table 6–3). Additionally, three studies (McConnell et al., 2003; MacIntyre et al., 2014; Gehring et al., 2013)<sup>68</sup> evaluated

copollutant models with NO<sub>2</sub> and PM<sub>2.5</sub>, and some findings suggest that associations for NO<sub>2</sub> with bronchitic symptoms, lung function, and respiratory infection are not robust because effect estimates decreased in magnitude and became imprecise when a copollutant was added in the model. Overall, examination of evidence from studies of other respiratory effects indicates moderate to high correlations between long-term NO<sub>2</sub> concentrations and traffic-related copollutants, with very limited evaluation of the potential for confounding. Thus, when considering the collective evidence, it is difficult to disentangle the independent effect of NO<sub>2</sub> from other traffic-related pollutants or mixtures in epidemiologic studies (U.S. EPA, 2016a, Sections 3.4.4 and 6.2.9.5).

While this uncertainty continues to apply to the epidemiologic evidence for asthma incidence in children, the ISA describes that the uncertainty is partly reduced by the coherence of findings from experimental studies and epidemiologic studies. Experimental studies demonstrate effects on key events in the mode of action proposed for the development of asthma and provide biological plausibility for the epidemiologic evidence. For example, one study demonstrated that airway hyperresponsiveness was induced in guinea pigs after long-term exposure to NO<sub>2</sub> [1,000–4,000 ppb; (Kobayashi and Miura, 1995)]. Other experimental studies examining oxidative stress report mixed results, but some evidence from short-term studies supports a relationship between NO<sub>2</sub> exposure and increased pulmonary inflammation in healthy humans. The ISA also points to supporting evidence from studies demonstrating that short-term exposure repeated over several days (260–1,000 ppb) and long-term NO<sub>2</sub> exposure (2,000–4,000 ppb) can induce T helper (Th)2 skewing/allergic sensitization in healthy humans and animal models by showing increased Th2 cytokines, airway eosinophils, and immunoglobulin E (IgE)-mediated responses (U.S. EPA, 2016a, Sections 4.3.5 and 6.2.2.3). Epidemiologic studies also provide some supporting evidence for these key events in the mode of action. Some evidence from epidemiologic studies demonstrates associations between short-term ambient NO<sub>2</sub> concentrations and increases in pulmonary inflammation in

healthy children and adults, giving a possible mechanistic understanding of this effect (U.S. EPA, 2016a, Section 5.2.2.5). Overall, evidence from experimental and epidemiologic studies provide support for a role of NO<sub>2</sub> in asthma development by describing a potential role for repeated exposures to lead to recurrent inflammation and allergic responses.

Overall, the ISA notes that there is new evidence available that strengthens conclusions from the last review regarding respiratory health effects attributable to long-term ambient NO<sub>2</sub> exposure. The majority of new evidence is from epidemiologic studies of asthma incidence in children with improved exposure assessment (*i.e.*, measured or modeled at or near children’s homes or schools), which builds upon previous evidence for associations of long-term NO<sub>2</sub> and asthma incidence and also partly reduces uncertainties related to measurement error. Explicit integration of evidence for individual outcome categories (e.g., asthma incidence, respiratory infection) provides improved characterization of biological plausibility and mode of action, including some new evidence from studies of short-term exposure supporting an effect on asthma development. Although this partly reduces the uncertainty regarding independent effects of NO<sub>2</sub>, the potential for confounding remains a concern when interpreting these epidemiologic studies as a result of the high correlation with other traffic-related copollutants and the general lack of copollutant models including these pollutants. In particular, it remains unclear the degree to which NO<sub>2</sub> itself may be causing the development of asthma versus serving as a surrogate for the broader traffic-pollutant mix.

#### ii. Cardiovascular Effects and Diabetes

In the previous review, the 2008 ISA stated that the evidence for cardiovascular effects attributable to long-term ambient NO<sub>2</sub> exposure was “inadequate to infer the presence or absence of a causal relationship.” The epidemiologic and experimental evidence was limited, with uncertainties related to traffic-related copollutant confounding (U.S. EPA, 2008a). For the current review, the body of epidemiologic evidence available is substantially larger than that in the last review and includes evidence for diabetes. The conclusion on causality is stronger in the current review with regard to the relationship between long-term exposure to NO<sub>2</sub> and cardiovascular effects and diabetes, as the ISA judged the evidence to be

<sup>68</sup> In single-pollutant models for various health endpoints, the studies reported the following effect estimates (95% CI): McConnell et al., 2003 (Bronchitic symptoms) 1.97 (1.22, 3.18); MacIntyre

et al., 2014 (Pneumonia) 1.30 (1.02, 1.65), (Otitis Media) 1.09 (1.02, 1.16), (Croup) 0.96 (0.83, 1.12); Gehring et al., 2013 (FEV1) –0.98 (–1.70, –0.26), (FVC) –2.14 (–4.20, –0.04), (PEF) –1.04 (–1.94, –0.13).

“suggestive, but not sufficient to infer” a causal relationship (U.S. EPA, 2016a, Section 6.3). The strongest evidence comes from recent epidemiologic studies reporting positive associations of NO<sub>2</sub> with heart disease and diabetes with improved exposure assessment (*i.e.*, residential estimates from models that well predict NO<sub>2</sub> concentrations in the study areas), but the evidence across experimental studies remains limited and inconsistent and does not provide sufficient biological plausibility for effects observed in epidemiologic studies. Specifically, the ISA concludes that “[e]pidemiologic studies have not adequately accounted for confounding by PM<sub>2.5</sub>, noise, or traffic-related copollutants, and there is limited coherence and biological plausibility for NO<sub>2</sub>-related development of heart disease” (U.S. EPA, 2016a, p. 6–98) or “for NO<sub>2</sub>-related development of diabetes” (U.S. EPA, 2016a, p. 6–99). Thus, substantial uncertainty exists regarding the independent effect of NO<sub>2</sub> and the total evidence is “suggestive of, but not sufficient to infer, a causal relationship” between long-term NO<sub>2</sub> exposure and cardiovascular effects and diabetes (U.S. EPA, 2016a, Section 6.3.9).

### iii. Reproductive and Developmental Effects

In the previous review, a limited number of epidemiologic and toxicological studies had assessed the relationship between long-term NO<sub>2</sub> exposure and reproductive and developmental effects. The 2008 ISA concluded that there was not consistent evidence for an association between NO<sub>2</sub> and birth outcomes and that evidence was “inadequate to infer the presence or absence of a causal relationship” with reproductive and developmental effects overall (U.S. EPA, 2008a). In the ISA for the current review, a number of recent studies added to the evidence base, and reproductive effects were considered as three separate categories: birth outcomes; fertility, reproduction, and pregnancy; and postnatal development (U.S. EPA, 2016a, Section 6.4). Overall, the ISA found the evidence to be “suggestive of, but not sufficient to infer, a causal relationship” between long-term exposure to NO<sub>2</sub> and birth outcomes and “inadequate to infer the presence or absence of a causal relationship” between long-term exposure to NO<sub>2</sub> and fertility, reproduction and pregnancy as well as postnatal development. Evidence for effects on fertility, reproduction, and pregnancy and for effects on postnatal development is inconsistent across both

epidemiologic and toxicological studies. Additionally, there are few toxicological studies available. The ISA concludes the change in the causal determination for birth outcomes reflects the large number of studies that generally observed associations with fetal growth restriction and the improved outcome assessment (*e.g.*, measurements throughout pregnancy via ultrasound) and exposure assessment (*e.g.*, well-validated LUR models) employed by many of these studies (U.S. EPA, 2016a, Section 6.4.5). For birth outcomes, there is uncertainty in whether the epidemiologic findings reflect an independent effect of NO<sub>2</sub> exposure.

### iv. Total Mortality

In the 2008 ISA, a limited number of epidemiologic studies assessed the relationship between long-term exposure to NO<sub>2</sub> and mortality in adults. The 2008 ISA concluded that the scarce amount of evidence was “inadequate to infer the presence or absence of a causal relationship” (U.S. EPA, 2008a). The ISA for the current review concludes that evidence is “suggestive of, but not sufficient to infer, a causal relationship” between long-term exposure to NO<sub>2</sub> and mortality among adults (U.S. EPA, 2016a, Section 6.5.3). This causal determination is based on evidence from recent studies demonstrating generally positive associations between long-term exposure to NO<sub>2</sub> and total mortality from extended analyses of existing cohorts as well as original results from new cohorts. In addition, there is evidence for associations between long-term NO<sub>2</sub> exposures and mortality due to respiratory and cardiovascular causes. However, there were several studies that did not observe an association between long-term exposure to NO<sub>2</sub> and mortality.

Some recent studies examined the potential for copollutant confounding by PM<sub>2.5</sub>, BC, or measures of traffic proximity or density in copollutant models with results from these models generally showing attenuation of the NO<sub>2</sub> effect on total mortality with the adjustment for PM<sub>2.5</sub> or BC. It remains difficult to disentangle the independent effect of NO<sub>2</sub> from the potential effect of the traffic-related pollution mixture or other components of that mixture. Further, as described above, there is large uncertainty whether long-term NO<sub>2</sub> exposure has an independent effect on the cardiovascular and respiratory morbidity outcomes that are major underlying causes of mortality. Thus, it is not clear by what biological pathways NO<sub>2</sub> exposure could lead to mortality. Considering the generally positive epidemiologic evidence together with

the uncertainty regarding an independent NO<sub>2</sub> effect, the ISA judged the evidence to be “suggestive of, but not sufficient to infer, a causal relationship” between long-term exposure to NO<sub>2</sub> and total mortality (U.S. EPA, 2016a, 6.5.3).

### v. Cancer

The evidence evaluated in the 2008 ISA was judged “inadequate to infer the presence or absence of a causal relationship” (U.S. EPA, 2008a) based on a few epidemiologic studies indicating associations between long-term NO<sub>2</sub> exposure and lung cancer incidence but lack of toxicological evidence demonstrating that NO<sub>2</sub> induces tumors. In the current review, the integration of recent and older studies on long-term NO<sub>2</sub> exposure and cancer yielded an evidence base judged “suggestive of, but not sufficient to infer, a causal relationship” (U.S. EPA, 2016a, Section 6.6.9). This conclusion is based primarily on recent epidemiologic evidence, some of which shows NO<sub>2</sub>-associated lung cancer incidence and mortality but does not address confounding by traffic-related copollutants, and is also based on some previous toxicological evidence that implicates NO<sub>2</sub> in tumor promotion (U.S. EPA, 2016a, Section 6.6.9).

### b. Long-Term NO<sub>2</sub> Concentrations in Health Studies

In evaluating what the available health evidence indicates with regard to the degree of public health protection provided by the current standards, it is appropriate to consider the long-term NO<sub>2</sub> concentrations that have been associated with various effects. The PA explicitly considers these NO<sub>2</sub> concentrations within the context of evaluating the public health protection provided by the current standards (U.S. EPA, 2017a, Section 3.2). This section summarizes those considerations from the PA.

In evaluating the long-term NO<sub>2</sub> concentrations associated with health effects within the context of considering the adequacy of the current standards, the PA focuses on the evidence for asthma incidence (*i.e.*, the strongest evidence supporting a likely to be causal relationship, as discussed above). The PA specifically considers (1) the extent to which epidemiologic studies indicate associations between long-term NO<sub>2</sub> exposures and asthma development for distributions of ambient NO<sub>2</sub> concentrations that would likely have met the existing standards and (2) the extent to which effects related to asthma development have been reported following the range of NO<sub>2</sub> exposure

concentrations examined in experimental studies. These considerations are discussed below for epidemiologic studies (II.C.2.b.i) and experimental studies (II.C.2.b.ii).

#### i. Ambient NO<sub>2</sub> Concentrations in Locations of Epidemiologic Studies

As discussed above for short-term exposures (Section II.C.1), when considering epidemiologic studies of long term NO<sub>2</sub> exposures within the context of evaluating the adequacy of the current NO<sub>2</sub> standards, the PA emphasizes studies conducted in the U.S. and Canada. The PA considers the extent to which these studies report positive and relatively precise associations with long-term NO<sub>2</sub> exposures, and the extent to which important uncertainties could impact the emphasis placed on particular studies. For the studies with potential to inform conclusions on adequacy, the PA also evaluates available air quality information in study locations, focusing on estimated DVs over the course of study periods.

The epidemiologic studies available in the current review that evaluate associations between long-term NO<sub>2</sub> exposures and asthma incidence are summarized in Table 6–1 of the ISA (U.S. EPA, 2016a, pp. 6–7). There are six longitudinal epidemiologic studies conducted in the U.S. or Canada that vary in terms of the populations examined and methods used. Of the six studies, the ISA identifies three as key studies supporting the causal determination (Carlsten et al., 2011; Clougherty et al., 2007; Jerrett et al., 2008). The other three studies, not identified as key studies in the ISA causality determination, had a greater degree of uncertainty inherent in their characterizations of NO<sub>2</sub> exposures (Clark et al., 2010; McConnell et al., 2010; Nishimura et al., 2013). In evaluating the adequacy of the current NO<sub>2</sub> standards, the PA places the greatest emphasis on the three U.S. and Canadian studies identified in the ISA as providing key supporting evidence for the causal determination. However, the PA also considers what the additional three U.S. and Canadian studies can indicate about the adequacy of the current standards, while noting the increased uncertainty in these studies.

Effect estimates in U.S. and Canadian studies are generally positive and, in some cases, statistically significant and relatively precise (U.S. EPA, 2016a, Table 6–1; U.S. EPA, 2017a, Figure). However, there are important uncertainties in this body of evidence for asthma incidence, limiting the extent

to which these studies can inform consideration of the adequacy of the current NO<sub>2</sub> standards to protect against long-term NO<sub>2</sub> exposures. For example, there is uncertainty in the degree to which reported associations are specific to NO<sub>2</sub>, rather than reflecting associations with another traffic-related copollutant or the broader mix of pollutants. Overall, the potential for copollutant confounding has not been well studied in this body of evidence, as described above (Section II.C.2.a). Of the U.S. and Canadian studies, Carlsten et al. (2011) reported correlations between NO<sub>2</sub> and traffic-related pollutants (0.7 for PM<sub>2.5</sub>, 0.5 for BC based on land use regression). Other U.S. and Canadian studies did not report quantitative results, but generally reported “moderate” to “high” correlations between NO<sub>2</sub> and other pollutants (U.S. EPA, 2016a, Table 6–1). Given the relatively high correlations for NO<sub>2</sub> with co-occurring pollutants, study authors often interpreted associations with NO<sub>2</sub> as reflecting associations with traffic-related pollution more broadly (*e.g.*, Jerrett et al., 2008; McConnell et al., 2010).

Another important uncertainty is the potential for exposure measurement error in these epidemiologic studies. The ISA states that “a key issue in evaluating the strength of inference about NO<sub>2</sub>-related asthma development from epidemiologic studies is the extent to which the NO<sub>2</sub> exposure assessment method used in a study captured the variability in exposure among study subjects” (U.S. EPA, 2016a, pp. 6–16). The ISA conclusion of a “likely to be a causal relationship” is based on the total body of evidence, with the strongest basis for inferring associations of NO<sub>2</sub> with asthma incidence coming from studies that “estimated residential NO<sub>2</sub> from LUR models that were demonstrated to predict well the variability in NO<sub>2</sub> in study locations or examined NO<sub>2</sub> measured at locations [within] 1–2 km of subjects’ school or home” (U.S. EPA, 2016a, pp. 6–21). The studies that meet this criterion were mostly conducted outside of the U.S. or Canada, with the exception of Carlsten et al. (2011), which used a LUR model with good predictive capacity. The other U.S. and Canadian studies employed LUR models with unknown validation, or central-site measurements that have well-recognized limitations in reflecting variability in ambient NO<sub>2</sub> concentrations in a community and may not well represent variability in NO<sub>2</sub> exposure among subjects. Thus, the extent to which these U.S. and Canadian studies provide reliable estimates of

asthma incidence for particular NO<sub>2</sub> concentrations is unclear.

Overall, in revisiting the first question posed above, the PA notes that U.S. and Canadian epidemiologic studies report positive, and in some cases relatively precise, associations between long-term NO<sub>2</sub> exposure and asthma incidence in children. While it is appropriate to consider what these studies can tell us with regard to the adequacy of the existing primary NO<sub>2</sub> standards (see below), the emphasis that is placed on these considerations will reflect important uncertainties related to the potential for confounding by traffic-related copollutants and for exposure measurement error.

While keeping in mind these uncertainties, the PA next considers the ambient NO<sub>2</sub> concentrations present at monitoring sites in locations and time periods of U.S. and Canadian epidemiologic studies. Specifically, the PA considers the following question: To what extent do U.S. and Canadian epidemiologic studies report associations with long-term NO<sub>2</sub> in locations likely to have met the current primary NO<sub>2</sub> standards?

As discussed above for short-term exposures (Section II.C.1), addressing this question can provide important insights into the extent to which NO<sub>2</sub>-health effect associations are present for distributions of ambient NO<sub>2</sub> concentrations that would be allowed by the current primary standards. The presence of such associations would support the potential for the current standards to allow the NO<sub>2</sub>-associated asthma development indicated by epidemiologic studies. To the degree studies have not reported associations in locations meeting the current primary NO<sub>2</sub> standards, there is greater uncertainty regarding the potential for the development of asthma to result from the NO<sub>2</sub> exposures associated with air quality meeting those standards.

To evaluate this issue, the PA compares NO<sub>2</sub> estimated DVs in study areas to the levels of the current primary NO<sub>2</sub> standards. In addition to comparing annual DVs to the level of the annual standard, support for consideration of 1-hour DVs comes from the ISA’s integrated mode of action information describing the biological plausibility for development of asthma (Section B.II.2., above). In particular, studies demonstrate the potential for repeated short-term NO<sub>2</sub> exposures to induce pulmonary inflammation and development of allergic responses. The ISA states that “findings for short-term NO<sub>2</sub> exposure support an effect on asthma development by describing a potential role for repeated exposures to

lead to recurrent inflammation and allergic responses,” which are “identified as key early events in the proposed mode of action for asthma development” (U.S. EPA, 2016a, p. 6–66 and p. 6–64). More specifically, the ISA states the following (U.S. EPA, 2016a, p. 4–64):

The initiating events in the development of respiratory effects due to long-term NO<sub>2</sub> exposure are recurrent and/or chronic respiratory tract inflammation and oxidative stress. These are the driving factors for potential downstream key events, allergic sensitization, airway inflammation, and airway remodeling, that may lead to the endpoint [airway hyperresponsiveness]. The resulting outcome may be new asthma onset, which presents as an asthma exacerbation that leads to physician-diagnosed asthma.

Thus, when considering the protection provided by the current standards against NO<sub>2</sub>-associated asthma development, the PA considers the combined protection afforded by the 1-hour and annual standards.<sup>69</sup>

To inform consideration of whether a study area’s air quality could have met the current primary NO<sub>2</sub> standards during study periods, the PA presents DV estimates based on the NO<sub>2</sub> concentrations measured at existing monitors during the years over which the epidemiologic studies of long-term NO<sub>2</sub> exposures were conducted.<sup>70 71</sup>

In interpreting these comparisons of DV estimates with the NO<sub>2</sub> standards, the PA also considers uncertainty in the extent to which identified DV estimates represent the higher NO<sub>2</sub> concentrations likely to have been present near major roads during study periods (II.B.3, above). In particular, as discussed above for short-term exposures, study area DV estimates are based on NO<sub>2</sub> concentrations from the generally area-wide NO<sub>2</sub> monitors that were present during study periods. Calculated DV estimates could have been higher if the

near-road monitors that are now required in major U.S. urban areas had been in place. On this issue, the PA notes that the published scientific literature supports the occurrence of higher NO<sub>2</sub> concentrations near roadways and that recent air quality information from the new near-road NO<sub>2</sub> monitoring network generally indicates higher NO<sub>2</sub> concentrations at near-road monitoring sites than at non-near road monitors in the same CBSA (Section II.B.3). In addition, mobile source NO<sub>x</sub> emissions were substantially higher during the majority of study periods (1986–2006) than they are today (Section II.B.2), and NO<sub>2</sub> concentration gradients around roadways were generally more pronounced during study periods than indicated by recent air quality information. Thus, even in cases where DV estimates during study periods are at or somewhat below the levels of current primary standards, it is not clear that study areas would have met the standards if the currently required near-road monitors had been in place.<sup>72</sup>

In considering the epidemiologic studies looking at long-term NO<sub>2</sub> exposure and asthma development (U.S. EPA, 2017a, Figure 3–2), the PA first notes the information from the key studies as identified in the ISA (Jerrett et al., 2008; Carlsten et al., 2011, Clougherty et al., 2007). Jerrett et al. (2008) reported positive and relatively precise associations with asthma incidence, based on analyses across several communities in Southern California. Of the 11 study communities evaluated by Jerrett et al. (2008), most (*i.e.*, seven) had maximum annual estimated DVs that were near (*i.e.*, 46 ppb for the four communities represented by the Riverside estimated DVs) or above (*i.e.*, 60 ppb for the three communities represented by the Los Angeles estimated DVs) 53 ppb.<sup>73</sup> These seven communities also had 1-hour estimated DVs (max and mean) that were well-above 100 ppb. The other key studies (*i.e.*, Carlsten et al., 2011; Clougherty et al., 2007), conducted in single cities, reported positive but

statistically imprecise associations. The annual estimated DVs in locations of these studies during study years were below 53 ppb, but maximum 1-hour estimated DVs were near (Clougherty)<sup>74</sup> or above (Carlsten) 100 ppb.

The PA also considers the information from the other U.S. and Canadian studies available that, due to additional uncertainties, were not identified as key studies in the ISA (Clark et al., 2010; McConnell et al., 2010; Nishimura et al., 2013). The multi-city study by Nishimura et al. (2013) reports a positive and relatively precise association with asthma incidence, based on five U.S. cities and Puerto Rico (see “combined” estimate in Figure 3–2 of the NO<sub>2</sub> PA). Annual estimated DVs in all study cities were below 53 ppb, while maximum 1-hour estimated DVs were above 100 ppb in four of the five study cities (mean 1-hour estimated DVs were also near or above 100 ppb in most study cities). Nishimura et al. (2013) also reported mixed results in city-specific effects estimates. McConnell et al. (2010) also conducted a multi-community study in Southern California and reported a positive and relatively precise association between asthma incidence and long-term NO<sub>2</sub> exposures based on central-site measurements. This study encompasses some of the same communities as Jerrett et al. (2008), and while the annual DV estimates for these study years are more mixed, the 1-hour DV estimates representing 10 of 13 communities are near or above 100 ppb. Finally, Clark et al. (2010) reported a relatively precise and statistically significant association in a study conducted over a two-year period in British Columbia, with annual and hourly DV estimates of 32 ppb and 67 ppb, respectively. However, this result was based on central-site NO<sub>2</sub> measurements that have well-recognized limitations in reflecting variability in ambient NO<sub>2</sub> concentrations in a community and variability in NO<sub>2</sub> exposure among subjects.

#### PA Conclusions on Ambient NO<sub>2</sub> Concentrations in Locations of Epidemiologic Studies

Based on the information discussed above, while epidemiologic studies provide support for NO<sub>2</sub>-associated asthma development at ambient NO<sub>2</sub> concentrations likely to have been above those allowed by the current standards,

<sup>69</sup> It is also the case that broad changes in NO<sub>2</sub> concentrations will affect both hourly and annual metrics. This is discussed in more detail in Section II.B.4. above, and in CASAC’s letter to the Administrator (Diez Roux and Sheppard, 2017). Thus, as in the recent review of the O<sub>3</sub> NAAQS (80 FR 65292, October 26, 2015), it is appropriate to consider the extent to which a short-term standard could provide protection against longer-term pollutant exposures.

<sup>70</sup> As discussed above for short-term exposures, the DVs estimates reported here are meant to approximate the values that are used when determining whether an area meets the primary NO<sub>2</sub> NAAQS (U.S. EPA, 2017a, Appendix A).

<sup>71</sup> The DV estimates for the epidemiologic studies of asthma incidence conducted in the U.S. and Canada are presented in Figure 3–2 of the NO<sub>2</sub> PA (U.S. EPA, 2017a).

<sup>72</sup> As noted above for studies of short-term NO<sub>2</sub> exposures (II.C.1.b.ii), epidemiologic studies that evaluate potential NO<sub>2</sub> health effect associations during time periods when near-road monitors are operational could reduce this uncertainty in future reviews.

<sup>73</sup> For the studies by Jerrett et al. (2008) and McConnell et al. (2010), the majority of communities were located within the Los Angeles and Riverside CBSAs. Because of this, and because community-specific NO<sub>2</sub> monitoring data were often not available in these areas (U.S. EPA, 2017a, Appendix A), DV estimates for the Los Angeles and Riverside CBSAs were used to represent multiple study communities.

<sup>74</sup> As noted above, even in cases where DV estimates during study periods are at or somewhat below the levels of current standards, it is not clear that study areas would have met the standards if the currently required near-road monitors had been in place.

these studies do not report such associations at ambient NO<sub>2</sub> concentrations that would have clearly met the current standards. Thus, in evaluating the adequacy of the public health protection provided by the current 1-hour and annual NO<sub>2</sub> standards, the PA concludes that epidemiologic studies do not provide a clear basis for concluding that ambient NO<sub>2</sub> concentrations allowed by the current standards are independently (*i.e.*, independent of co-occurring roadway pollutants) associated with the development of asthma (U.S. EPA, 2017, section 3.3.2). This conclusion stems from consideration of the available evidence from U.S. and Canadian studies for NO<sub>2</sub>-associated asthma incidence, the ambient NO<sub>2</sub> concentrations present in study locations during study periods, and the uncertainties and limitations inherent in the evidence and in the analysis of study area DV estimates.

With regard to uncertainties in the evidence, the PA particularly notes the potential for confounding by co-occurring pollutants, as described above, given the following: (1) The relatively high correlations observed between long-term concentrations of NO<sub>2</sub> and long-term concentrations of other roadway-associated pollutants; (2) the general lack of information from copollutant models on the potential for NO<sub>2</sub> associations that are independent of another traffic-related pollutant or mix of pollutants. This uncertainty is an important consideration in evaluating the potential support for adverse effects occurring below the levels of the current primary NO<sub>2</sub> standards.

Furthermore, the analysis of study area estimated DVs does not provide support for the occurrence of NO<sub>2</sub>-associated asthma incidence in locations with ambient NO<sub>2</sub> concentrations clearly meeting the current NAAQS. In particular, for most of the study locations evaluated in the lone key U.S. multi-community study (Jerrett et al., 2008), 1-hour estimated DV were above 100 ppb and annual DVs were near or above 53 ppb. In addition, the two key single-city studies evaluated reported positive, but relatively imprecise, associations in locations with 1-hour estimated DVs near (Clougherty et al., 2007 in Boston) or above (Carlsten et al., 2011 in Vancouver) 100 ppb. Had currently required near-road monitors been in operation during study periods, estimated DVs in U.S. study locations would likely have been higher. Other U.S. and Canadian studies evaluated were subject to greater uncertainties in the characterization of NO<sub>2</sub> exposures. Given this information and

consideration of these uncertainties, the degree to which these epidemiologic studies can inform whether adverse NO<sub>2</sub>-associated effects are occurring below the levels of the current primary NO<sub>2</sub> standards is limited.

#### ii. NO<sub>2</sub> Concentrations in Experimental Studies of Long-Term Exposure

In addition to the evidence from epidemiologic studies, the PA also considers evidence from experimental studies in animals and humans.<sup>75</sup> Experimental studies examining asthma-related effects attributable to long-term NO<sub>2</sub> exposures are largely limited to animals exposed to NO<sub>2</sub> concentrations well-above those found in the ambient air (*i.e.*,  $\geq 1,000$  ppb). As discussed above, the ISA indicates evidence from these animal studies supports the causal determination by characterizing “a potential mode of action linking NO<sub>2</sub> exposure with asthma development” (U.S. EPA, 2016a, p. 1–20). In particular, there is limited evidence for increased airway responsiveness in guinea pigs with exposures to 1,000–4,000 ppb for 6–12 weeks. There is inconsistent evidence for pulmonary inflammation across all studies, though effects were reported following NO<sub>2</sub> exposures of 500–2,000 ppb for 12 weeks. Despite providing support for the “likely to be a causal” relationship, evidence from these experimental studies, by themselves, does not provide insight into the occurrence of adverse health effects following exposures below the levels of the existing primary NO<sub>2</sub> standards.<sup>76</sup>

#### iii. Overall Conclusions

Taking all of the evidence and information together, including important uncertainties, the PA revisits the extent to which the evidence supports the occurrence of NO<sub>2</sub>-attributable asthma development in children at NO<sub>2</sub> concentrations below the existing standards. Based on the considerations discussed above, the PA concludes that the available evidence does not provide support for asthma development attributable to long-term exposures to NO<sub>2</sub> concentrations that would clearly meet the existing annual and 1-hour primary NO<sub>2</sub> standards. This conclusion recognizes the NO<sub>2</sub> air

<sup>75</sup> While there are not controlled human exposure studies for long-term exposures, the ISA and the PA consider the extent to which evidence from short-term studies can provide support for effects observed in long-term exposure studies.

<sup>76</sup> In addition, the ISA draws from experimental evidence for short-term exposures to support the biological plausibility of asthma development. Consideration of the NO<sub>2</sub> exposure concentrations evaluated in these studies is discussed in Section II.C.1 above.

quality relationships, which indicate that meeting the 1-hour NO<sub>2</sub> standard would be expected to limit annual NO<sub>2</sub> concentrations to well-below the level of the current annual standard (Section II.B.4, above). This conclusion also recognizes the uncertainties in interpreting the epidemiologic evidence within the context of evaluating the existing standards due to the lack of near-road monitors during study periods and due to the potential for confounding by co-occurring pollutants. Thus, the PA concludes that epidemiologic studies of long-term NO<sub>2</sub> exposures and asthma development do not provide a clear basis for concluding that ambient NO<sub>2</sub> concentrations allowed by the current primary NO<sub>2</sub> standards are independently (*i.e.*, independent of co-occurring roadway pollutants) associated with the development of asthma. In addition, while experimental studies provide support for NO<sub>2</sub>-attributable effects that are plausibly related to asthma development, the relatively high NO<sub>2</sub> exposure concentrations used in these studies do not provide insight into whether such effects would occur at NO<sub>2</sub> exposure concentrations that would be allowed by the current standards.

#### 3. Potential Public Health Implications

Evaluation of the public health protection provided against ambient NO<sub>2</sub> exposures requires consideration of populations and lifestages that may be at greater risk of experiencing NO<sub>2</sub>-attributable health effects. In the last review, the 2008 ISA for Oxides of Nitrogen noted that a considerable fraction of the U.S. population lives, works, or attends school near major roadways, where ambient NO<sub>2</sub> concentrations are often elevated (U.S. EPA, 2008a, Section 4.3). Of this population, the 2008 ISA concluded that “those with physiological susceptibility will have even greater risks of health effects related to NO<sub>2</sub>” (U.S. EPA, 2008a, p. 4–12). With regard to susceptibility, the 2008 ISA concluded that “[p]ersons with preexisting respiratory disease, children, and older adults may be more susceptible to the effects of NO<sub>2</sub> exposure” (U.S. EPA, 2008a, p. 4–12).

In the current review, the 2016 ISA again notes because of the large populations attending school, living, working, and commuting on or near roads, where ambient NO<sub>2</sub> concentrations can be higher than in many other locations (U.S. EPA, 2016a,



Section 7.5.6),<sup>77</sup> there is widespread potential for elevated ambient NO<sub>2</sub> exposures. For example, Rowangould et al. (2013) found that over 19% of the U.S. population lives within 100 m of roads with an annual average daily traffic (AADT) of 25,000 vehicles, and 1.3% lives near roads with AADT greater than 200,000. The proportion is much larger in certain parts of the country, mostly coinciding with urban areas. Among California residents, 40% live within 100 m of roads with AADT of 25,000 (Rowangould, 2013). In addition, 7% of U.S. schools serving a total of 3,152,000 school children are located within 100 m of a major roadway, and 15% of U.S. schools serving a total of 6,357,000 school children are located within 250 m of a major roadway (Kingsley et al., 2014). Thus, as in the last review, the available information indicates that large proportions of the U.S. population potentially have elevated NO<sub>2</sub> exposures as a result of living, working, attending school, or commuting on or near roadways.

The impacts of exposures to elevated NO<sub>2</sub> concentrations, such as those that can occur around roadways, are of particular concern for populations at increased risk of experiencing adverse effects. In the current review, the PA's consideration of potential at-risk populations draws from the 2016 ISA's assessment of the evidence (U.S. EPA, 2016a, Chapter 7). The ISA uses a systematic approach to evaluate factors that may increase risks in a particular population or during a particular lifestage, noting that increased risk could be due to "intrinsic or extrinsic factors, differences in internal dose, or differences in exposure" (U.S. EPA, 2016a, p. 7–1).

The ISA evaluates the evidence for a number of potential at-risk factors, including pre-existing diseases like asthma (U.S. EPA, 2016a, Section 7.3), genetic factors (U.S. EPA, 2016a, Section 7.4), sociodemographic factors (U.S. EPA, 2016a, Section 7.5), and behavioral and other factors (U.S. EPA, 2016a, Section 7.6). The ISA then uses a systematic approach for classifying the evidence for each potential at-risk factor (U.S. EPA, 2015, Preamble, Section 6.a, Table III). The categories considered are "adequate evidence," "suggestive evidence," "inadequate evidence," and "evidence of no effect" (U.S. EPA, 2016a, Table 7–1). Consistent with other recent NAAQS reviews (e.g., 80 FR

65292, October 26, 2015), the PA focuses the consideration of potential at-risk populations on those factors for which the ISA determines there is "adequate" evidence (U.S. EPA, 2016a, Table 7–27). In the case of NO<sub>2</sub>, this includes people with asthma, children and older adults (U.S. EPA, 2016a, Table 7–27), based primarily on evidence for asthma exacerbation or asthma development as evidence for an independent relationship of NO<sub>2</sub> exposure with other health effects is more uncertain.

The PA's consideration of the evidence supporting these at-risk populations specifically focuses on the following question: To what extent does the currently available scientific evidence expand the understanding of populations and/or lifestages that may be at greater risk for NO<sub>2</sub>-related health effects?

In addressing this question, the PA considers the evidence for effects in people with asthma, children, and older adults (U.S. EPA, 2016a, Chapter 7, Table 7–27). This section presents the PA's overall conclusions regarding the populations at increased risk of NO<sub>2</sub>-related effects.

#### a. People With Asthma

Approximately 8.0% of adults and 9.3% of children (age <18 years) in the U.S. currently have asthma (Blackwell et al., 2014; Bloom et al., 2013), and it is the leading chronic illness affecting children (U.S. EPA, 2016a, Section 7.3.1). Individuals with pre-existing diseases like asthma may be at greater risk for some air pollution-related health effects if they are in a compromised biological state.

As in the last review, controlled human exposure studies demonstrating NO<sub>2</sub>-induced increases in AR provide key evidence that people with asthma are more sensitive than people without asthma to the effects of short-term NO<sub>2</sub> exposures. In particular, a meta-analysis conducted by Folinsbee et al. (1992) demonstrated that NO<sub>2</sub> exposures from 100 to 300 ppb increased AR in the majority of adults with asthma, while AR in adults without asthma was increased only for NO<sub>2</sub> exposure concentrations greater than 1,000 ppb (U.S. EPA, 2016a, Section 7.3.1). Brown (2015) showed that following resting exposures to NO<sub>2</sub> concentrations in the range of 100 to 530 ppb, about a quarter of individuals with asthma experience clinically relevant increases in AR to non-specific bronchial challenge. Results of epidemiologic studies are less clear regarding potential differences between populations with and without asthma (U.S. EPA, 2016a, Section 7.3.1).

Additionally, studies of activity patterns do not clearly indicate difference in time spent outdoors to suggest differences in NO<sub>2</sub> exposure. However, the meta-analysis of information from controlled human exposure studies, which supported the ISA's determination of a causal relationship between short-term exposures and respiratory effects, clearly demonstrates increased sensitivity of adults with asthma compared to healthy adults.<sup>78</sup> Thus, consistent with observations made in the 2008 ISA (U.S. EPA, 2008a), in the current review the ISA determines that the "evidence is adequate to conclude that people with asthma are at increased risk for NO<sub>2</sub>-related health effects" (U.S. EPA, 2016a, p. 7–7).

#### b. Children

According to the 2010 census, 24% of the U.S. population is less than 18 years of age, with 6.5% less than age 6 years (Howden and Meyer, 2011). The National Human Activity Pattern Survey shows that children spend more time than adults outdoors (Klepeis et al., 1996), and a longitudinal study in California showed a larger proportion of children reported spending time engaged in moderate or vigorous outdoor physical activity (Wu et al., 2011b). In addition, children have a higher propensity than adults for oronasal breathing (U.S. EPA, 2016a, Section 4.2.2.3) and the human respiratory system is not fully developed until 18–20 years of age (U.S. EPA, 2016a, Section 7.5.1). All of these factors could contribute to children being at higher risk than adults for effects attributable to ambient NO<sub>2</sub> exposures (U.S. EPA, 2016a, Section 7.5.1.1).

Epidemiologic evidence across diverse locations (U.S., Canada, Europe, Asia, Australia) consistently demonstrates adverse effects of both short- and long-term NO<sub>2</sub> exposures in children. In particular, short-term increases in ambient NO<sub>2</sub> concentrations are consistently associated with larger increases in asthma-related hospital admissions, ED visits or outpatient visits in children than in adults (U.S. EPA, 2016a, Section 7.5.1.1, Table 7–13). These results seem to indicate NO<sub>2</sub>-associated impacts that are 1.8 to 3.4-fold larger in children (Son et al., 2013; Ko et al., 2007; Atkinson et al., 1999; Anderson et al., 1998). In addition, asthma development

<sup>78</sup>Though, as discussed above (Section II.C.1), there is uncertainty in the extent to which increases in AR following exposures to NO<sub>2</sub> concentrations near those found in the ambient air (*i.e.*, around 100 ppb) would be clearly adverse.

<sup>77</sup>The ISA specifically notes that a zone of elevated NO<sub>2</sub> concentrations typically extends 200 to 500 m from roads with heavy traffic (U.S. EPA, 2016a, Section 2.5.3).

in children has been reported to be associated with long-term NO<sub>2</sub> exposures, based on exposure periods spanning infancy to adolescence (U.S. EPA, 2016a, Section 6.2.2.1). Given the consistent epidemiologic evidence for associations between ambient NO<sub>2</sub> and asthma-related outcomes, including the larger associations with short-term exposures observed in children, the ISA concludes the evidence “is adequate to conclude that children are at increased risk for NO<sub>2</sub>-related health effects” (U.S. EPA, 2016a, p. 7–32).

#### c. Older Adults

According to the 2012 National Population Projections issued by the U.S. Census Bureau, 13% of the U.S. population was age 65 years or older in 2010, and by 2030, this fraction is estimated to grow to 20% (Ortman et al., 2014). Recent epidemiologic findings expand on evidence available in the 2008 ISA that older adults may be at increased risk for NO<sub>2</sub>-related health effects. (U.S. EPA, 2016a Table 7–15). While it is not clear that older adults experience greater NO<sub>2</sub> exposures or doses, epidemiologic evidence generally indicates greater risk of NO<sub>2</sub>-related health effects in older adults compared with younger adults. For example, comparisons of older and younger adults with respect to NO<sub>2</sub>-related asthma exacerbation generally show larger (one to threefold) effects in adults ages 65 years or older than among individuals ages 15–64 years or 15–65 years (Ko et al., 2007; Villeneuve et al., 2007; Migliaretti et al., 2005; Anderson et al., 1998). Results for all respiratory hospital admissions combined also tend to show larger associations with NO<sub>2</sub> among older adults ages 65 years or older (Arbex et al., 2009; Wong et al., 2009; Hinwood et al., 2006; Atkinson et al., 1999). The ISA determined that, overall, the consistent epidemiologic evidence for asthma-related hospital admissions and ED visits “is adequate to conclude that older adults are at increased risk for NO<sub>2</sub>-related health effects” (U.S. EPA, 2016a, p. 7–37).

#### d. PA Conclusions on At-Risk Populations

As described in the PA, and consistent with the last review, the ISA determined that the available evidence is adequate to conclude that people with asthma, children, and older adults are at increased risk for NO<sub>2</sub>-related health effects. The large proportions of the U.S. population that encompass each of these groups and lifestages (*i.e.*, 8% adults and 9.3% children with asthma, 24% children, 13% older adults) underscores the potential for important public health

impacts attributable to NO<sub>2</sub> exposures. These impacts are of particular concern for members of these populations and lifestages who live, work, attend school or otherwise spend a large amount of time in locations of elevated ambient NO<sub>2</sub>, including near heavily trafficked roadways.

#### D. Human Exposure and Health Risk Characterization

Beyond the consideration of the scientific evidence, discussed above in Section II.C, the EPA also considers the extent to which new or updated quantitative analyses of NO<sub>2</sub> air quality, exposures or health risks could inform conclusions on the adequacy of the public health protection provided by the current primary NO<sub>2</sub> standards. Conducting such quantitative analyses, if appropriate, could inform judgments about the public health impacts of NO<sub>2</sub>-related health effects and could help to place the evidence for specific effects into a broader public health context. To this end, in the REA Planning document (U.S. EPA, 2015) and in the PA, the staff evaluated the extent to which the available evidence and information provide support for conducting new or updated analyses of NO<sub>2</sub> exposures and/or health risks, beyond the analyses conducted in the 2008 REA (U.S. EPA, 2008b). In doing so, staff carefully considered the assessments developed as part of the last review of the primary NO<sub>2</sub> NAAQS (U.S. EPA, 2008b) and the newly available scientific and technical information, particularly considering the degree to which updated analyses in the current review are likely to substantially add to the understanding of NO<sub>2</sub> exposures and/or health risks. The final PA also considers the CASAC advice and public input received on the REA Planning document (U.S. EPA, 2017a, Chapter 4), and on the draft PA (Diez Roux and Sheppard, 2017). Based on these considerations, the PA included updated analyses examining the occurrence of NO<sub>2</sub> air quality concentrations (*i.e.*, as surrogates for potential NO<sub>2</sub> exposures) that may be of public health concern (see below and Appendix B of U.S. EPA, 2017a). These analyses, summarized below and discussed in more detail in Chapter 4 of the PA (U.S. EPA, 2017a), have been informed by advice from the CASAC and input from the public on the REA Planning document (Diez Roux and Frey, 2015b) and on the draft PA (Diez Roux and Sheppard, 2017). Updated risk estimates based on information from epidemiology studies were not conducted in the current review given that these analyses would be subject to the same uncertainties identified in the

2008 REA (U.S. EPA, 2017a, Section 4–1). The CASAC agreed with this conclusion in its review of the REA Planning document (Diez Roux and Frey, 2015b, p. 5).

#### 1. Overview of Approach to Estimating Potential NO<sub>2</sub> Exposures

To provide insight into the potential occurrence of NO<sub>2</sub> air quality concentrations that may be of public health concern, the PA included analyses comparing NO<sub>2</sub> air quality to health-based benchmarks in 23 study areas (U.S. EPA, 2017a Table 4–1). The selection of study areas focused on CBSAs with near-road monitors in operation,<sup>79</sup> CBSAs with the highest NO<sub>2</sub> design values, and CBSAs with a relatively large number of NO<sub>2</sub> monitors overall (*i.e.*, providing improved spatial characterization).<sup>80</sup>

Air quality-benchmark comparisons were conducted in study areas with unadjusted air quality and with air quality adjusted upward to just meet the existing 1-hour standard.<sup>81</sup> Upward adjustment was required because all locations in the U.S. meet the current NO<sub>2</sub> NAAQS.

In identifying the range of NO<sub>2</sub> health-based benchmarks to evaluate, and the weight to place on specific benchmarks within this range, the PA considered both the group mean responses reported in individual studies of AR and the results of a meta-analysis that combined individual-level data from multiple studies (Brown, 2015; U.S. EPA, 2016a, Section 5.2.2.1). When taken together, the results of controlled human exposure studies and of the meta-analysis by Brown (2015) support consideration of NO<sub>2</sub> benchmarks from

<sup>79</sup> As discussed above (Sections I.C and II.B.3), the regulations require near-road monitors were required within 50 m of major roads in large urban areas that met certain criteria for population size or traffic volume. Most near-road monitors are sited within about 30 m of the road, and in some cases they are sited almost at the roadside (*i.e.*, as close as 2 m from the road; <http://www3.epa.gov/ttn/amtic/nearroad.html>) (U.S. EPA, 2017a, Section 2.2.2).

<sup>80</sup> Based on these criteria, a total of 23 CBSAs from across the U.S. were selected as study areas (U.S. EPA, 2017a, Appendix B, Figure B2–1). Further evaluation indicates that these 23 study areas are among the most populated CBSAs in the U.S.; they have among the highest total NO<sub>x</sub> emissions and mobile source NO<sub>x</sub> emissions in the U.S.; and they include a wide range of stationary source NO<sub>x</sub> emissions (U.S. EPA, 2017a, Appendix B, Figures B2–2 to B2–8).

<sup>81</sup> In all study areas, ambient NO<sub>2</sub> concentrations required smaller upward adjustments to just meet the 1-hour standard than to just meet the annual standard. Therefore, when adjusting air quality to just meet the current primary NO<sub>2</sub> NAAQS, the PA applied the adjustment needed to just meet the 1-hour standard. For additional information on the air quality adjustment approach see Appendix B, Section B2.4.1 in the PA (U.S. EPA, 2017a).

100 to 300 ppb, based largely on studies of non-specific AR in study participants exposed at rest.<sup>82</sup> Given uncertainties in the evidence, including the lack of an apparent dose-response relationship and uncertainty in the potential adversity of reported increases in AR, caution is appropriate when interpreting the potential public health implications of 1-hour NO<sub>2</sub> concentrations at or above these benchmarks. This is particularly the case for the 100 ppb benchmark, given the less consistent results across individual studies at this exposure concentration (see Section II.C.1 above and U.S. EPA, 2017a, Section 4.2.1).

## 2. Results of Updated Analyses

In considering the results of these updated analyses, the EPA focuses on the number of days per year that such 1-hour NO<sub>2</sub> concentrations could occur at each monitoring site in each study area.

Based on the results of these analyses (U.S. EPA, 2017a, Tables 4–1 and 4–2), the EPA makes the following key observations for study areas when air quality was unadjusted (“as-is”) and when air quality was adjusted to just meet the current 1-hour NO<sub>2</sub> standard<sup>83</sup> (U.S. EPA, 2017a, Section 4.2.1.2).

For unadjusted air quality:

- One-hour ambient NO<sub>2</sub> concentrations in study areas, including those near major roadways, were always below 200 ppb, and were virtually always below 150 ppb.

- Even in the worst-case years (*i.e.*, the years with the largest number of days at or above benchmarks), no study areas had any days with 1-hour NO<sub>2</sub> concentrations at or above 200 ppb, and only one area had any days (*i.e.*, one day) with 1-hour concentrations at or above 150 ppb.

- One-hour ambient NO<sub>2</sub> concentrations in study areas, including those near major roadways, only rarely reached or exceeded 100 ppb. On average in all study areas, 1-hour NO<sub>2</sub> concentrations at or above 100 ppb occurred on less than one day per year.

<sup>82</sup> Benchmarks from the upper end of this range are supported by the results of individual studies, the majority of which most consistently reported statistically significant increases in AR following NO<sub>2</sub> exposures at or above 250 ppb, and by the results of the meta-analysis by Brown (2015). Benchmarks from the lower end of this range are supported by the results of the meta-analysis, even though individual studies generally do not report statistically significant NO<sub>2</sub>-induced increases in AR following exposures below 200 ppb.

<sup>83</sup> As discussed in the PA (U.S. EPA, 2017a, Section 4.2.1), in all study areas, ambient NO<sub>2</sub> concentrations required smaller upward adjustments to just meet the 1-hour standard than to just meet the annual standard. Therefore, when adjusting air quality to just meet the current NO<sub>2</sub> NAAQS, the adjustment needed to just meet the 1-hour standard was applied.

- Even in the worst-case years, most study areas had either zero or one day with 1-hour NO<sub>2</sub> concentrations at or above 100 ppb (7 days in the single worst-case location and worst-case year).

For air quality adjusted to just meet the current primary 1-hour NO<sub>2</sub> standard:

- The current standard is estimated to allow no days in study areas with 1-hour ambient NO<sub>2</sub> concentrations at or above 200 ppb. This is true for both area-wide and near-road monitoring sites, even in the worst-case years.

- The current standard is estimated to allow almost no days with 1-hour ambient NO<sub>2</sub> concentrations at or above 150 ppb, based on both area-wide and near-road monitoring sites (*i.e.*, zero to one day per year, on average).

- In the worst-case years in most study areas, the current standard is estimated to allow either zero or one day with 1-hour ambient NO<sub>2</sub> concentrations at or above 150 ppb. In the single worst-case year and location, the current standard is estimated to allow eight such days.

- At area-wide monitoring sites in most of the study areas, the current standard is estimated to allow from one to seven days per year, on average, with 1-hour ambient NO<sub>2</sub> concentrations at or above 100 ppb. At near-road monitoring sites in most of the study areas, the current standard is estimated to allow from about one to 10 days per year with such 1-hour concentrations.

- In the worst-case years in most of the study areas, the current standard is estimated to allow from about 5 to 20 days with 1-hour NO<sub>2</sub> concentrations at or above 100 ppb (30 days in the single worst-case location and year).

## 3. Uncertainties

There are a variety of limitations and uncertainties in these comparisons of NO<sub>2</sub> air quality with health-based benchmarks. In particular, there are uncertainties in the evidence underlying the benchmarks themselves, as well as uncertainties in the upward adjustment of NO<sub>2</sub> air quality concentrations, and uncertainty in the degree to which monitored NO<sub>2</sub> concentrations reflect the highest potential NO<sub>2</sub> concentrations. Each of these is discussed below.

### a. Health-Based Benchmarks

The primary goal of this analysis is to inform conclusions regarding the potential for the existing primary NO<sub>2</sub> standards to allow exposures to ambient NO<sub>2</sub> concentrations that may be of concern for public health. As discussed in detail above (Sections II.C.1), the

meta-analysis by Brown (2015) indicates the potential for increased AR in some people with asthma following NO<sub>2</sub> exposures from 100 to 530 ppb. While it is possible that certain individuals could be more severely affected by NO<sub>2</sub> exposures than indicated by existing studies, which have generally evaluated adults with mild asthma,<sup>84</sup> there remains uncertainty in the degree to which the effects identified in these studies would be of public health concern. In particular, both the lack of an apparent dose-response relationship between NO<sub>2</sub> exposure and AR and the uncertainties in the magnitude and potential adversity of the increase in AR following NO<sub>2</sub> exposures complicate the interpretation of comparisons between ambient NO<sub>2</sub> concentrations and health-based benchmarks. When considered in the context of the less consistent results observed across individual studies following exposures to 100 ppb NO<sub>2</sub>, in comparison to the more consistent results at higher exposure concentrations,<sup>85</sup> these uncertainties have the potential to be of particular importance for interpreting the public health implications of ambient NO<sub>2</sub> concentrations at or above the 100 ppb benchmark.<sup>86</sup>

With regard to the magnitude and clinical relevance of the NO<sub>2</sub>-induced increase in AR in particular, the meta-analysis by Brown (2015) attempts to address this uncertainty and inconsistency across individual studies. Specifically, as discussed above (Section II.C.1), the meta-analysis evaluates the available individual-level data on the magnitude of the change in AR following resting NO<sub>2</sub> exposures. Brown (2015) reports that the magnitude of the increases in AR observed following resting NO<sub>2</sub> exposures from 100 to 530 ppb were large enough to be of potential clinical relevance in about a quarter of the 72 study volunteers with available data. This is based on the fraction of exposed individuals who

<sup>84</sup> Brown (2015, p. 3) notes, however, that one study included in the meta-analysis (Avol et al., 1989) evaluated children aged 8 to 16 years and that disease status varied across studies, ranging from “inactive asthma up to severe asthma in a few studies.”

<sup>85</sup> As discussed previously, while the meta-analysis indicates that the majority of study volunteers experienced increased non-specific AR following exposures to 100 ppb NO<sub>2</sub>, results were marginally significant when specific AR was also included in the analysis. In addition, individual studies do not consistently indicate increases in AR following exposures to 100 ppb NO<sub>2</sub>.

<sup>86</sup> Sensitivity analyses included in Appendix B of the PA (U.S. EPA, 2017a, Section 3.2, table B3–1) also evaluated 1-hour NO<sub>2</sub> benchmarks below 100 ppb (*i.e.*, 85, 90, 95 ppb), though the available health evidence does not provide a clear basis for determining what exposures to such NO<sub>2</sub> concentrations might mean for public health.

experienced a halving of the provocative dose of challenge agent following NO<sub>2</sub> exposures. This magnitude of change has been recognized by the American Thoracic Society (ATS) and the European Respiratory Society as a “potential indicator, although not a validated estimate, of clinically relevant changes in [AR]” (Reddel et al., 2009) (U.S. EPA, 2016a, p. 5–12). Although there is uncertainty in using this approach to characterize whether a particular response in an individual is “adverse,” it can provide insight into the potential for adversity, particularly when applied to a population of exposed individuals. While this analysis by Brown (2015) indicates the potential for some people with asthma to experience effects of clinical relevance following resting NO<sub>2</sub> exposures from 100 to 530 ppb, it is based on a relatively small subset of volunteers and the interpretation of these results for any specific exposure concentration within the range of 100 to 530 ppb is uncertain (see section II.C.1, above).

#### b. Approach to Adjusting Ambient NO<sub>2</sub> Concentrations

These analyses use historical air quality relationships as the basis for adjusting ambient NO<sub>2</sub> concentrations to just meet the current 1-hour standard (U.S. EPA, 2017a, Appendix B). The adjusted air quality is meant to illustrate a hypothetical scenario, and does not represent expectations regarding future air quality trends. If ambient NO<sub>2</sub> concentrations were to increase in some locations to the point of just meeting the current standards, it is not clear that the spatial and temporal relationships reflected in the historical data would persist. In particular, as discussed in Section 2.1.2 of the PA (U.S. EPA, 2017a), ongoing implementation of existing regulations is expected to result in continued reductions in ambient NO<sub>2</sub> concentrations over much of the U.S. (*i.e.*, reductions beyond the “unadjusted” air quality used in these analyses). Thus, if ambient NO<sub>2</sub> concentrations were to increase to the point of just meeting the existing 1-hour NO<sub>2</sub> standard in some areas, the resulting air quality patterns may not be similar to those estimated in the PA’s air quality adjustments.

There is also uncertainty in the upward adjustment of NO<sub>2</sub> air quality because three years of data are not yet available from most near-road monitors. In most study areas, estimated DVs were not calculated at near-road monitors and, therefore, near-road monitors were generally not used as the basis for identifying adjustment factors for just

meeting the existing standard.<sup>87</sup> In locations where near-road monitors measure the highest NO<sub>2</sub> DVs, reliance on those near-road monitors to identify air quality adjustment factors would result in smaller adjustments being applied to monitors in the study area. Thus, monitors in such study areas would be adjusted upward by smaller increments, potentially reducing the number of days on which the current standard is estimated to allow 1-hour NO<sub>2</sub> concentrations at or above benchmarks. Given that near-road monitors in most areas measure higher 1-hour NO<sub>2</sub> concentrations than the area-wide monitors in the same CBSA (U.S. EPA, 2017a, Figures 2–7 to 2–10), this uncertainty has the potential to impact results in many of the study areas. While the magnitude of the impact is unknown at present, the inclusion of additional years of near-road monitoring information in the determination of air quality adjustments could result in fewer estimated 1-hour NO<sub>2</sub> concentrations at or above benchmarks in some study areas.

#### c. Degree to Which Monitored NO<sub>2</sub> Concentrations Reflect the Highest Potential NO<sub>2</sub> Exposures

To the extent there are unmonitored locations where ambient NO<sub>2</sub> concentrations exceed those measured by monitors in the current network, the potential for NO<sub>2</sub> exposures at or above benchmarks could be underestimated. In the last review, this uncertainty was determined to be particularly important for potential exposures around roads. The 2008 REA estimated that the large majority of modeled exposures to ambient NO<sub>2</sub> concentrations at or above benchmarks occurred on or near roads (U.S. EPA, 2008b, Figures 8–17 and 8–18). When characterizing ambient NO<sub>2</sub> concentrations, the 2008 REA attempted to address this uncertainty by estimating the elevated NO<sub>2</sub> concentrations that can occur on or near the road. These estimates were generated by applying literature-derived adjustment factors to NO<sub>2</sub> concentrations at monitoring sites located away from the road.<sup>88</sup>

<sup>87</sup> Though in a few study locations, near-road monitors did contribute to the calculation of air quality adjustments, as described in Appendix B of the PA (U.S. EPA, 2017a, Table B2–7).

<sup>88</sup> Sensitivity analyses included in Appendix B of the PA use updated data from the scientific literature (Richmond-Bryant et al., 2016) to estimate “on-road” NO<sub>2</sub> concentrations based on monitored concentrations around a roadway in Las Vegas (Appendix B, Section B2.4.2). However, there remains considerable uncertainty in the relationship between on-road and near-road NO<sub>2</sub> concentrations, and in the degree to which they may differ. Therefore, in evaluating the potential for roadway-associated NO<sub>2</sub> exposures, the PA focuses

on the concentrations at locations of near-road monitors (U.S. EPA, 2017a, Chapter 4).

In the current review, given that the 23 selected study areas have among the highest NO<sub>x</sub> emissions in the U.S., and given the siting characteristics of existing NO<sub>2</sub> monitors, this uncertainty likely has only a limited impact on the results of the air quality-benchmark comparisons. In particular, as described above, mobile sources tend to dominate NO<sub>x</sub> emissions within most CBSAs, and the 23 study areas evaluated have among the highest mobile source NO<sub>x</sub> emissions in the U.S. (U.S. EPA, 2017a, Appendix B, Section B2.3.2). Most study areas have near-road NO<sub>2</sub> monitors in operation, which are required within 50 m of the most heavily trafficked roadways in large urban areas. The majority of these near-road monitors are sited within 30 m of the road, and several are sited within 10 m (see Atlanta, Cincinnati, Denver, Detroit, Los Angeles in EPA’s database of metadata for near-road monitors<sup>89</sup>). Thus, as explained in the PA, even though the location of highest NO<sub>2</sub> concentrations around roads can vary (U.S. EPA, 2017a, Section 2.1), the near-road NO<sub>2</sub> monitoring network, with monitors sited from 2 to 50 m away from heavily trafficked roads, are likely to effectively capture the types of locations around roads where the highest NO<sub>2</sub> concentrations can occur.<sup>90</sup>

This conclusion is consistent with the ISA’s analysis of available data from near-road NO<sub>2</sub> monitors, which indicates that near-road monitors with target roads having the highest traffic counts also had among the highest 98th percentiles of 1-hour daily maximum NO<sub>2</sub> concentrations (U.S. EPA, 2016a, Section 2.5.3.2). The ISA concludes that “[o]verall, the very highest 98th percentile 1-hour maximum concentrations were generally observed at the monitors adjacent to roads with the highest traffic counts” (U.S. EPA, 2016a, p. 2–66).

It is also important to consider the degree to which air quality-benchmark comparisons appropriately characterize the potential for NO<sub>2</sub> exposures near non-roadway sources of NO<sub>x</sub> emissions. As noted in the PA, the 23 selected study areas include CBSAs with large non-roadway sources of NO<sub>x</sub> emissions. This includes study areas with among the highest NO<sub>x</sub> emissions from electric

on the concentrations at locations of near-road monitors (U.S. EPA, 2017a, Chapter 4).

<sup>89</sup> This database is found at <http://www3.epa.gov/ttn/amtic/nearroad.html>.

<sup>90</sup> However, it remains possible that some areas (*e.g.*, street canyons in urban environments) could have higher ambient NO<sub>2</sub> concentrations than indicated by near-road monitors. Sensitivity analyses estimating the potential for on-road NO<sub>2</sub> exposures are described in Appendix B of the PA (U.S. EPA, 2017a).

power generation facilities (EGUs) and airports, the two types of non-roadway sources that emit the most NO<sub>x</sub> in the U.S. (U.S. EPA, 2017a, Appendix B, Section B2.3.2). As discussed below, several study areas have non-near-road NO<sub>2</sub> monitors sited to determine the impacts of such sources.

Table 2-12 in the ISA (U.S. EPA, 2016a) summarizes NO<sub>2</sub> concentrations at selected monitoring sites that are likely to be influenced by non-road sources, including ports, airports, border crossings, petroleum refining, or oil and gas drilling. For example, the Los Angeles, CA CBSA includes one of the busiest ports and one of the busiest airports in the U.S. Out of 18 monitors in the Los Angeles CBSA, three of the five highest 98th percentile 1-hour maximum concentrations were observed at the near-road site, the site nearest the port, and the site adjacent to the airport (U.S. EPA, 2016a, section 2.5.3.2). In the Chicago, IL CBSA, the highest hourly NO<sub>2</sub> concentration measured in 2014 (105 ppb) occurred at the Schiller Park, IL monitoring site, located adjacent to O'Hare International airport, a four-lane arterial (U.S. 12 and U.S. 45), and very close to a major rail yard (*i.e.*, Bedford Park Rail Yard) (U.S. EPA, 2016a, Section 2.5.3.2).<sup>91</sup> In addition, one of the highest 1-hour daily maximum NO<sub>2</sub> concentrations recorded in recent years (136 ppb) was observed at a Denver, CO non-near-road site. This concentration was observed at a monitor located one block from high-rise buildings that form the edge of the high-density central business district. This monitor is likely influenced by local traffic, as well as by commercial heating and other activities (U.S. EPA, 2016a, Section 2.5.3.2).<sup>92</sup> Thus, beyond the NO<sub>2</sub> near-road monitors, some NO<sub>2</sub> monitors in study areas are also sited to capture high ambient NO<sub>2</sub> concentrations around important non-roadway sources of NO<sub>x</sub> emissions.

#### 4. Conclusions

As discussed above and in the REA Planning document (U.S. EPA, 2015, Section 2.1.1), an important uncertainty identified in the 2008 REA was the characterization of 1-hour NO<sub>2</sub> concentrations around major roadways. In the current review, data from recently

<sup>91</sup> Sections B5.1 and B5.2 of Appendix B in the PA (U.S. EPA, 2017a) provide data on the large sources of NO<sub>x</sub> emissions in study areas.

<sup>92</sup> Recent traffic counts on the nearest streets were 44,850 (in 2014) and 23,389 (in 2013) vehicles per day, respectively. Traffic counts on other streets within one block of this monitor were 22,000, 13,000, 5,000, and 2,490 vehicles per day. Together, this adds up to more than 100,000 vehicles per day on streets within one block of this non-near-road monitor (U.S. EPA, 2016A, Section 2.5.3.2).

deployed near-road NO<sub>2</sub> monitors improves understanding of such ambient NO<sub>2</sub> concentrations.

As discussed in Section II.B.2, recent NO<sub>2</sub> concentrations measured in all U.S. locations meet the existing primary NO<sub>2</sub> NAAQS. Based on these recent (*i.e.*, unadjusted) ambient measurements, analyses estimate almost no potential for 1-hour exposures to NO<sub>2</sub> concentrations at or above benchmarks, even at the lowest benchmark examined (*i.e.*, 100 ppb).

Analyses of air quality adjusted upwards to just meet the current 1-hour standard estimate no days with 1-hour NO<sub>2</sub> concentrations at or above the 200 ppb benchmark, and virtually none for exposures at or above 150 ppb. This is the case for both average and worst-case years, including in study areas with near-road monitors sited within a few meters of heavily trafficked roads. With respect to the lowest benchmark evaluated, analyses estimate that the current 1-hour standard allows the potential for exposures to 1-hour NO<sub>2</sub> concentrations at or above 100 ppb on some days (*e.g.*, in most study areas, about one to 10 days per year, on average).<sup>93</sup>

These results are consistent with expectations, given that the current 1-hour standard, with its 98th percentile form, is anticipated to limit, but not eliminate, exposures to 1-hour NO<sub>2</sub> concentrations at or above 100 ppb.<sup>94</sup> These results are similar to the results presented in the REA from the last review, based on NO<sub>2</sub> concentrations at the locations of area-wide ambient monitors (U.S. EPA, 2017a, Appendix B, Section B5.9, Table B5-66). In contrast, compared to the on/near road simulations in the last review, these results indicate substantially less potential for 1-hour exposures to NO<sub>2</sub> concentrations at or above these benchmarks (U.S. EPA, 2017a, Appendix B, Section B5.9, Table B5-66).<sup>95</sup>

When these results and associated uncertainties are taken together, the current 1-hour NO<sub>2</sub> standard is expected to allow virtually no potential for

<sup>93</sup> Because the results show almost no days with 1-hour ambient NO<sub>2</sub> concentrations above 150 ppb, the results for the 100 ppb benchmark are due primarily to 1-hour NO<sub>2</sub> concentrations that are closer to 100 ppb than 200 ppb.

<sup>94</sup> The 98th percentile generally corresponds to the 7th or 8th highest 1-hour concentration in a year.

<sup>95</sup> On-/near-road simulations in the last review estimated that a 1-hour NO<sub>2</sub> standard with a 98th percentile form and a 100 ppb level could allow about 20 to 70 days per year with 1-hour NO<sub>2</sub> concentrations at or above the 200 ppb benchmark and about 50 to 150 days per year with 1-hour concentrations at or above the 100 ppb benchmark (U.S. EPA, 2017a, Appendix B, Table B5-56).

exposures to the NO<sub>2</sub> concentrations that have been shown most consistently to increase AR in people with asthma (*i.e.*, above 200 ppb), even under worst-case conditions across a variety of study areas with among the highest NO<sub>x</sub> emissions in the U.S. Such NO<sub>2</sub> concentrations were not estimated to occur, even at monitoring sites adjacent to some of the most heavily trafficked roadways. In addition, the current standard is expected to limit, though not eliminate, exposures to 1-hour concentrations at or above 100 ppb. Though the current standard is estimated to allow 1-hour NO<sub>2</sub> concentrations at or above 100 ppb on some days, there is uncertainty regarding the potential public health implications of exposures to 100 ppb NO<sub>2</sub>. However, in limiting exposures to NO<sub>2</sub> concentrations at or above 100 ppb, the current standard provides protection against exposures to higher NO<sub>2</sub> concentrations, for which the evidence of adverse NO<sub>2</sub>-attributable effects is more certain, as well as against exposures to NO<sub>2</sub> concentrations at 100 ppb, for which the evidence of adverse NO<sub>2</sub>-attributable effects is less certain.

Given the results of these analyses, and the uncertainties inherent in their interpretation, the PA concludes that there is little potential for exposures to ambient NO<sub>2</sub> concentrations that would be of clear public health concern in locations meeting the current 1-hour standard. Additionally, while a lower standard level (*i.e.*, lower than 100 ppb) would be expected to further limit the potential for exposures to 100 ppb NO<sub>2</sub>, the public health implications of such reductions are unclear, particularly given that no additional protection would be expected against exposures to NO<sub>2</sub> concentrations at or above the higher benchmarks (*i.e.*, 200 ppb and above). Thus, the PA concludes that these analyses comparing ambient NO<sub>2</sub> concentrations to health-based benchmarks do not provide support for considering potential alternative standards to increase public health protection, beyond the protection provided by the current standards.

#### E. Summary of CASAC Advice

In the current review of the primary NO<sub>2</sub> standards the CASAC has provided advice and recommendations based on its review of drafts of the ISA (Diez Roux and Frey, 2015a), of the REA Planning document (Diez Roux and Frey, 2015b), and of the draft PA (Diez Roux and Sheppard, 2017). This section summarizes key CASAC advice regarding the strength of the evidence for respiratory effects, the quantitative analyses conducted and presented in

the PA, and the adequacy of the current primary NO<sub>2</sub> standards to protect the public health.

Briefly, with regard to the strength of the evidence for respiratory effects, the CASAC agreed with the ISA conclusions. In particular, the CASAC concurred “with the finding that short-term exposures to NO<sub>2</sub> are causal for respiratory effects based on evidence for asthma exacerbation” (Diez Roux and Sheppard 2017, p. 7). It further noted that “[t]he strongest evidence is for an increase in airway responsiveness based on controlled human exposure studies, with supporting evidence from epidemiologic studies” (Diez Roux and Sheppard 2017, p. 7). The CASAC also agreed with the ISA conclusions on long-term exposures and respiratory effects, specifically stating the following (Diez Roux and Sheppard 2017, p. 7):

Long-term exposures to NO<sub>2</sub> are likely to be causal for respiratory effects, based on asthma development. The strongest evidence is for asthma incidence in children in epidemiologic studies, with supporting evidence from experimental animal studies. Current scientific evidence for respiratory effects related to long-term exposures is stronger since the last review, although uncertainties remain related to the influence of copollutants on the association between NO<sub>2</sub> and asthma incidence.

With regard to support for the updated quantitative analyses conducted in the current review, the CASAC agreed with the conclusions in the PA.<sup>96</sup> In particular, the CASAC noted that it was “satisfied with the short-term exposure health-based benchmark analysis presented in the Draft PA and agree[d] with the decision to not conduct any new model-based or epidemiologic-based analyses” (Diez Roux and Sheppard, 2017, p. 5). The CASAC further supported “the decision not to conduct any new or updated quantitative risk analyses related to long-term exposure to NO<sub>2</sub>” noting “that existing uncertainties in the epidemiologic literature limit the ability to properly estimate and interpret population risk associated with NO<sub>2</sub>, specifically within a formal risk assessment framework” (Diez Roux and Sheppard, 2017, p. 5).

In addition, in its review of the draft PA, the CASAC concurred with staff’s overall preliminary conclusions that it is appropriate to consider retaining the current primary NO<sub>2</sub> standards without revision, stating that, “the CASAC recommends retaining, and not changing the existing suite of

standards” (Diez Roux and Sheppard, 2017). The CASAC’s advice on the current standards is discussed in more detail below (Section II.F.3).

#### *F. Proposed Conclusions on the Adequacy of the Current Primary NO<sub>2</sub> Standards*

In evaluating whether, in view of the advances in scientific knowledge and additional information now available, it is appropriate to retain or revise the current primary NO<sub>2</sub> standards, the Administrator builds upon the last review and reflects upon the body of evidence and information now available. The Administrator has taken into account evidence-based and quantitative exposure- and risk-based considerations, as well as advice from the CASAC, and his own public health policy judgements in developing proposed conclusions on the adequacy of the current primary NO<sub>2</sub> standards. Evidence-based considerations draw upon the ISA’s assessment and integrated synthesis of the scientific evidence from epidemiologic studies, controlled human exposure studies, and experimental animal studies evaluating health effects related to exposures to NO<sub>2</sub>, with a focus on policy-relevant considerations. The exposure-/risk-based considerations draw from the comparisons of NO<sub>2</sub> air quality with health-based benchmarks presented in the PA. Together with careful consideration of advice from CASAC, these evidence-based and exposure-/risk-based considerations have informed the Administrator’s proposed conclusions related to the adequacy of the current NO<sub>2</sub> standards.

The following sections summarize these evidence-based (Section II.F.1) and exposure-/risk-based (Section II.F.2) considerations and the advice received from CASAC (Section II.F.3). Section II.F.4 presents the Administrator’s proposed conclusions regarding the adequacy of the current primary NO<sub>2</sub> standards.

##### 1. Evidence-Based Considerations

As discussed in Section II.C, in considering the evidence available in the current review with regard to adequacy of the current 1-hour and annual NO<sub>2</sub> standards, the first topic of consideration is the nature of the health effects attributable to NO<sub>2</sub> exposures, drawing upon the integrated synthesis of the health evidence in the ISA and the evaluations in the PA (Sections II.C.1 and II.C.2). The following questions guide those considerations: (1) To what extent does the currently available scientific evidence alter or strengthen conclusions from the last

review regarding health effects attributable to ambient NO<sub>2</sub> exposures? (2) Are previously identified uncertainties reduced or do important uncertainties remain? (3) Have new uncertainties been identified? These questions are addressed for both short-term and long-term NO<sub>2</sub> exposures, with a focus on health endpoints for which the ISA concludes that the evidence indicates there is a “causal” or “likely to be a causal” relationship.

With regard to short-term NO<sub>2</sub> exposures, as in the last review, the strongest evidence continues to come from studies examining respiratory effects. In particular, the ISA concludes that evidence indicates a “causal” relationship between short-term NO<sub>2</sub> exposure and respiratory effects, based on evidence related to asthma exacerbation. While this conclusion reflects a strengthening of the causal determination, compared to the last review, this strengthening is based largely on a more specific integration of the evidence related to asthma exacerbations rather than on the availability of new, stronger evidence. Additional evidence has become available since the last review, as summarized below; however, this evidence has not fundamentally altered the understanding of the relationship between short-term NO<sub>2</sub> exposures and respiratory effects.

The strongest evidence supporting this ISA causal determination comes from controlled human exposure studies demonstrating NO<sub>2</sub>-induced increases in AR in individuals with asthma. A meta-analysis of data from these studies indicates the majority of exposed individuals, generally with mild asthma, experienced increased AR following exposures to NO<sub>2</sub> concentrations as low as 100 ppb, while individual studies most consistently report such increases following exposures to NO<sub>2</sub> concentrations at or above 250 ppb. Most of the controlled human exposure studies assessed in the ISA were available in the last review, particularly studies of non-specific AR. As in the last review, there remains uncertainty due to the lack of an apparent dose-response relationship between NO<sub>2</sub> exposures and AR and uncertainty in the potential adversity of NO<sub>2</sub>-induced increases in AR.

Supporting evidence for a range of NO<sub>2</sub>-associated respiratory effects also comes from epidemiologic studies. While some recent epidemiologic studies provide new evidence based on improved exposure characterizations and copollutant modeling, these studies are consistent with the evidence from the last review and do not

<sup>96</sup> The PA conclusions build upon the preliminary conclusions presented in the REA Planning document, which was also reviewed by the CASAC (Diez Roux and Frey, 2015b).

fundamentally alter the understanding of the respiratory effects associated with ambient NO<sub>2</sub> exposures. Due to limitations in the available epidemiologic methods, uncertainty remains in the current review regarding the extent to which findings for NO<sub>2</sub> are confounded by traffic-related copollutants (e.g., PM<sub>2.5</sub>, EC/BC, CO).

Thus, while some new evidence is available in this review, that new evidence has not substantially altered the understanding of the respiratory effects that occur following short-term NO<sub>2</sub> exposures. This evidence is summarized in Section II.C.1 above, and is discussed in detail in the ISA (U.S. EPA, 2016a, section 5.2.2).

With regard to long-term NO<sub>2</sub> exposures, the ISA concludes that there is “likely to be a causal relationship” between long-term NO<sub>2</sub> exposure and respiratory effects, based largely on the evidence for asthma development in children. New epidemiologic studies of asthma development have increasingly utilized improved exposure assessment methods (i.e., measured or modeled concentrations at or near children’s homes and followed for many years), which partly reduces uncertainties from the last review related to exposure measurement error. Explicit integration of evidence for individual outcome categories (e.g., asthma incidence, respiratory infection) provides an improved characterization of biological plausibility and mode of action. This improved characterization includes the assessment of new evidence supporting a potential role for repeated short-term NO<sub>2</sub> exposures in the development of asthma. High correlations between long-term average ambient concentrations of NO<sub>2</sub> and long-term concentrations of other traffic-related pollutants, together with the general lack of epidemiologic studies evaluating copollutant models that include traffic-related pollutants, remains a concern in interpreting associations with asthma development. Specifically, the extent to which NO<sub>2</sub> may be serving primarily as a surrogate for the broader traffic-related pollutant mix remains unclear. Thus, while the evidence for respiratory effects related to long-term NO<sub>2</sub> exposures has become stronger since the last review, there remain important uncertainties to consider in evaluating this evidence within the context of the adequacy of the current standards. This evidence is summarized in Section II.C.2 above, and is discussed in detail in the ISA (U.S. EPA, 2016a, section 6.2.2).

Given the evaluation of the evidence in the ISA, and the ISA’s causal determinations, the EPA’s further consideration of the evidence focuses on

studies of asthma exacerbation (short-term exposures) and asthma development (long-term exposures), and on what these bodies of evidence indicate with regard to the basic elements of the current primary NO<sub>2</sub> standards. In particular, the EPA considers the following question: To what extent does the available evidence for respiratory effects attributable to either short- or long-term NO<sub>2</sub> exposures support or call into question the basic elements of the current primary NO<sub>2</sub> standards? In addressing this question, the sections below summarize the PA’s consideration of the evidence in the context of the indicator, averaging times, levels, and forms of the current standards.

#### a. Indicator

The indicator for both the current annual and 1-hour NAAQS for oxides of nitrogen is NO<sub>2</sub>. While the presence of gaseous species other than NO<sub>2</sub> has long been recognized (discussed in Section II.B.1, above), no alternative to NO<sub>2</sub> has been advanced as being a more appropriate surrogate for ambient gaseous oxides of nitrogen. Both previous and recent controlled human exposure studies and animal toxicology studies provide specific evidence for health effects following exposure to NO<sub>2</sub>. Similarly, the large majority of epidemiologic studies report health effect associations with NO<sub>2</sub>, as opposed to other gaseous oxides of nitrogen. In addition, because emissions that lead to the formation of NO<sub>2</sub> generally also lead to the formation of other NO<sub>x</sub> oxidation products, measures leading to reductions in population exposures to NO<sub>2</sub> can generally be expected to lead to reductions in population exposures to other gaseous oxides of nitrogen. Therefore, an NO<sub>2</sub> standard can also be expected to provide some degree of protection against potential health effects that may be independently associated with other gaseous oxides of nitrogen even though such effects are not discernable from currently available studies. Given these considerations, the PA reached the conclusion that it is appropriate in the current review to consider retaining the NO<sub>2</sub> indicator for standards meant to protect against exposures to gaseous oxides of nitrogen. In its review of the draft PA, CASAC agreed with this conclusion (Diez Roux and Sheppard, 2017).

#### b. Averaging Time

The current primary NO<sub>2</sub> standards are based on 1-hour and annual averaging times. Together, these standards can provide protection against short- and long-term NO<sub>2</sub> exposures.

In establishing the 1-hour standard in the last review, the Administrator considered evidence from both experimental and epidemiologic studies. She noted that controlled human exposure studies and animal toxicological studies provided evidence that NO<sub>2</sub> exposures from less than one hour up to three hours can result in respiratory effects such as increased AR and inflammation. These included five controlled human exposure studies that evaluated the potential for increased AR following 1-hour exposures to 100 ppb NO<sub>2</sub> in people with asthma. In addition, epidemiologic studies had reported health effect associations with both 1-hour and 24-hour NO<sub>2</sub> concentrations, without indicating that either of these averaging periods was more closely linked with reported effects. Thus, the available experimental evidence provided support for considering an averaging time of shorter duration than 24 hours while the epidemiologic evidence provided support for considering both 1-hour and 24-hour averaging times. Given this evidence, the Administrator concluded that, at a minimum, a primary concern with regard to averaging time was the level of protection provided against 1-hour NO<sub>2</sub> exposures. Based on available analyses of NO<sub>2</sub> air quality, she further concluded that a standard with a 1-hour averaging time could also be effective at protecting against effects associated with 24-hour NO<sub>2</sub> exposures (75 FR 6502, February 9, 2010).

Based on the considerations summarized above, the Administrator judged in the last review that it was appropriate to set a new NO<sub>2</sub> standard with a 1-hour averaging time. She concluded that such a standard would be expected to effectively limit short-term (e.g., 1- to 24-hours) NO<sub>2</sub> exposures that had been linked to adverse respiratory effects. She also retained the existing annual standard to continue to provide protection against effects potentially associated with long-term exposures to oxides of nitrogen (75 FR 6502, February 9, 2010). These decisions were consistent with CASAC advice to establish a short-term primary standard for oxides of nitrogen based on using 1-hour maximum NO<sub>2</sub> concentrations and to retain the current annual standard (Samet, 2008, p. 2; Samet, 2009, p. 2).

As in the last review, support for a standard with a 1-hour averaging time comes from both the experimental and epidemiologic evidence. Controlled human exposure studies evaluated in the ISA continue to provide evidence that NO<sub>2</sub> exposures from less than 1-hour up to three hours can result in

increased AR in individuals with asthma (U.S. EPA, 2016a, Tables 5–1 and 5–2). These controlled human exposure studies provide key evidence supporting the ISA’s determination that “[a] causal relationship exists between short-term NO<sub>2</sub> exposure and respiratory effects based on evidence for asthma exacerbation” (U.S. EPA, 2016a, p. 1–17). In addition, the epidemiologic literature assessed in the ISA provides support for short-term averaging times ranging from 1-hour up to 24-hours (e.g., U.S. EPA, 2016a Figures 5–3, 5–4 and Table 5–12). Consistent with the evidence in the last review, the ISA concludes that there is no indication of a stronger association for any particular short-term duration of NO<sub>2</sub> exposure (U.S. EPA, 2016a, section 1.6.1). Thus, a 1-hour averaging time reasonably reflects the exposure durations used in the controlled human exposure studies that provide the strongest support for the ISA’s determination of a causal relationship. In addition, a standard with a 1-hour averaging time is expected to provide protection against the range of short-term exposure durations that have been associated with respiratory effects in epidemiologic studies (i.e., 1-hour to 24-hours). In the PA, staff reached the conclusion that when taken together, the combined evidence from experimental and epidemiologic studies continues to support an NO<sub>2</sub> standard with a 1-hour averaging time to protect against health effects related to short-term NO<sub>2</sub> exposures. In its review of the draft PA, the CASAC found that there continued to be scientific support for the 1-hour averaging time (Diez Roux and Sheppard, 2017, p. 7).

With regard to protecting against long-term exposures, the evidence supports considering the overall protection provided by the combination of the annual and 1-hour standards. The current annual standard was originally promulgated in 1971 (36 FR 8186, April 30, 1971), based on epidemiologic studies reporting associations between respiratory disease and long-term exposure to NO<sub>2</sub>. The annual standard was retained in subsequent reviews, in part to provide a margin of safety against the serious effects reported in animal studies using long-term exposures to high NO<sub>2</sub> concentrations (e.g., above 8,000 ppb) (U.S. EPA, 1995).

As described above, evidence newly available in the current review demonstrates associations between long-term NO<sub>2</sub> exposures and asthma development in children, based on NO<sub>2</sub> concentrations averaged over year of birth, year of diagnosis, or entire lifetime. Supporting evidence indicates that repeated short-term NO<sub>2</sub> exposures

could contribute to this asthma development. In particular, the ISA states that “findings for short-term NO<sub>2</sub> exposure support an effect on asthma development by describing a potential role for repeated exposures to lead to recurrent inflammation and allergic responses,” which are “identified as key early events in the proposed mode of action for asthma development” (U.S. EPA, 2016a, p. 6–64 and p. 6–65). Taken together, the evidence supports the potential for recurrent short-term NO<sub>2</sub> exposures to contribute to the asthma development that has been reported in epidemiologic studies to be associated with long-term exposures. For these reasons, the PA reached the conclusion that, in establishing standards to protect against adverse health effects related to long-term NO<sub>2</sub> exposures, the evidence supports the consideration of both 1-hour and annual averaging times. In its review of the draft PA, CASAC supported this approach to considering the protection provided against long-term NO<sub>2</sub> exposures by considering the combination of the annual and 1-hour NO<sub>2</sub> standards. With reference to the current annual standard, CASAC specifically noted that “it is the suite of the current 1-hour and annual standards, together, that provide protection against adverse effects” (Diez Roux and Sheppard, 2017, p. 9).

#### c. Level and Form

In evaluating the extent to which evidence supports or calls into question the levels or forms of the current NO<sub>2</sub> standards, the EPA considers the following question: To what extent does the evidence indicate adverse respiratory effects attributable to short- or long-term NO<sub>2</sub> exposures lower than previously identified or below the existing standards? In addressing this question, it is useful to consider the range of NO<sub>2</sub> exposure concentrations that have been evaluated in experimental studies (controlled human exposure and animal toxicology) and the ambient NO<sub>2</sub> concentrations in locations where epidemiologic studies have reported associations with adverse outcomes. The PA’s consideration of these issues is discussed below for short-term (II.F.1.c.i) and long-term (II.F.1.c.ii) NO<sub>2</sub> exposures.

##### i. Short-Term

Controlled human exposure studies demonstrate the potential for increased AR in some people with asthma following 30-minute to 1-hour exposures to NO<sub>2</sub> concentrations near those in the ambient air (U.S. EPA,

2017a, Section 3.2.2).<sup>97</sup> In evaluating the NO<sub>2</sub> exposure concentrations at which increased AR has been observed, both the group mean results reported in individual studies and the results from a recent meta-analysis evaluating individual-level data are considered (Brown, 2015; U.S. EPA, 2016a, Section 5.2.2.1). Group mean responses in individual studies, and the variability in those responses, can provide insight into the extent to which observed changes in AR are due to NO<sub>2</sub> exposures, rather than to chance alone, and have the advantage of being based on the same exposure conditions. The meta-analysis can aid in identifying trends in individual-level responses across studies and can have the advantage of increased power to detect effects, even in the absence of statistically significant effects in individual studies.

When individual-level data were combined in a meta-analysis, Brown (2015) reported that statistically significant majorities of study participants experienced increased AR following resting exposures to NO<sub>2</sub> concentrations from 100 to 530 ppb. In some affected individuals, the magnitudes of these increases were large enough to have potential clinical relevance. Following exposures to 100 ppb NO<sub>2</sub> specifically, the lowest exposure concentration evaluated, a marginally statistically significant majority of study participants experienced increased AR.<sup>98</sup> As discussed in more detail in Section II.C.1, individual studies consistently report statistically significant NO<sub>2</sub>-induced increases in AR following resting exposures to NO<sub>2</sub> concentrations at or above 250 ppb, but have generally not reported statistically significant increases in AR following resting exposures to NO<sub>2</sub> concentrations from 100 to 200 ppb. Limitations in this evidence include the lack of an apparent dose-response relationship between NO<sub>2</sub> and AR and remaining uncertainty in the adversity of the reported increases in AR. These uncertainties become increasingly important at the lower NO<sub>2</sub>

<sup>97</sup> As discussed in Section II.C, experimental studies have not reported other respiratory effects following short-term exposures to NO<sub>2</sub> concentrations at or near those found in the ambient air.

<sup>98</sup> Brown (2015) reported a p-value of 0.08 when data were combined from studies of specific and non-specific AR. When the analysis was restricted only to non-specific AR following exposures to 100 ppb NO<sub>2</sub>, the percentage who experienced increased AR was larger and statistically significant. In contrast, when the analysis was restricted only to specific AR following exposures to 100 ppb NO<sub>2</sub>, the majority of study participants did not experience increased AR (U.S. EPA, 2016a; Brown 2015).



exposure concentrations (*i.e.*, at or near 100 ppb), as the evidence for NO<sub>2</sub>-induced increases in AR becomes less consistent across studies at these lower concentrations.

The epidemiologic evidence from U.S. and Canadian studies, as considered in the PA, provides information about the ambient NO<sub>2</sub> concentrations in locations where such studies have examined associations with asthma-related hospital admissions or emergency department visits (short-term) or with asthma incidence (long-term). In particular, these studies inform consideration of the extent to which NO<sub>2</sub>-health effect associations are consistent, precise, statistically significant, and present for distributions of ambient NO<sub>2</sub> concentrations that likely would have met the current standards. To the extent NO<sub>2</sub>-health effect associations are reported in study areas that would likely have met the current standards, the evidence would support the potential for the current standards to allow the NO<sub>2</sub>-associated effects indicated by those studies. In the absence of studies reporting associations in locations meeting the current NO<sub>2</sub> standards, there would be greater uncertainty regarding the potential for reported effects to be caused by NO<sub>2</sub> exposures that occur with air quality meeting those standards. There are also important uncertainties in the evidence which warrant consideration, including the potential for copollutant confounding and exposure measurement error, and the extent to which near-road NO<sub>2</sub> concentrations are reflected in the available air quality data.

With regard to epidemiologic studies of short-term NO<sub>2</sub> exposures conducted in the U.S. or Canada, the PA notes the following. First, the only recent multicity study evaluated (Stieb et al., 2009), which had maximum 1-hour DVs ranging from 67 to 242 ppb, did not report a positive association between NO<sub>2</sub> and ED visits. In addition, of the single-city studies (U.S. EPA, 2017a, Figure 3–1) that reported positive and relatively precise associations between NO<sub>2</sub> and asthma hospital admissions and ED visits, most locations had NO<sub>2</sub> concentrations likely to have violated the current 1-hour NO<sub>2</sub> standard over at least part of the study period. Specifically, most of these locations had maximum estimated DVs at or above 100 ppb and, had near-road NO<sub>2</sub> monitors been in place during study periods, DVs would likely have been higher. Thus, it is likely that even the one study location with a maximum DV of 100 ppb (Atlanta) would have violated the existing 1-hour standard

during study periods.<sup>99</sup> For the study locations with maximum DVs below 100 ppb, mixed results have been reported, with associations that are generally statistically non-significant and imprecise. As with the studies reporting more precise associations, near-road monitors were not in place during these study periods. If they had been, 1-hour DVs could have been above 100 ppb. In drawing conclusions based on this epidemiologic evidence, the PA also considers the potential for copollutant confounding as ambient NO<sub>2</sub> concentrations are often highly correlated with other pollutants. This can complicate attempts to distinguish between independent effects of NO<sub>2</sub> and effects of the broader pollutant mixture. While this has been addressed to some extent in available studies, uncertainty remains for the most relevant copollutants (*i.e.*, those related to traffic such as PM<sub>2.5</sub>, EC/BC, and CO). Taken together, while available U.S. and Canadian epidemiologic studies report NO<sub>2</sub>-associated hospital admissions and emergency department visits in locations likely to have violated the current 1-hour NO<sub>2</sub> standard, the PA concludes that these studies do not indicate the occurrence of such NO<sub>2</sub>-associated effects in locations and time periods with NO<sub>2</sub> concentrations that would clearly have met the current 1-hour NO<sub>2</sub> standard (*i.e.*, with its level of 100 ppb and 98th percentile form).

In giving further consideration specifically to the form of 1-hour standard, the PA notes that the available evidence and information in this review is consistent with that informing consideration of form in the last review. The last review focused on the upper percentiles of the distribution of NO<sub>2</sub> concentrations based, in part, on evidence for health effects associated with short-term NO<sub>2</sub> exposures from experimental studies which provided information on specific exposure concentrations that were linked to respiratory effects (75 FR 6475, February 9, 2010). In that review, the EPA specified a 98th percentile form, rather than a 99th percentile, for the new 1-hour standard. In combination with the 1-hour averaging time and 100 ppb level, a 98th percentile form was judged to provide appropriate public health protection. In addition, compared to the

99th percentile, a 98th percentile form was expected to provide greater regulatory stability.<sup>100</sup> In addition, a 98th percentile form is consistent with the PA's consideration of uncertainties in the health effects that have the potential to occur at 100 ppb. Specifically, when combined with the 1-hour averaging time and the level of 100 ppb, the 98th percentile form limits, but does not eliminate, the potential for exposures to 100 ppb NO<sub>2</sub>.<sup>101</sup>

#### ii. Long-Term

With regard to health effects related to long-term NO<sub>2</sub> exposures, the PA first considers the basis for the current annual standard. It was originally set to protect against NO<sub>2</sub>-associated respiratory disease in children reported in some epidemiologic studies (36 FR 8186, April 30, 1973). In subsequent reviews, the EPA has retained the annual standard, judging that it provides protection with an adequate margin of safety against the effects that have been reported in animal studies following long-term exposures to NO<sub>2</sub> concentrations well-above those found in the ambient air (*e.g.*, above 8,000 ppb for the development of lesions similar to those found in humans with emphysema) (60 FR 52879, October 11, 1995). In the 2010 review, the EPA noted that, though some evidence supported the need to limit long-term exposures to NO<sub>2</sub>, the evidence for adverse health effects attributable to long-term NO<sub>2</sub> exposures did not support changing the level of the annual standard.

In the current review, the strengthened “likely to be causal” relationship between long-term NO<sub>2</sub> exposures and respiratory effects is supported by epidemiologic studies of asthma development and related effects demonstrated in animal toxicological studies. While these studies strengthen the evidence for effects of long-term exposures, compared to the last review, they are subject to important uncertainties, including the potential for confounding by traffic-related copollutants. The potential for such confounding is particularly important to consider when interpreting epidemiologic studies of long-term NO<sub>2</sub> exposures given (1) the relatively high correlations observed between measured

<sup>99</sup>Based on recent air quality information for Atlanta, 98th percentiles of daily maximum 1-hour NO<sub>2</sub> concentrations are higher at near-road monitors than non-near-road monitors (U.S. EPA, 2017a, Figures 2–9 and 2–10). These differences could have been even more pronounced during study periods, when NO<sub>x</sub> emissions from traffic sources were higher (U.S. EPA, 2017a, Section 2.1.2).

<sup>100</sup>As noted in the last review, a less stable form could result in more frequent year-to-year shifts between meeting and violating the standard, potentially disrupting ongoing air quality planning without achieving public health goals (75 FR 6493, February 9, 2010).

<sup>101</sup>The 98th percentile corresponds to about the 7th or 8th highest daily maximum 1-hour NO<sub>2</sub> concentration in a year.

and modeled long-term ambient concentrations of NO<sub>2</sub> and long-term concentrations of other roadway-associated pollutants; (2) the general lack of information from copollutant models on the potential for NO<sub>2</sub> associations that are independent of other traffic-related pollutants or mixtures; and (3) the general lack of supporting information from experimental studies that evaluate long-term exposures to NO<sub>2</sub> concentrations near those in the ambient air. Thus, it is unclear the degree to which the observed effects in these studies are independently related to exposure to ambient concentrations of NO<sub>2</sub>. The epidemiologic evidence from some U.S. and Canadian studies is also subject to uncertainty with regard to the extent to which the studies accurately characterized exposures of the study populations, further limiting what these studies can tell us regarding the adequacy of the current primary NO<sub>2</sub> standards.

While the PA recognizes the above uncertainties, it considers what studies of long-term NO<sub>2</sub> and asthma development indicate with regard to the adequacy of the current primary NO<sub>2</sub> standards. As discussed above for short-term exposures, the PA considers the degree to which the evidence indicates adverse respiratory effects associated with long-term NO<sub>2</sub> exposures in locations that would have met the NAAQS. As summarized in Section II.C.2, the causal determination for long-term exposures is supported both by studies of long-term NO<sub>2</sub> exposures and studies indicating a potential role in asthma development for repeated short-term exposures to high NO<sub>2</sub> concentrations.

As such, when considering the ambient NO<sub>2</sub> concentrations present during study periods, the PA considers these concentrations within the context of both the 1-hour and annual NO<sub>2</sub> standards. Analyses of historical data indicate that 1-hour DVs at or below 100 ppb generally correspond to annual DVs below 35 ppb.<sup>102</sup> CASAC noted this relationship, stating that “attainment of the 1-hour standard corresponds with annual design value averages of 30 ppb NO<sub>2</sub>” (Diez Roux and Sheppard, 2017). Thus, meeting the 1-hour standard with its level of 100 ppb would be expected to maintain annual average NO<sub>2</sub> concentrations below the 53 ppb level of the current annual standard.

As discussed in Section II.C.1, while annual estimated DVs in study locations

were often below 53 ppb, maximum 1-hour estimated DVs in most locations were near or above 100 ppb. Because these study-specific estimated DVs are based on the area-wide NO<sub>2</sub> monitors in place during study periods, they do not reflect the NO<sub>2</sub> concentrations near the largest roadways, which are expected to be higher in most urban areas. Had near-road monitors been in place during study periods, estimated NO<sub>2</sub> DVs based on near-road concentrations likely would have been higher in many locations, and would have been more likely to exceed the level of the annual and/or 1-hour standard(s).

Given the paucity of epidemiologic studies conducted in areas that were close to or below the current standards, and considering that no near road monitors were in place during the study periods, the PA concludes that the epidemiologic evidence does not provide support for NO<sub>2</sub>-attributable asthma development in children in locations with NO<sub>2</sub> concentrations that would have clearly met the current annual and 1-hour NO<sub>2</sub> standards. The strongest epidemiologic evidence informing the level at which effects may occur comes from U.S. and Canadian epidemiologic studies that are subject to critical uncertainties related to copollutant confounding and exposure assessment. Furthermore, the PA’s evaluation indicates that most of the locations included in epidemiologic studies of long-term NO<sub>2</sub> exposure and asthma incidence would likely have violated either one or both of the current NO<sub>2</sub> standards, over at least parts of the study periods.

### iii. PA Conclusions

Taking note of the conclusions in the PA, and based on the information discussed above, the EPA revisits the question posed above: To what extent does the evidence indicate adverse respiratory effects attributable to short- or long-term NO<sub>2</sub> exposures lower than previously identified or below the existing standards?

In addressing this question, the PA notes that (1) experimental studies do not indicate adverse respiratory effects attributable to either short- or long-term NO<sub>2</sub> exposures lower than previously identified and that (2) epidemiologic studies do not provide support for associations between adverse effects and ambient NO<sub>2</sub> concentrations that would have clearly met the current standards. Taken together, the PA concludes that the available evidence does not support the need for increased protection against short- or long-term NO<sub>2</sub> exposures, beyond that provided by the existing standards. In its review of the draft PA,

the CASAC agreed with this conclusion, stating that “[t]he CASAC concurs with the EPA that the current scientific literature does not support a revision to the primary NAAQS for nitrogen dioxide” (Diez Roux and Sheppard, 2017, p. 9). Therefore, the PA did not identify potential alternative standard levels or forms for consideration.

### 2. Exposure- and Risk-Based Considerations

As described in greater detail in Section II.D above, and in the REA Planning document (U.S. EPA, 2015, Section 2.1.1) and the PA (U.S. EPA, 2017a, Chapter 4), the EPA conducted updated analyses comparing ambient NO<sub>2</sub> concentrations (*i.e.*, as surrogates of potential exposures) to health-based benchmarks, with a particular focus on study areas where near-road monitors have been deployed. In the PA, staff concluded that updated quantitative risk assessments were not supported in the current review, based on uncertainties in the available evidence and the likelihood that such analyses would be subject to the same uncertainties identified in the risk estimates in the prior review (U.S. EPA, 2017a, Chapter 4). The CASAC stated that it was “satisfied with the short-term exposure health-based benchmark analysis presented in the draft PA” and that it “support[ed] the decision not to conduct any new or updated quantitative risk analyses related to long-term exposure to NO<sub>2</sub>” (Diez Roux and Sheppard, 2017).

When considering analyses comparing NO<sub>2</sub> air quality with health-based benchmarks, the PA focuses on the following specific questions: (1) To what extent are ambient NO<sub>2</sub> concentrations that may be of public health concern estimated to occur in locations meeting the current NO<sub>2</sub> standards? (2) What are the important uncertainties associated with those estimates?

As discussed in Section II.D, benchmarks are based on information from controlled human exposure studies of NO<sub>2</sub> exposures and AR. In identifying specific NO<sub>2</sub> benchmarks, and considering the weight to place on each, the PA considers both the group mean results reported in individual studies and the results of a meta-analysis that combined data from multiple studies (Brown, 2015; U.S. EPA, 2016a, Section 5.2.2.1), as described above.

When taken together, the results of individual controlled human exposure studies and of the meta-analysis by Brown (2015) support consideration of NO<sub>2</sub> benchmarks between 100 and 300 ppb, based largely on studies of non-

<sup>102</sup> As noted in the PA, near-road monitors were not included in this analysis due to the limited amount of data available.

specific AR in people with asthma exposed at rest. As discussed in more detail in II.D, benchmarks from the upper end of this range are supported by the results of individual studies, the majority of which reported statistically significant increases in AR following NO<sub>2</sub> exposures at or above 250 ppb, and by the results of the meta-analysis by Brown (2015). Benchmarks from the lower end of this range, including 100 ppb, are supported by the results of the meta-analysis, even though individual studies do not consistently report statistically significant NO<sub>2</sub>-induced increases in AR at these lower concentrations. In particular, while the meta-analysis indicates that the majority of study participants with asthma experienced an increase in AR following exposures to 100 ppb NO<sub>2</sub> (Brown, 2015), individual studies have not generally reported statistically significant increases in AR following resting exposures to 100 ppb NO<sub>2</sub>.<sup>103</sup>

In further considering the potential public health implications of exposures to NO<sub>2</sub> concentrations at or above benchmarks, there are multiple uncertainties, as discussed in Section II.C.I. As discussed in more detail in that section, there is no indication of a dose-response relationship between NO<sub>2</sub> and AR in people with asthma, and there is uncertainty in the clinical relevance and potential adversity of the reported NO<sub>2</sub>-induced increases in AR.

As discussed in Section II.D, analyses of unadjusted air quality, which meets the current standards in all locations, indicate almost no potential for 1-hour exposures to NO<sub>2</sub> concentrations at or above any of the benchmarks examined, including 100 ppb. Analyses of air quality adjusted upwards to just meet the current 1-hour standard<sup>104</sup> indicate virtually no potential for 1-hour exposures to NO<sub>2</sub> concentrations at or above 200 ppb (or 300 ppb), and almost none for exposures at or above 150 ppb. This is the case for both estimates averaged over multiple years and estimates in worst-case years, including at near-road monitoring sites within a few meters of heavily trafficked roads. With respect to the lowest benchmark evaluated, analyses estimate that there

is potential for exposures to 1-hour NO<sub>2</sub> concentrations at or above 100 ppb on some days (e.g., about one to 10 days per year, on average, at near-road monitoring sites). As described above, this result is consistent with expectations, given that the current 1-hour standard, with its 98th percentile form, is expected to limit, but not eliminate, the occurrence of 1-hour NO<sub>2</sub> concentrations of 100 ppb.

These analyses indicate that the current 1-hour NO<sub>2</sub> standard is expected to allow virtually no potential for exposures to the NO<sub>2</sub> concentrations that have been shown most consistently to increase AR in people with asthma, even under worst-case conditions across a variety of study areas with among the highest NO<sub>x</sub> emissions in the U.S. Such NO<sub>2</sub> concentrations are not estimated to occur, even at monitoring sites adjacent to some of the most heavily trafficked roadways. In addition, the current 1-hour standard provides protection against NO<sub>2</sub> exposures that have the potential to exacerbate asthma symptoms, but for which the evidence indicates greater uncertainty in both the occurrence of such exacerbations and in their severity, should they occur (i.e., at or near 100 ppb). Given the results of these analyses, and the uncertainties inherent in their interpretation, the PA concludes that there is little potential for exposures to ambient NO<sub>2</sub> concentrations that would be of public health concern in locations meeting the current 1-hour standard.

### 3. CASAC Advice

As discussed above (Section II.E), in the current review of the primary standards for NO<sub>2</sub>, the CASAC has provided advice and recommendations based on its review of drafts of the ISA, of the REA Planning document, and of the draft PA. The CASAC's advice on the adequacy of the current primary NO<sub>2</sub> standards was provided as part of its review of the draft PA (Diez Roux and Sheppard, 2017). Overall, the CASAC concurred with the draft PA's preliminary conclusion that it is appropriate to consider retaining the current primary NO<sub>2</sub> standards without revision, stating that, "the CASAC recommends retaining, and not changing the existing suite of standards" (Diez Roux and Sheppard, 2017). The CASAC provided the following advice with respect to the individual elements of the standards:

- *Indicator and averaging time:* The CASAC stated "there is strong evidence for the selection of NO<sub>2</sub> as the indicator of oxides of nitrogen" and "for the selection of 1-hour and annual averaging times" (Diez Roux and

Sheppard, 2017 p. 9). With regard with to averaging time in particular, the CASAC stated that "[c]ontrolled human and animal studies provide scientific support for a 1-hour averaging time as being representative of an exposure duration that can lead to adverse effects" (Diez Roux and Sheppard, 2017, p. 7). The CASAC further concluded that "[e]pidemiologic studies provide support for the annual averaging time, representative of likely to be causal associations between long-term exposures, or repeated short-term exposures, and asthma development" (Diez Roux and Sheppard, 2017, p. 7).

- *Level of the 1-hour standard:* The CASAC stated "there are notable adverse effects at levels that exceed the current standard, but not at the level of the current standard. Thus, the CASAC advises that the current 1-hour standard is protective of adverse effects and that there is not a scientific basis for a standard lower than the current 1-hour standard" (Diez Roux, and Sheppard 2017, p. 9).

- *Form of the 1-hour standard:* The CASAC also "recommends retaining the current form" for the 1-hour standard (Diez Roux and Sheppard 2017). Recognizing that the form allowed for some 1-hour concentrations that exceeded 100 ppb, the CASAC explained that the "scientific rationale for this form is there is uncertainty regarding the severity of adverse effects at a level of 100 ppb NO<sub>2</sub>, and thus some potential for maximum daily levels to exceed this benchmark with limited frequency may nonetheless be protective of public health" (Diez Roux and Sheppard, 2017, p. 10). It further noted that the choice of form reflected the Administrator's policy judgment. (Diez Roux and Sheppard, 2017, p. 10).

- *Level of the annual standard:* In providing advice on the level of the annual standard, the CASAC commented that the long-term epidemiologic studies "imply the possibility of adverse effects at levels below that of the current annual standard" (Diez Roux and Sheppard, p. 8). However, CASAC recognized that these studies "are also subject to uncertainty, including possible confounding with other traffic-related pollutants" (Diez Roux and Sheppard, p. 8). CASAC also commented that these epidemiologic studies may have uncertainty related to exposure error and pointed out that estimated DVs in study areas do not account for near-road monitoring. Furthermore, CASAC recognized the causal associations between long-term exposures, or repeated short-term exposures, and asthma development (Diez Roux and

<sup>103</sup> Meta-analysis results for exposures to 100 ppb NO<sub>2</sub> were statistically significant when analyses were restricted to non-specific AR, but not when analyses were restricted to specific AR (Brown, 2015).

<sup>104</sup> In all study areas, ambient NO<sub>2</sub> concentrations required smaller upward adjustments to just meet the 1-hour standard than to just meet the annual standard. Therefore, as noted above and in the PA (U.S. EPA, 2017a, Section 4.2.1), when adjusting air quality to just meet the current NO<sub>2</sub> NAAQS, the adjustment needed to just meet the 1-hour standard was applied.

Sheppard, p. 7) and the appropriateness of considering the protection provided by the current suite of standards together (Diez Roux and Sheppard, p. 9). Therefore, the CASAC's advice on the annual standard takes into account the degree of protection provided by this standard, in combination with the current 1-hour standard. In particular, the CASAC recognized that meeting the 1-hour NO<sub>2</sub> standard can limit long-term NO<sub>2</sub> concentrations to below the level of the annual standard, observing that "an hourly DV of 100 ppb NO<sub>2</sub> is associated with DV values that average approximately 30 ppb NO<sub>2</sub>" and that "there is insufficient evidence to make a scientific judgment that adverse effects occur at annual DVs less than 30 ppb NO<sub>2</sub>" (Diez Roux and Sheppard, 2017, p. 9). Thus, in providing support for retaining the existing annual standard, the CASAC specifically noted that "the current suite of standards is more protective of annual exposures compared to the annual standard by itself" and that "it is the suite of the current 1-hour and annual standards, together, that provide protection against adverse effects" (Diez Roux and Sheppard, 2017, p. 9). Therefore, the CASAC "recommends retaining the existing suite of standards" (Diez Roux and Sheppard, 2017, p. 9), including the current annual standard.

In addition, CASAC also provided advice on areas for additional research based on key areas of uncertainty that came up during the review cycle (Diez Roux and Sheppard, 2017, p. 10–12). As part of this advice, CASAC stated that "[t]here is an ongoing need for research in multipollutant exposure and epidemiology to attempt to distinguish the contribution to NO<sub>2</sub> exposure to human health risk" (Diez Roux and Sheppard, 2017, p. 10). More specifically, CASAC pointed to the importance of further understanding the effects of co-pollutant exposures and the variability in ambient NO<sub>2</sub> concentrations, particularly considering "locations of peak exposure occurrences (e.g., on road in vehicles, roadside for active commuters, in street canyons, near other non-road facilities such as rail yards or industrial facilities)" (Diez Roux and Sheppard, 2017, p. 11). In particular, CASAC recognized the importance of the new near-road monitoring data in reducing those uncertainties, stating that "[t]he amount of data from near-road monitoring will increase between now and the next review cycle and should be analyzed and evaluated" (Diez Roux and Sheppard, 2017, p. 11).

#### 4. Administrator's Proposed Conclusions Regarding the Adequacy of the Current Primary NO<sub>2</sub> Standards

Taking into consideration the large body of evidence concerning NO<sub>2</sub>-related health effects and available estimates of the potential for NO<sub>2</sub> exposures, including the uncertainties and limitations inherent in the evidence and those estimates, the Administrator proposes to conclude that the current primary NO<sub>2</sub> standards provide the requisite protection of public health, with an adequate margin of safety, and should be retained without revision in this review. The Administrator's proposed conclusions are informed by a careful consideration of the full body of information available in this review, giving particular weight to the assessment of the scientific evidence in the ISA; analyses in the PA comparing NO<sub>2</sub> air quality with health-based benchmarks; the PA's consideration of the evidence and analyses; and the advice and recommendations from the CASAC. The basis for the Administrator's proposed conclusions on the current primary NO<sub>2</sub> standards is discussed below.

As an initial matter, the Administrator takes note of the well-established body of scientific evidence supporting the occurrence of respiratory effects following NO<sub>2</sub> exposures. As in the last review, the clearest evidence indicates the occurrence of respiratory effects following short-term NO<sub>2</sub> exposures. The strongest support for this relationship comes from controlled human exposure studies demonstrating NO<sub>2</sub>-induced increases in AR in individuals with asthma. As discussed above, the Administrator notes that most of the controlled human exposure studies assessed in the ISA were available in the last review, with the addition in this review of an updated meta-analysis that synthesizes data from these studies. He also notes that these studies provided an important part of the body of evidence supporting the decision in the last review to establish the 1-hour NO<sub>2</sub> standard with its level of 100 ppb. Beyond the controlled human exposure studies, additional supporting evidence comes from epidemiologic studies reporting associations with a range of asthma-related respiratory effects, including effects serious enough to result in emergency room visits or hospital admissions. While there is some new evidence in the current review from such epidemiologic studies of short-term NO<sub>2</sub> exposures, the results of these newer studies are generally consistent

with the epidemiologic studies that were available in the last review.

With regard to long-term NO<sub>2</sub> exposures, the Administrator notes that the evidence supporting associations with asthma development in children has become stronger since the last review, though uncertainties remain regarding the degree to which estimates of long-term NO<sub>2</sub> concentrations in these studies are serving primarily as surrogates for exposures to the broader mixture of traffic-related pollutants. Supporting evidence also includes studies indicating a potential role for repeated short-term NO<sub>2</sub> exposures in the development of asthma (U.S. EPA, 2016a, p. 6–64 and p. 6–65).

In addition, the Administrator acknowledges that the evidence for some non-respiratory effects has strengthened since the last review. In particular, based on the assessment of the evidence in the ISA, he notes the stronger evidence for NO<sub>2</sub>-associated cardiovascular effects (short- and long-term exposures), premature mortality (long-term exposures), and certain reproductive effects (long-term exposures). As detailed in the ISA, while this evidence has generally become stronger since the last review, it remains subject to greater uncertainty than the evidence of asthma-related respiratory effects (U.S. EPA, 2016a).

The Administrator's evaluation of the public health protection provided against ambient NO<sub>2</sub> exposures also involves consideration of populations and lifestages that may be at greater risk of experiencing NO<sub>2</sub>-attributable health effects. In the current review, the Administrator's consideration of potential at-risk populations draws from the 2016 ISA's assessment of the evidence (U.S. EPA, 2016a, Chapter 7). Based on the ISA's systematic approach to evaluating factors that may increase risks in a particular population or during a particular lifestage, the Administrator is most concerned about the potential effects of NO<sub>2</sub> exposures in people with asthma, children, and older adults (U.S. EPA, 2016a, Table 7–27). Support for potentially higher risks in these populations is based primarily on evidence for asthma exacerbation or asthma development. Evidence for other health effects is subject to greater uncertainty (U.S. EPA, 2017a, Section 3.4).

The Administrator further uses the scientific evidence outlined above, and described in detail in the ISA (U.S. EPA, 2016a), to directly inform his consideration of the adequacy of the public health protection provided by the current primary NO<sub>2</sub> standards. Consistent with the approach in the PA

(U.S. EPA, 2017a), and with CASAC advice (Diez Roux and Sheppard, 2017), the Administrator specifically considers the evidence within the context of the degree of public health protection provided by the current 1-hour and annual standards together, including the combination of all elements of these standards (*i.e.*, indicator, averaging times, forms, levels).

In doing so, the Administrator focuses on the results of controlled human exposure studies of AR in people with asthma and on the results of U.S. and Canadian epidemiologic studies of asthma-related hospital admissions, asthma-related emergency department visits, and asthma development in children. He particularly emphasizes the results of controlled human exposure studies, which were identified in the ISA as providing “[t]he key evidence that NO<sub>2</sub> exposure can independently exacerbate asthma” (U.S. EPA, 2016a, p. 1–18). The Administrator’s decision to focus on these studies is in agreement with the CASAC, which stated that, of the evidence for asthma exacerbation, “[t]he strongest evidence is for an increase in AR based on controlled human exposure studies, with supporting evidence from epidemiologic studies” (Diez Roux and Sheppard, 2017).

In considering the controlled human exposure studies of AR, the Administrator focuses both on the results of an updated meta-analysis of data from these studies and on the consistency of findings across individual studies. As discussed above, and consistent with the evidence in the last review, the meta-analysis indicates that the majority of study volunteers, generally with mild asthma, experienced increased AR following 30-minute to 1-hour resting exposures to NO<sub>2</sub> concentrations from 100 to 530 ppb. Based on these results, the Administrator notes the potential for people with asthma to experience NO<sub>2</sub>-induced respiratory effects following exposures in this range, and that people with more severe asthma could experience more serious effects. The Administrator further notes that individual studies consistently report statistically significant increases in AR following exposures to NO<sub>2</sub> concentrations at or above 250 ppb, with less consistent results across studies conducted at lower exposure concentrations, particularly 100 ppb (II.C.1). Uncertainties in this evidence, discussed in sections II.C.1, II.D.3, and II.F.2 above, include the lack of an apparent dose-response relationship and uncertainty in the potential adversity of responses.

When the information discussed above is taken together, the Administrator judges it appropriate to consider the degree of protection provided against exposures to NO<sub>2</sub> concentrations at and above 100 ppb, though his concern is greater for exposures to higher concentrations. In particular, based on the results of the meta-analysis and on the consistent results across individual studies, the Administrator is most concerned about the potential for people with asthma to experience adverse respiratory effects following NO<sub>2</sub> exposures at or above 250 ppb. Because results are less consistent across individual studies that evaluated lower exposure concentrations, the Administrator becomes increasingly concerned about uncertainties in the evidence as he considers the potential implications of such exposures. While taking these uncertainties into consideration, the Administrator remains concerned about the potential for respiratory effects following exposures to NO<sub>2</sub> concentrations as low as 100 ppb, particularly in people with more severe cases of asthma than have generally been evaluated in the available NO<sub>2</sub> controlled human exposure studies. Thus, when the evidence and uncertainties are taken together, the Administrator judges that it is appropriate to consider the degree of protection provided against potential exposures to NO<sub>2</sub> concentrations at or above 100 ppb, with the most emphasis on the potential for exposures at or above 250 ppb.

In further considering the potential public health implications of controlled human exposure studies, the Administrator looks to the results of quantitative comparisons between NO<sub>2</sub> air quality and health-based benchmarks. As discussed in the PA, these comparisons can help to place the results of the controlled human exposure studies, which provide the basis for the benchmark concentrations, into a broader public health context. In considering the results of the analyses comparing NO<sub>2</sub> air quality to specific health-based benchmarks, the Administrator first recognizes that all areas of the U.S. meet the current primary NO<sub>2</sub> standards. When based on recent unadjusted NO<sub>2</sub> air quality, these analyses estimate almost no days with the potential for 1-hour exposures to NO<sub>2</sub> concentrations at or above health-based benchmarks, including the lowest benchmark examined (*i.e.*, 100 ppb).

The Administrator additionally recognizes that, even when ambient NO<sub>2</sub> concentrations are adjusted upward to just meet the existing 1-hour standard,

the analyses estimate no days with the potential for exposures to the NO<sub>2</sub> concentrations that have been shown most consistently to increase AR in people with asthma (*i.e.*, above 250 ppb). Such NO<sub>2</sub> concentrations were not estimated to occur, even under worst-case conditions across a variety of study areas with among the highest NO<sub>x</sub> emissions in the U.S., and at monitoring sites adjacent to some of the most heavily trafficked roadways in the U.S. In addition, analyses with adjusted air quality indicate a limited number of days with the potential for exposures to 1-hour NO<sub>2</sub> concentrations at or above 100 ppb, an exposure concentration with the potential to exacerbate asthma-related respiratory effects, but for which uncertainties in the evidence become increasingly important.

Based on the information above, the Administrator reaches the proposed conclusion that evidence from controlled human exposure studies of AR, together with analyses comparing ambient NO<sub>2</sub> concentrations to health-based benchmarks, supports the degree of the public health protection provided by the current primary NO<sub>2</sub> NAAQS. In particular, he is concerned about exposures to NO<sub>2</sub> concentrations at and above 250 ppb, where the potential for NO<sub>2</sub>-induced respiratory effects is supported by results of the meta-analysis and by consistent results reported across individual studies. With regard to this, the Administrator notes that meeting the current standards is estimated to allow no potential for exposures to 1-hour NO<sub>2</sub> concentrations at or above 250 ppb. The Administrator is also concerned about exposures to lower NO<sub>2</sub> concentrations, including concentrations as low as 100 ppb though, as described above, he becomes increasingly concerned about the uncertainties in the evidence at such low exposure concentrations. In considering the degree of protection provided against exposures to 100 ppb NO<sub>2</sub>, in light of uncertainties, the Administrator judges it appropriate to limit such exposures, but not necessarily to eliminate them. With regard to this, he notes that the current standard is estimated to allow limited potential for exposures to NO<sub>2</sub> concentrations at or above 100 ppb. Thus, given the substantial protection provided against exposures to NO<sub>2</sub> concentrations at and above 250 ppb, and the protection provided against exposures to concentrations as low as 100 ppb, the Administrator reaches the proposed conclusion that the evidence, when considered in light of its uncertainties, supports the degree of

public health protection provided by the current primary NO<sub>2</sub> NAAQS.

Although the NO<sub>2</sub> epidemiologic evidence is subject to greater uncertainty than the controlled human exposure studies of NO<sub>2</sub>-induced changes in AR, the Administrator also considers what the available epidemiologic studies indicate with regard to the adequacy of the public health protection provided by the current standards. In particular, he considers analyses of NO<sub>2</sub> air quality in the locations, and during the time periods, of available U.S. and Canadian epidemiologic studies. These analyses can provide insights into the extent to which NO<sub>2</sub>-health effect associations are present for distributions of ambient NO<sub>2</sub> concentrations that would be allowed by the current standards. The presence of such associations would support the potential for the current standards to allow the NO<sub>2</sub>-associated effects indicated by epidemiologic studies. To the degree studies have not reported associations in locations meeting the current NO<sub>2</sub> standards, there is greater uncertainty regarding the potential for reported effects to occur following the NO<sub>2</sub> exposures that are associated with air quality meeting those standards.

With regard to studies of short-term NO<sub>2</sub> exposures, the Administrator notes that epidemiologic studies provide consistent evidence for asthma-related emergency department visits and hospital admissions with exposure to NO<sub>2</sub> in locations likely to have violated the current standards over at least parts of study periods (based on the presence of relatively precise and generally statistically significant associations across several studies). These studies have not consistently shown such NO<sub>2</sub>-associated outcomes in areas that would have clearly met the current standards. In this regard, the Administrator recognizes that the NO<sub>2</sub> concentrations identified in these epidemiologic studies are based on an NO<sub>2</sub> monitoring network that, during study periods, did not include monitors meeting the current near-road monitoring requirements. This is particularly important given that NO<sub>2</sub> concentrations near the most heavily-trafficked roadways were likely to have been higher than those reflected by the NO<sub>2</sub> concentrations measured at monitors in operation during study years. As such, the estimated DVs associated with the areas at the times of the studies could have been higher had a near-road monitoring network been in place. Thus, while these epidemiologic studies provide consistent evidence for associations with asthma-related effects, the Administrator notes that studies

conducted in the U.S. and Canada do not provide support for associations with asthma-related hospital admissions or emergency department visits in locations that would have clearly met the current standards.

With regard to studies of long-term NO<sub>2</sub> exposures, the Administrator notes that the preponderance of evidence for respiratory health effects comes from epidemiologic studies evaluating asthma development in children. As discussed above, these studies report associations with long-term average NO<sub>2</sub> concentrations, while the broader body of evidence indicates the potential for repeated short-term NO<sub>2</sub> exposures to contribute to the development of asthma. Because of this, and because air quality analyses indicate that meeting the current 1-hour standard can also limit annual NO<sub>2</sub> concentrations, when considering these studies of asthma development, the Administrator considers the protection provided by the combination of both the annual and 1-hour standards. While available epidemiologic studies conducted in the U.S. and Canada consistently report associations between long-term NO<sub>2</sub> exposures and asthma development in children in locations likely to have violated the current standards over at least parts of study periods, those studies do not indicate such associations in locations that would have clearly met the current annual and 1-hour standards. This is particularly the case given that NO<sub>2</sub> concentrations near the most heavily-trafficked roadways are not likely reflected by monitors in operation during study years. Thus, while recognizing the public health significance of asthma development in children, and recognizing that NO<sub>2</sub> concentrations violating the current standards have been associated with asthma development, the Administrator places weight on the PA's conclusion that the evidence does not provide support for NO<sub>2</sub>-attributable asthma development in children in locations with NO<sub>2</sub> concentrations that would have clearly met both the annual and 1-hour standards.

Taking all of these considerations into account, the Administrator reaches the proposed conclusion that the current body of scientific evidence, in combination with the results of quantitative analyses comparing NO<sub>2</sub> air quality with health-based benchmarks, supports the degree of public health protection provided by the current 1-hour and annual primary NO<sub>2</sub> standards and does not call into question any of the elements of those standards. He further reaches the proposed conclusion

that the current 1-hour and annual NO<sub>2</sub> primary standards, together, are requisite to protect public health with an adequate margin of safety.

In particular, with regard to short-term exposures and the current 1-hour standard, the Administrator takes note of the well-established body of scientific evidence supporting the occurrence of respiratory effects following short-term NO<sub>2</sub> exposures. In reaching the proposed conclusion that the current standards provide requisite protection against these effects, the Administrator notes:

- Meeting the current 1-hour NO<sub>2</sub> standard provides a substantial margin of safety against exposures to NO<sub>2</sub> concentrations that have been shown most consistently to increase AR in people with asthma, even under worst-case conditions across a variety of study areas with among the highest NO<sub>x</sub> emissions in the U.S. Such NO<sub>2</sub> concentrations were not estimated to occur, even at monitoring sites adjacent to some of the most heavily trafficked roadways.

- Meeting the current 1-hour standard limits the potential for exposures to 1-hour concentrations at or above 100 ppb. Thus, the current standard provides protection against NO<sub>2</sub> exposures with the potential to exacerbate symptoms in some people with asthma, but for which uncertainties in the evidence become increasingly important.

- Meeting the current 1-hour standard is expected to maintain ambient NO<sub>2</sub> concentrations below those present in locations where key U.S. and Canadian epidemiologic studies reported precise and statistically significant associations between short-term NO<sub>2</sub> and asthma-related hospitalizations.

In addition, with regard to long-term NO<sub>2</sub> exposures, the Administrator notes that the evidence supporting associations with asthma development in children has become stronger since the last review, though important uncertainties remain. As discussed above, meeting the current annual and 1-hour standards is expected to maintain ambient NO<sub>2</sub> concentrations below those present in locations where key U.S. and Canadian epidemiologic studies reported such associations between long-term NO<sub>2</sub> and asthma development. In considering the protection provided against exposures that could contribute to asthma development, the Administrator recognizes the air quality relationship between the current 1-hour standard and annual standard, and that analyses of historical ambient NO<sub>2</sub> concentrations suggest that meeting the 1-hour standard with its level of 100 ppb would be expected to maintain annual average NO<sub>2</sub> concentrations well-below the 53 ppb level of the annual standard, and generally below 35

ppb.<sup>105</sup> The Administrator judges that, as additional years of data become available from the recently deployed near-road NO<sub>2</sub> monitors, it will be important to evaluate the degree to which this relationship is also observed in the near-road environment, and the degree to which the annual standard provides additional protection, beyond that provided by the 1-hour standard. Such an evaluation could inform future reviews of the primary NO<sub>2</sub> NAAQS, consistent with the CASAC advice that “in the next review cycle for oxides of nitrogen . . . EPA should review the annual standard to determine if there is need for revision or revocation” (Diez Roux and Sheppard, 2017, p. 9).

Therefore, in this review, the Administrator proposes to retain the current primary NO<sub>2</sub> standards, without revision. As described in section II.F.3 above, the Administrator notes that his proposed decision to retain the current primary NO<sub>2</sub> standards in this review is consistent with CASAC advice provided as part of its review of the draft PA. In particular, the Administrator notes that “the CASAC recommends retaining, and not changing the existing suite of standards” (Diez Roux and Sheppard, 2017). CASAC specifically focused its conclusions on the degree of protection provided by the combination of the 1-hour and annual standards against short- and long-term NO<sub>2</sub> exposures. In particular, the CASAC stated that “it is the suite of the current 1-hour and annual standards, together, that provide protection against adverse effects” (Diez Roux and Sheppard, 2017, p. 9).

Inherent in the Administrator’s proposed conclusions are public health policy judgments on the public health implications of the available scientific evidence and analyses, including how to weigh associated uncertainties. These public health policy judgments include judgments related to the appropriate degree of public health protection that should be afforded against risk of respiratory morbidity in at-risk populations, such as the potential for worsened respiratory effects in people with asthma, as well judgments related to the appropriate weight to be given to various aspects of the evidence and quantitative analyses, including how to consider their associated uncertainties. Based on these considerations and the judgments identified here, the Administrator reaches the proposed conclusion that the current standards provide the requisite protection of

public health with an adequate margin of safety, including protection of at-risk populations, such as people with asthma.

In reaching this proposed conclusion, the Administrator recognizes that in establishing primary standards under the Act that are requisite to protect public health with an adequate margin of safety, he is seeking to establish standards that are neither more nor less stringent than necessary for this purpose. The Act 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. In this context, the Administrator’s proposed conclusion is that the current standards provide the requisite protection and that more or less stringent standards would not be requisite.

More specifically, given the adverse effects reported to be associated with NO<sub>2</sub> concentrations above the current standards, the Administrator does not believe standards less stringent than the current standards would be sufficient to protect public health with an adequate margin of safety. In this regard, he particularly notes that, compared to the current standards, less stringent standards would be more likely to allow (1) NO<sub>2</sub> exposures that could exacerbate respiratory effects in people with asthma, particularly those with more severe asthma and (2) ambient NO<sub>2</sub> concentrations that have been reported in epidemiologic studies to be associated with asthma-related hospitalizations and with asthma development in children. Consistent with these observations, the Administrator further notes CASAC’s conclusion, based on its consideration of the evidence, that “there are notable adverse effects at levels that exceed the current standard, but not at the level of the current standard” (Diez Roux and Sheppard, 2017 pg. 9). Therefore, the Administrator reaches the proposed conclusion that standards less stringent than the current 1-hour and annual standards (e.g., with levels higher than 100 ppb and 53 ppb, respectively) would not be sufficient to protect public health with an adequate margin of safety.

The Administrator additionally recognizes that the uncertainties and limitations associated with the many aspects of the estimated relationships between respiratory morbidity and NO<sub>2</sub> exposures are amplified with consideration of progressively lower ambient NO<sub>2</sub> concentrations. In his view, and consistent with the conclusions in the PA, there is appreciable uncertainty in the extent to

which reductions in asthma exacerbations or asthma development would result from revising the primary NO<sub>2</sub> NAAQS to be more stringent than the current standards. Therefore, the Administrator also does not believe standards more stringent than the current standards would be appropriate. With regard to this, CASAC advised that “there is not a scientific basis for a standard lower than the current 1-hour standard” (Diez Roux and Sheppard, 2017 pg. 9). The CASAC also did not advise setting the level of the annual standard lower than the current level of 53 ppb, noting that the 1-hour standard can generally maintain long-term NO<sub>2</sub> concentrations below the level of the annual standard (Diez Roux and Sheppard, 2017).

Based on all of the above considerations, and consistent with CASAC advice, the Administrator reaches the proposed conclusion that it is appropriate to retain the current standards, without revision, in this review. He further proposes that the available evidence and information do not warrant the identification of potential alternative standards that provide a different degree of public health protection. In reaching these proposed conclusions, the Administrator recognizes that different public health policy judgments could lead to different conclusions regarding the extent to which the current standards protect the public health. Such judgments include those related to the appropriate degree of public health protection that should be afforded as well as the appropriate weight to be given to various aspects of the evidence and information, including how to consider uncertainties. Therefore, the Administrator solicits comment on his proposed conclusions regarding the public health protection provided by the current primary NO<sub>2</sub> standards and on his proposal to retain those standards, without revision, in this review. He invites comment on all aspects of these proposed conclusions and their underlying rationales, including on his proposal that the current standards are requisite, *i.e.*, neither more nor less stringent than necessary, to protect the public health with an adequate margin of safety and on the evidence-based and exposure-/risk-based considerations supporting that proposal.

### III. Statutory and Executive Order Reviews

Additional information about these statutes and Executive Orders can be found at <http://www2.epa.gov/laws-regulations/laws-and-executive-orders>.

<sup>105</sup> This air quality relationship was discussed in the PA where it was noted that the analysis did not include data from near-road monitors due to the limited amount of data available for the years analyzed (1980–2015).

*A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review*

The Office of Management and Budget (OMB) determined that this action is a significant regulatory action. Accordingly, it was submitted to OMB for review. Any changes made in response to OMB recommendations have been documented in the docket. Because this rule does not propose to change the existing NAAQS for NO<sub>2</sub>, it does not impose costs or benefits relative to the baseline of continuing with the current NAAQS in effect. EPA has thus not prepared a Regulatory Impact Analysis for this rule.

*B. Paperwork Reduction Act (PRA)*

This action does not impose an information collection burden under the PRA. There are no information collection requirements directly associated with a decision to retain a NAAQS without any revision under section 109 of the CAA and this action proposes to retain the current primary NO<sub>2</sub> NAAQS without any revisions.

*C. Regulatory Flexibility Act (RFA)*

I certify that this action will not have a significant economic impact on a substantial number of small entities under the RFA. This action will not impose any requirements on small entities. Rather, this action proposes to retain, without revision, existing national standards for allowable concentrations of NO<sub>2</sub> in ambient air as required by section 109 of the CAA. *See also American Trucking Associations v. EPA*, 175 F.3d at 1044–45 (NAAQS do not have significant impacts upon small entities because NAAQS themselves impose no regulations upon small entities).

*D. Unfunded Mandates Reform Act (UMRA)*

This action does not contain any unfunded mandate as described in the UMRA, 2 U.S.C. 1531–1538 and does not significantly or uniquely affect small governments. This action imposes no enforceable duty on any state, local or tribal governments or the private sector.

*E. Executive Order 13132: Federalism*

This action does not have federalism implications. It will not have substantial direct effects on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government.

*F. Executive Order 13175: Consultation and Coordination With Indian Tribal Governments*

This action does not have tribal implications, as specified in Executive Order 13175. This action does not change existing regulations. It does not have a substantial direct effect on one or more Indian Tribes, since Tribes are not obligated to adopt or implement any NAAQS. The Tribal Authority Rule gives Tribes the opportunity to develop and implement CAA programs such as the primary NO<sub>2</sub> NAAQS, but it leaves to the discretion of the Tribe whether to develop these programs and which programs, or appropriate elements of a program, they will adopt. Thus, Executive Order 13175 does not apply to this action.

*G. Executive Order 13045: Protection of Children From Environmental Health and Safety Risks*

This action is not subject to Executive Order 13045 because it is not economically significant as defined in Executive Order 12866. The health effects evidence and risk assessment information for this action, which focuses on children, people with asthma, and older adults, in addressing the at-risk populations, is summarized in section II.C.3 above and described in the ISA and PA, copies of which are in the public docket for this action.

*H. Executive Order 13211: Actions That Significantly Affect Energy Supply, Distribution or Use*

This action is not a “significant energy action” because it is not likely to have a significant adverse effect on the supply, distribution, or use of energy. The purpose of this notice is to propose to retain the current primary NO<sub>2</sub> NAAQS. This proposal does not change existing requirements. Thus, the EPA concludes that this proposal does not constitute a significant energy action as defined in Executive Order 13211.

*I. National Technology Transfer and Advancement Act (NTTAA)*

This action does not involve technical standards.

*J. Executive Order 12898: Federal Actions To Address Environmental Justice in Minority Populations and Low-Income Populations*

The EPA believes that this action does not have disproportionately high and adverse human health or environmental effects on minority, low-income populations and/or indigenous peoples, as specified in Executive Order 12898 (59 FR 7629, February 16, 1994). The documentation for this decision is

contained in Section II. The action proposed in this notice is to retain without revision the existing primary NAAQS for oxides of nitrogen based on the Administrator’s conclusion that the existing standards protect public health, including the health of sensitive groups, with an adequate margin of safety. The EPA expressly considered the available information regarding health effects among at-risk populations in reaching the proposed decision that the existing standards are requisite.

*K. Determination Under Section 307(d)*

Section 307(d)(1)(V) of the CAA provides that the provisions of section 307(d) apply to “such other actions as the Administrator may determine.” Pursuant to section 307(d)(1)(V), the Administrator determines that this action is subject to the provisions of section 307(d).

**References**

- Ahmed, T; Dougherty, R; Sackner, MA. (1983a). Effect of 0.1 ppm NO<sub>2</sub> on pulmonary functions and non-specific bronchial reactivity of normals and asthmatics [final report]. (CR–83/11/BI). Warren, MI: General Motors Research Laboratories.
- Ahmed, T; Dougherty, R; Sackner, MA. (1983b). Effect of NO<sub>2</sub> exposure on specific bronchial reactivity in subjects with allergic bronchial asthma [final report]. (CR–83/07/BI). Warren, MI: General Motors Research Laboratories.
- Anderson, HR; Ponce de Leon, A; Bland, JM; Bower, JS; Emberlin, J; Strachan, DP. (1998). Air pollution, pollens, and daily admissions for asthma in London 1987–92. *Thorax* 53: 842–848. <http://dx.doi.org/10.1136/thx.53.10.842>.
- Arbex, MA; de Souza Conceição, GM; Cendon, SP; Arbex, FF; Lopes, AC; Moysés, EP; Santiago, SL; Saldiva, PHN; Pereira, LAA; Braga, ALF. (2009). Urban air pollution and chronic obstructive pulmonary disease-related emergency department visits. *J Epidemiol Community Health* 63: 777–783. <http://dx.doi.org/10.1136/jech.2008.078360>.
- Atkinson, RW; Anderson, HR; Strachan, DP; Bland, JM; Bremner, SA; Ponce de Leon, A. (1999a). Short-term associations between outdoor air pollution and visits to accident and emergency departments in London for respiratory complaints. *Eur Respir J* 13: 257–265.
- ATSDR (Agency for Toxic Substances and Disease Registry). (2006). A study of ambient air contaminants and asthma in New York City: Part A and B. Atlanta, GA: U.S. Department of Health and Human Services. [http://permanent.access.gpo.gov/lps88357/ASTHMA\\_BRONX\\_FINAL\\_REPORT.pdf](http://permanent.access.gpo.gov/lps88357/ASTHMA_BRONX_FINAL_REPORT.pdf).
- Avol, EL; Linn, WS; Peng, RC; Whynot, JD; Shamoo, DA; Little, DE; Smith, MN; Hackney, JD. (1989). Experimental exposures of young asthmatic volunteers to 0.3 ppm nitrogen dioxide and to



- ambient air pollution. *Toxicol Ind Health* 5: 1025–1034.
- Blackwell, DL; Lucas, JW; Clarke, TC. (2014). Summary health statistics for U.S. adults: National health interview survey, 2012. In *Vital and health statistics*. Hyattsville, MD: National Center for Health Statistics, U.S. Department of Health and Human Services. [http://www.cdc.gov/nchs/data/series/sr\\_10/sr10\\_260.pdf](http://www.cdc.gov/nchs/data/series/sr_10/sr10_260.pdf).
- Bloom, B; Jones, LI; Freeman, G. (2013). Summary health statistics for U.S. children: National health interview survey, 2012. In *Vital and health statistics*. Hyattsville, MD: National Center for Health Statistics, U.S. Department of Health and Human Services. [http://www.cdc.gov/nchs/data/series/sr\\_10/sr10\\_258.pdf](http://www.cdc.gov/nchs/data/series/sr_10/sr10_258.pdf).
- Brown, JS. (2015). Nitrogen dioxide exposure and airway responsiveness in individuals with asthma. *Inhal Toxicol* 27: 1–14. <http://dx.doi.org/10.3109/08958378.2014.979960>.
- Burnett, RT; Smith-Doiron, M; Stieb, D; Cakmak, S; Brook, JR. (1999). Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. *Arch Environ Health* 54: 130–139. <http://dx.doi.org/10.1080/00039899909602248>.
- Bylin, G; Hedenstierna, G; Lindvall, T; Sundin, B. (1988). Ambient nitrogen dioxide concentrations increase bronchial responsiveness in subjects with mild asthma. *Eur Respir J* 1: 606–612.
- Carlsten, C; Dybuncio, A; Becker, A; Chan-Yeung, M; Brauer, M. (2011). Traffic-related air pollution and incident asthma in a high-risk birth cohort. *Occup Environ Med* 68: 291–295. <http://dx.doi.org/10.1136/oem.2010.055152>.
- Clark, NA; Demers, PA; Karr, CJ; Koehoorn, M; Lencar, C; Tamburic, L; Brauer, M. (2010). Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect* 118: 284–290. <http://dx.doi.org/10.1289/ehp.0900916>.
- Clougherty, JE; Levy, JI; Kubzansky, LD; Ryan, PB; Suglia, SF; Canner, MJ; Wright, RJ. (2007). Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology. *Environ Health Perspect* 115: 1140–1146. <http://dx.doi.org/10.1289/ehp.9863>.
- Diez Roux, A; Frey HC (2015a). Letter from Drs. Ana Diez Roux, Chair and H. Christopher Frey, Immediate Past Chair, Clean Air Scientific Advisory Committee to EPA Administrator Gina McCarthy. CASAC Review of the EPA's Integrated Science Assessment for Oxides of Nitrogen—Health Criteria (Second External Review Draft). EPA–CASAC-15-001. September 9, 2015. Available at: [https://yosemite.epa.gov/sab/sabproduct.nsf/6612DAF24438687B85257EBB0070369C/\\$File/EPA-CASAC-15-001+unsigned.pdf](https://yosemite.epa.gov/sab/sabproduct.nsf/6612DAF24438687B85257EBB0070369C/$File/EPA-CASAC-15-001+unsigned.pdf).
- Diez Roux, A; Frey HC (2015b). Letter from Drs. Ana Diez Roux, Chair and H. Christopher Frey, Immediate Past Chair, Clean Air Scientific Advisory Committee to EPA Administrator Gina McCarthy. CASAC Review of the EPA's Review of the Primary National Ambient Air Quality Standards for Nitrogen Dioxide: Risk and Exposure Assessment Planning Document. EPA–CASAC-15-002. September 9, 2015. Available at: [https://yosemite.epa.gov/sab/sabproduct.nsf/264cb1227d55e02c85257402007446a4/A7922887D5BDD8D485257EBB0071A3AD/\\$File/EPA-CASAC-15-002+unsigned.pdf](https://yosemite.epa.gov/sab/sabproduct.nsf/264cb1227d55e02c85257402007446a4/A7922887D5BDD8D485257EBB0071A3AD/$File/EPA-CASAC-15-002+unsigned.pdf).
- Diez Roux, A; Sheppard, E (2017). Letter from Dr. Elizabeth A. (Lianne) Sheppard, Chair, Clean Air Scientific Advisory Committee to EPA Administrator E. Scott Pruitt. CASAC Review of the EPA's Policy Assessment for the Review of the Primary National Ambient Air Quality Standards for Nitrogen Dioxide (External Review Draft—September 2016). EPA–CASAC-17-001. March 7, 2017. Available at: [https://yosemite.epa.gov/sab/sabproduct.nsf/LookupWebProjectsCurrentCASAC/7C2807D0D9BB4CC8852580DD004EBC32/\\$File/EPA-CASAC-17-001.pdf](https://yosemite.epa.gov/sab/sabproduct.nsf/LookupWebProjectsCurrentCASAC/7C2807D0D9BB4CC8852580DD004EBC32/$File/EPA-CASAC-17-001.pdf).
- Düring, I; Bächlin, W; Ketzel, M; Baum, A; Friedrich, U; Wurzler, S. (2011). A new simplified NO/NO<sub>2</sub> conversion model under consideration of direct NO<sub>2</sub>-emissions. *Meteor Z* 20: 67–73. <http://dx.doi.org/10.1127/0941-2948/2011/0491>.
- Folinsbee, LJ. (1992). Does nitrogen dioxide exposure increase airways responsiveness? *Toxicol Ind Health* 8: 273–283.
- Frey HC (2014a). Letter from Dr. H. Christopher Frey, Clean Air Scientific Advisory Committee to EPA Administrator Gina McCarthy. CASAC Review of the EPA's Integrated Science Assessment for Oxides of Nitrogen—Health Criteria (First External Review Draft). EPA–CASAC-14-002. June 10, 2014. Available at: [https://yosemite.epa.gov/sab/sabproduct.nsf/15E4619D3CD3409A85257CF30069387D/\\$File/EPA-CASAC-14-002+unsigned.pdf](https://yosemite.epa.gov/sab/sabproduct.nsf/15E4619D3CD3409A85257CF30069387D/$File/EPA-CASAC-14-002+unsigned.pdf).
- Frey HC (2014b). Letter from Dr. H. Christopher Frey, Clean Air Scientific Advisory Committee to EPA Administrator Gina McCarthy. CASAC Review of the EPA's Integrated Review Plan for the Primary National Ambient Air Quality Standards for Nitrogen Dioxide (External Review Draft). EPA–CASAC-14-001. June 10, 2014. Available at: [https://yosemite.epa.gov/sab/sabproduct.nsf/89989229944F36B085257CF300692E2A/\\$File/EPA-CASAC-14-001+unsigned.pdf](https://yosemite.epa.gov/sab/sabproduct.nsf/89989229944F36B085257CF300692E2A/$File/EPA-CASAC-14-001+unsigned.pdf).
- Gehring, U; Gruzieva, O; Agius, RM; Beelen, R; Custovic, A; Cyrys, J; Eeftens, M; Flexeder, C; Fuertes, E; Heinrich, J; Hoffmann, B; de Jongste, JC; Kerkhof, M; Klümper, C; Korek, M; Mölter, A; Schultze, ES; Simpson, A; Sugiri, D; Svartengren, M; von Berg, A; Wijga, AH; Pershagen, G; Brunekreef, B. (2013). Air pollution exposure and lung function in children: the ESCAPE project. *Environ Health Perspect* 121: 1357–1364. <http://dx.doi.org/10.1289/ehp.1306770>.
- Goodman, JE; Chandalia, JK; Thakali, S; Seeley, M. (2009). Meta-analysis of nitrogen dioxide exposure and airway hyper-responsiveness in asthmatics. *Crit Rev Toxicol* 39: 719–742. <http://dx.doi.org/10.3109/10408440903283641>.
- Hazucha, MJ; Ginsberg, JF; McDonnell, WF; Haak, ED, Jr; Pimmel, RL; Salaam, SA; House, DE; Bromberg, PA. (1983). Effects of 0.1 ppm nitrogen dioxide on airways of normal and asthmatic subjects. *J Appl Physiol Respir Environ Exerc Physiol* 54: 730–739.
- Hinwood, AL; De Klerk, N; Rodriguez, C; Jacoby, P; Runnion, T; Rye, P; Landau, L; Murray, F; Feldwick, M; Spickett, J. (2006). The relationship between changes in daily air pollution and hospitalizations in Perth, Australia 1992–1998: A case-crossover study. *Int J Environ Health Res* 16: 27–46. <http://dx.doi.org/10.1080/09603120500397680>.
- Howden, LM; Meyer, JA. (2011). Age and sex composition: 2010. (2010 Census Briefs, C2010BR-03). Washington, DC: U.S. Department of Commerce, Economics and Statistics Administration, U.S. Census Bureau. <http://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf>.
- Itano, Y et al. (2014). Estimation of Primary NO<sub>2</sub>/NO<sub>x</sub> Emission Ratio from Road Vehicles Using Ambient Monitoring Data. *Studies in Atm Sci*, 1–7.
- Ito, K; Mathes, R; Ross, Z; Nádas, A; Thurston, G; Matte, T. (2011). Fine particulate matter constituents associated with cardiovascular hospitalizations and mortality in New York City. *Environ Health Perspect* 119: 467–473. <http://dx.doi.org/10.1289/ehp.1002667>.
- Jaffe, DH; Singer, ME; Rimm, AA. (2003). Air pollution and emergency department visits for asthma among Ohio Medicaid recipients, 1991–1996. *Environ Res* 91: 21–28. [http://dx.doi.org/10.1016/S0013-9351\(02\)00004-X](http://dx.doi.org/10.1016/S0013-9351(02)00004-X).
- Jenkins, HS; Devalia, JL; Mister, RL; Bevan, AM; Rusznak, C; Davies, RJ. (1999). The effect of exposure to ozone and nitrogen dioxide on the airway response of atopic asthmatics to inhaled allergen: Dose- and time-dependent effects. *Am J Respir Crit Care Med* 160: 33–39. <http://dx.doi.org/10.1164/ajrccm.160.1.9808119>.
- Jerrett, M; Shankardass, K; Berhane, K; Gauderman, WJ; Künzli, N; Avol, E; Gilliland, F; Lurmann, F; Molitor, JN; Molitor, JT; Thomas, DC; Peters, J; McConnell, R. (2008). Traffic-related air pollution and asthma onset in children: A prospective cohort study with individual exposure measurement. *Environ Health Perspect* 116: 1433–1438. <http://dx.doi.org/10.1289/ehp.10968>.
- Jimenez, JL et al. (2000). Remote sensing of NO and NO<sub>2</sub> emissions from heavy-duty diesel trucks using tunable diode lasers. *Environ Sci Technol*, 2380–2387.
- Kleinman, MT; Bailey, RM; Linn, WS; Anderson, KR; Whynot, JD; Shamoo, DA; Hackney, JD. (1983). Effects of 0.2 ppm nitrogen dioxide on pulmonary function and response to bronchoprovocation in asthmatics. *J Toxicol Environ Health* 12: 815–826. <http://dx.doi.org/10.1080/15287398309530472>.

- Klepeis, NE; Tsang, AM; Behar, JV. (1996). Analysis of the national human activity pattern survey (NHAPS) respondents from a standpoint of exposure assessment [EPA Report]. (EPA/600/R-96/074). Washington, DC: U.S. Environmental Protection Agency. [http://exposurescience.org/pub/reports/NHAPS\\_Report1.pdf#...LocalSettingsTemporaryInternetFilesContent.Outlook3JQ221FPBApproachesPopulationTables.docx](http://exposurescience.org/pub/reports/NHAPS_Report1.pdf#...LocalSettingsTemporaryInternetFilesContent.Outlook3JQ221FPBApproachesPopulationTables.docx).
- Ko, FWS; Tam, W; Wong, TW; Lai, CKW; Wong, GWK; Leung, TF; Ng, SSS; Hui, DSC. (2007). Effects of air pollution on asthma hospitalization rates in different age groups in Hong Kong. *Clin Exp Allergy* 37: 1312–1319. <http://dx.doi.org/10.1111/j.1365-2222.2007.02791.x>.
- Kota, SH et al. (2013). Simulating near-road reactive dispersion of gaseous air pollutants using a three-dimensional eulerian model. *Sci Total Environ*, Simulating near-road reactive dispersion of gaseous air pollutants using a three-dimensional eulerian model.
- Li, S; Batterman, S; Wasilevich, E; Wahl, R; Wirth, J; Su, FC; Mukherjee, B. (2011). Association of daily asthma emergency department visits and hospital admissions with ambient air pollutants among the pediatric Medicaid population in Detroit: Time-series and time-stratified case-crossover analyses with threshold effects. *Environ Res* 111: 1137–1147. <http://dx.doi.org/10.1016/j.envres.2011.06.002>.
- Linn, WS; Szlachcic, Y; Gong, H, Jr; Kinney, PL; Berhane, KT. (2000). Air pollution and daily hospital admissions in metropolitan Los Angeles. *Environ Health Perspect* 108: 427–434.
- MacIntyre, EA; Gehring, U; Mölter, A; Fuentes, E; Klümper, C; Krämer, U; Quass, U; Hoffmann, B; Gascon, M; Brunekreef, B; Koppelman, GH; Beelen, R; Hoek, G; Birk, M; de Jongste, JC; Smit, HA; Cyrus, J; Gruzjeva, O; Korek, M; Bergström, A; Agius, RM; de Vocht, F; Simpson, A; Porta, D; Forastiere, F; Badaloni, C; Cesaroni, G; Esplugues, A; Fernández-Somoano, A; Lerxundi, A; Sunyer, J; Cirach, M; Nieuwenhuijsen, MJ; Pershagen, G; Heinrich, J. (2014). Air pollution and respiratory infections during early childhood: an analysis of 10 European birth cohorts within the ESCAPE Project. *Environ Health Perspect* 122: 107–113. <http://dx.doi.org/10.1289/ehp.1306755>.
- McConnell, R; Islam, T; Shankardass, K; Jerrett, M; Lurmann, F; Gilliland, F; Gauderman, J; Avol, E; Künzli, N; Yao, L; Peters, J; Berhane, K. (2010). Childhood incident asthma and traffic-related air pollution at home and school. *Environ Health Perspect* 118: 1021–1026. <http://dx.doi.org/10.1289/ehp.0901232>.
- Migliaretti, G; Cadum, E; Migliore, E; Cavallo, F. (2005). Traffic air pollution and hospital admission for asthma: a case-control approach in a Turin (Italy) population. *Int Arch Occup Environ Health* 78: 164–169. <http://dx.doi.org/10.1007/s00420-004-0569-3>.
- Nishimura, KK; Galanter, JM; Roth, LA; Oh, SS; Thakur, N; Nguyen, EA; Thyne, S; Farber, HJ; Serebrisky, D; Kumar, R; Brigno-Buenaventura, E; Davis, A; LeNoir, MA; Meade, K; Rodriguez-Cintron, W; Avila, PC; Borrell, LN; Bibbins-Domingo, K; Rodriguez-Santana, JR; Sen, S; Lurmann, F; Balmes, JR; Burchard, EG. (2013). Early-life air pollution and asthma risk in minority children: The GALA II and SAGE II studies. *Am J Respir Crit Care Med* 188: 309–318. <http://dx.doi.org/10.1164/rccm.201302-0264OC>.
- Orehek, J; Massari, JP; Gayraud, P; Grimaud, C; Charpin, J. (1976). Effect of short-term, low-level nitrogen dioxide exposure on bronchial sensitivity of asthmatic patients. *J Clin Invest* 57: 301–307. <http://dx.doi.org/10.1172/JCI108281>.
- Ortman, JM; Velkoff, VA; Hogan, H. (2014). An aging nation: The older population in the United States (pp. 1–28). (P25–1140). United States Census Bureau. <http://www.census.gov/library/publications/2014/demo/p25-1140.html>.
- Peel, JL; Tolbert, PE; Klein, M; Metzger, KB; Flanders, WD; Todd, K; Mulholland, JA; Ryan, PB; Frumkin, H. (2005). Ambient air pollution and respiratory emergency department visits. *Epidemiology* 16: 164–174. <http://dx.doi.org/10.1097/01.ede.0000152905.42113.db>.
- Reddel, HK; Taylor, DR; Bateman, ED; Boulet, LP; Boushey, HA; Busse, WW; Casale, TB; Chanez, P; Enright, PL; Gibson, PG; de Jongste, JC; Kerstjens, HA; Lazarus, SC; Levy, ML; O'Byrne, PM; Partridge, MR; Pavord, ID; Sears, MR; Sterk, PJ; Stoloff, SW; Sullivan, SD; Szeffler, SJ; Thomas, MD; Wenzel, SE. (2009). An official American Thoracic Society/European Respiratory Society statement: Asthma control and exacerbations: Standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 180: 59–99. <http://dx.doi.org/10.1164/rccm.200801-060ST>.
- Richmond-Bryant, J; Reff, A. (2012). Air pollution retention within a complex of urban street canyons: A two-city comparison. *Atmos Environ* 49: 24–32. <http://dx.doi.org/10.1016/j.atmosenv.2011.12.036>.
- Richmond-Bryant, J et al. (2016). Estimation of on-road NO<sub>2</sub> concentrations, NO<sub>2</sub>/NO<sub>x</sub> ratios, and related roadway gradients from near-road monitoring data. *Submitted to Air Quality, Atm and Health*.
- Riedl, MA; Diaz-Sanchez, D; Linn, WS; Gong, H, Jr; Clark, KW; Effros, RM; Miller, JW; Cocker, DR; Berhane, KT. (2012). Allergic inflammation in the human lower respiratory tract affected by exposure to diesel exhaust [HEI] (pp. 5–43; discussion 45–64). (ISSN 1041–5505 Research Report 165). Boston, MA: Health Effects Institute. <http://pubs.healtheffects.org/view.php?id=373>.
- Roger, LJ; Horstman, DH; McDonnell, W; Kehrl, H; Ives, PJ; Seal, E; Chapman, R; Massaro, E. (1990). Pulmonary function, airway responsiveness, and respiratory symptoms in asthmatics following exercise in NO<sub>2</sub>. *Toxicol Ind Health* 6: 155–171. <http://dx.doi.org/10.1177/074823379000600110>.
- Rowangould, GM. (2013). A census of the US near-roadway population: Public health and environmental justice considerations. *Transport Res Transport Environ* 25: 59–67. <http://dx.doi.org/10.1016/j.trd.2013.08.003>.
- Samet, J (2008a). Letter from Dr. Jonathan M. Samet, Chair, Clean Air Scientific Advisory Committee to EPA Administrator Stephen Johnson. Clean Air Scientific Advisory Committee's (CASAC) Peer Review of Draft Chapter 8 of EPA's Risk and Exposure Assessment to Support the Review of the NO<sub>2</sub> Primary National Ambient Air Quality Standard. EPA-CASAC-09-001. October 28, 2008. Available at: [http://yosemite.epa.gov/sab/sabproduct.nsf/264cb1227d55e02c85257402007446a4/87D38275673D66B8852574F00069D45E/\\$File/EPA-CASAC-09-001-unsigned.pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/264cb1227d55e02c85257402007446a4/87D38275673D66B8852574F00069D45E/$File/EPA-CASAC-09-001-unsigned.pdf).
- Samet, J (2008b). Letter from Dr. Jonathan M. Samet, Chair, Clean Air Scientific Advisory Committee to EPA Administrator Stephen Johnson. Clean Air Scientific Advisory Committee's (CASAC) Review comments on EPA's Risk and Exposure Assessment to Support the Review of the NO<sub>2</sub> Primary National Ambient Air Quality Standard. EPA-CASAC-09-003. December 16, 2008. Available at: [http://yosemite.epa.gov/sab/sabproduct.nsf/264cb1227d55e02c85257402007446a4/9C4A540D86BFB67A852575210074A7AE/\\$File/EPA-CASAC-09-003-unsigned.pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/264cb1227d55e02c85257402007446a4/9C4A540D86BFB67A852575210074A7AE/$File/EPA-CASAC-09-003-unsigned.pdf).
- Samet, J (2009). Letter from Dr. Jonathan M. Samet, Chair, Clean Air Scientific Advisory Committee to EPA Administrator Lisa P. Jackson. Comments and Recommendations Concerning EPA's Proposed Rule for the Revision of the National Ambient Air Quality Standards (NAAQS) for Nitrogen Dioxide. EPA-CASAC-09-014. September 9, 2009. Available at: [http://yosemite.epa.gov/sab/sabproduct.nsf/264cb1227d55e02c85257402007446a4/0067573718EDA17F8525762C0074059E/\\$File/EPA-CASAC-09-014-unsigned.pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/264cb1227d55e02c85257402007446a4/0067573718EDA17F8525762C0074059E/$File/EPA-CASAC-09-014-unsigned.pdf).
- Son, JY; Lee, JT; Park, YH; Bell, ML. (2013). Short-term effects of air pollution on hospital admissions in Korea. *Epidemiology* 24: 545–554. <http://dx.doi.org/10.1097/EDE.0b013e3182953244>.
- Stieb, DM; Szyszkowicz, M; Rowe, BH; Leech, JA. (2009). Air pollution and emergency department visits for cardiac and respiratory conditions: A multi-city time-series analysis. *Environ Health* 8. <http://dx.doi.org/10.1186/1476-069X-8-25>.
- Strand, V; Svartengren, M; Rak, S; Barck, C; Bylin, G. (1998). Repeated exposure to an ambient level of NO<sub>2</sub> enhances asthmatic response to a nonsymptomatic allergen dose. *Eur Respir J* 12: 6–12. <http://dx.doi.org/10.1183/09031936.98.12010006>.
- Strickland, MJ; Darrow, LA; Klein, M; Flanders, WD; Sarnat, JA; Waller, LA; Sarnat, SE; Mulholland, JA; Tolbert, PE. (2010). Short-term associations between ambient air pollutants and pediatric

- asthma emergency department visits. *Am J Respir Crit Care Med* 182: 307–316. <http://dx.doi.org/10.1164/rccm.200908-1201OC>.
- Tunnicliffe, WS; Burge, PS; Ayres, JG. (1994). Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. *Lancet* 344: 1733–1736. [http://dx.doi.org/10.1016/s0140-6736\(94\)92886-x](http://dx.doi.org/10.1016/s0140-6736(94)92886-x).
- U.S. EPA (1971). Air Quality Criteria for Nitrogen Oxides. U.S. Environmental Protection Agency, Air Pollution Control Office, Washington, DC January 1971. Air Pollution Control Office Publication No. AP-84.
- U.S. EPA (1993). Air Quality Criteria for Oxides of Nitrogen. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. Research Triangle Park, NC. EPA-600/8-91-049aF-cF, August 1993. Available at: <http://cfpub.epa.gov/ncea/cfm/recorddisplay.cfm?deid=40179>.
- U.S. EPA (1995). Review of the National Ambient Air Quality Standards for Nitrogen Oxides: Assessment of Scientific and Technical Information, OAQPS Staff Paper. U.S. EPA, Office of Air Quality Planning and Standards, Research Triangle Park, NC. EPA-452/R-95-005, September 1995. Available at: <http://www.epa.gov/ttn/naaqs/standards/nox/data/noxsp1995.pdf>.
- U.S. EPA (2008a). Integrated Science Assessment for Oxides of Nitrogen—Health Criteria. U.S. EPA, National Center for Environmental Assessment and Office, Research Triangle Park, NC. EPA/600/R-08/071. July 2008. Available at: <http://cfpub.epa.gov/ncea/cfm/recorddisplay.cfm?deid=194645>.
- U.S. EPA (2008b). Risk and Exposure Assessment to Support the Review of the NO<sub>2</sub> Primary National Ambient Air Quality Standard. U.S. EPA, Office of Air Quality Planning and Standards. Research Triangle Park, NC. EPA 452/R-08-008a/b. November 2008. Available at: [http://www.epa.gov/ttn/naaqs/standards/nox/s\\_nox\\_cr\\_rea.html](http://www.epa.gov/ttn/naaqs/standards/nox/s_nox_cr_rea.html).
- U.S. EPA (2011). Policy Assessment for the Review of the Particulate Matter National Ambient Air Quality Standards. Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency, Research Triangle Park, NC. EPA 452/R-11-003. April 2011. Available at: [https://www3.epa.gov/ttn/naaqs/standards/pm/s\\_pm\\_2007\\_pa.html](https://www3.epa.gov/ttn/naaqs/standards/pm/s_pm_2007_pa.html).
- U.S. EPA (2014a). Integrated Review Plan for the Primary National Ambient Air Quality Standards for Nitrogen Dioxide. U.S. EPA, National Center for Environmental Assessment and Office of Air Quality Planning and Standards, Research Triangle Park, NC. EPA-452/R-14-003. June 2014. Available at: <http://www.epa.gov/ttn/naaqs/standards/nox/data/201406finalirpprimaryno2.pdf>.
- U.S. EPA (2014b). Policy Assessment for the Review of the Ozone National Ambient Air Quality Standards. Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency, Research Triangle Park, NC. EPA 452/R-14-006. August 2014. Available at: [https://www3.epa.gov/ttn/naaqs/standards/ozone/s\\_o3\\_2008\\_pa.html](https://www3.epa.gov/ttn/naaqs/standards/ozone/s_o3_2008_pa.html).
- U.S. EPA (2015a). Preamble to the Integrated Science Assessments. U.S. EPA, Washington, DC, EPA/600/R-15/067. November 2015. Available at: <https://cfpub.epa.gov/ncea/isa/recorddisplay.cfm?deid=310244>.
- U.S. EPA (2015b). Review of the Primary National Ambient Air Quality Standards for Nitrogen Dioxide: Risk and Exposure Assessment Planning Document. U.S. EPA, Office of Air Quality Planning and Standards, Research Triangle Park, NC. EPA-452/D-15-001. May 13, 2015. Available at: <https://www3.epa.gov/ttn/naaqs/standards/nox/data/20150504reapanning.pdf>.
- U.S. EPA (2016a). Integrated Science Assessment for Oxides of Nitrogen—Health Criteria (2016 Final Report). U.S. EPA, National Center for Environmental Assessment, Research Triangle Park, NC. EPA/600/R-15/068. January 2016. Available at: <https://cfpub.epa.gov/ncea/isa/recorddisplay.cfm?deid=310879>.
- U.S. EPA (2016b). Integrated Review Plan for the National Ambient Air Quality Standards for Particulate Matter. U.S. EPA, National Center for Environmental Assessment and Office of Air Quality Planning and Standards, Research Triangle Park, NC. EPA/452/R-16/005. December 2016. Available at: <https://www3.epa.gov/ttn/naaqs/standards/pm/data/201612-final-integrated-review-plan.pdf>.
- U.S. EPA (2017a). Policy Assessment for the Review of the Primary National Ambient Air Quality Standards for Oxides of Nitrogen. U.S. EPA, National Center for Environmental Assessment, Research Triangle Park, NC. EPA-452/R-17-003. April 2017. Available at: [https://www.epa.gov/sites/production/files/2017-04/documents/policy\\_assessment\\_for\\_the\\_review\\_of\\_the\\_no2\\_naaqs\\_-\\_final\\_report.pdf](https://www.epa.gov/sites/production/files/2017-04/documents/policy_assessment_for_the_review_of_the_no2_naaqs_-_final_report.pdf).
- U.S. EPA (2017b). Integrated Review Plan for the Secondary National Ambient Air Quality Standards for Ecological Effects of Oxides of Nitrogen, Oxides of Sulfur, and Particulate Matter. U.S. EPA, National Center for Environmental Assessment, Research Triangle Park, NC. EPA-452/R-17-002. January 2017. Available at: [http://ofmpub.epa.gov/eims/eimscmm.getfile?p\\_download\\_id=530335](http://ofmpub.epa.gov/eims/eimscmm.getfile?p_download_id=530335).
- Villeneuve, PJ; Chen, L; Rowe, BH; Coates, F. (2007). Outdoor air pollution and emergency department visits for asthma among children and adults: A case-crossover study in northern Alberta, Canada. *Environ Health* 6: 40. <http://dx.doi.org/10.1186/1476-069X-6-40>.
- Witten, A; Solomon, C; Abbritti, E; Arjomandi, M; Zhai, W; Kleinman, M; Balmes, J. (2005). Effects of nitrogen dioxide on allergic airway responses in subjects with asthma. *J Occup Environ Med* 47: 1250–1259. <http://dx.doi.org/10.1097/01.jom.0000177081.62204.8d>.
- Wong, CM; Yang, L; Thach, TQ; Chau, PY; Chan, KP; Thomas, GN; Lam, TH; Wong, TW; Hedley, AJ; Peiris, JS. (2009). Modification by influenza on health effects of air pollution in Hong Kong. *Environ Health Perspect* 117: 248–253. <http://dx.doi.org/10.1289/ehp.11605>.

#### List of Subjects in 40 CFR Part 50

Environmental protection, Air pollution control, Carbon monoxide, Lead, Nitrogen dioxide, Ozone, Particulate matter, Sulfur oxides.

Dated: July 14, 2017.

**E. Scott Pruitt,**  
Administrator.

[FR Doc. 2017-15591 Filed 7-25-17; 8:45 am]

**BILLING CODE 6560-50-P**