**ENVIRONMENTAL PROTECTION AGENCY**

**40 CFR Part 50**

**[EPA–HQ–OAR–2013–0146; FRL–9976–78–OAR]**

**RIN 2060–AR57**

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

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

**ACTION:** Final action.

**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 oxides of nitrogen, as measured by nitrogen dioxide ($NO_2$), the EPA is retaining the current standards, without revision.

**DATES:** This final action is effective on May 18, 2018.

**ADDRESSES:** The EPA has established a docket for this action under Docket ID No. EPA–HQ–OAR–2013–0146. Incorporated into this docket is a separate docket established for the Integrated Science Assessment for this review (Docket ID No. EPA–HQ–ORD–2013–0232). All documents in these dockets are listed on the *www.regulations.gov* website. 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 will be publicly available only in hard copy form. It may be viewed, with prior arrangement, at the EPA Docket Center. Publicly available docket materials are available either electronically in *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.

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### Availability of Information Related to This Action

A number of the documents that are relevant to this decision are available through the EPA's website 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/201406finalirpprimaryno2.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.

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### Executive Summary

This document describes the completion of the EPA's current review of the primary NAAQS for oxides of nitrogen, of which nitrogen dioxide ($NO_2$) is the component of greatest concern for health and is the indicator for the primary NAAQS. This review of the standards and the air quality criteria (the scientific information upon which the standards are based) is required by the Clean Air Act (CAA) on a periodic basis. In conducting this review, the EPA has carefully evaluated the currently available scientific literature on the health effects of $NO_2$, focusing particularly on the information newly available since the conclusion of the last review. This section briefly summarizes background information about this action and the Administrator's decision to retain the current primary $NO_2$ standards. A full discussion of these topics is provided later in this document.

#### *Summary of Background Information*

There are currently two primary standards for oxides of nitrogen: A 1-hour standard established in 2010 at a level of 100 parts per billion (ppb) based on the 98th percentile of the annual distribution of daily maximum 1-hour $NO_2$ concentrations, averaged over 3 years, and an annual standard, originally set in 1971, at a level of 53 ppb based on annual average $NO_2$ concentrations.

Sections 108 and 109 of the 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) $NO_2$ 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 notice setting forth the EPA's final decision by April 6, 2018.

The last review of the primary $NO_2$ NAAQS was completed in 2010. In that review, the EPA supplemented the existing primary annual $NO_2$ 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 $NO_2$ 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 $NO_2$ standards. The gaseous oxides of nitrogen include $NO_2$ and nitric oxide (NO), as well as their gaseous reaction products. Total oxides of nitrogen include these gaseous species as well as particulate species (*e.g.,* nitrates). 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 welfare effects associated with $NO_X$ and $SO_X$ and the ecological welfare effects associated with PM. (U.S. EPA, 2017b).

*Summary of Decision*

In this action, the EPA is retaining the current primary $NO_2$ standards, without revision. This 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 2016 $NO_X$ Integrated Science Assessment (ISA); analyses and considerations in the Policy Assessment (PA); the advice and recommendations of the Clean Air Scientific Advisory Committee (CASAC); and public comments.

Based on these considerations, the Administrator reaches the conclusion that the current body of scientific evidence and the results of quantitative analyses supports his judgment that the current 1-hour and annual primary $NO_2$ standards, together, are requisite to protect public health with an adequate margin of safety, and do not call into question any of the elements of those standards. These conclusions are consistent with the CASAC recommendations. In its advice to the Administrator, the CASAC ''recommend[ed] 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 EPA is retaining the current 1-hour and annual $NO_2$ primary standards, without revision.

As in the last review, the strongest evidence continues to come from studies examining respiratory effects following short-term $NO_2$ exposures.[1] In particular, the 2016 $NO_X$ ISA concludes that ''[a] causal relationship exists between short-term $NO_2$ exposure and respiratory effects based on evidence for asthma exacerbation'' (U.S. EPA, 2016a, p. 1–17). The strongest support for this conclusion comes from controlled human exposure studies examining the potential for $NO_2$-induced increases in airway responsiveness (AR) (which is a hallmark of asthma) in individuals with asthma. Additional supporting evidence comes from epidemiologic studies reporting associations between short-term $NO_2$ exposures and an array of respiratory outcomes related to asthma exacerbation (*e.g.,* asthma-related hospital admissions and emergency department (ED) visits in children and adults).

In addition to the effects of short-term exposures, the 2016 $NO_X$ ISA concludes that there is ''likely to be a causal relationship'' between long-term $NO_2$ 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 $NO_2$ exposures and asthma incidence. Additional support comes from experimental studies supporting the biological plausibility of a potential mode of action by which $NO_2$ exposures could cause asthma development.

While the evidence supports the occurrence of adverse $NO_2$-related respiratory effects at ambient $NO_2$ concentrations likely to have been above those allowed by the current primary $NO_2$ NAAQS, that evidence, together with analyses of the potential for $NO_2$ exposures, does 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 $NO_2$ exposure concentrations that cause increased AR. Analyses based on information from these studies indicate that the current standards provide protection against the potential for $NO_2$ exposures that could increase AR in people with asthma. In addition, while epidemiologic studies report relatively precise associations with serious $NO_2$-related health outcomes (*i.e.,* ED 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 $NO_2$ concentrations that would have clearly met those standards.

After considering the current body of scientific evidence, the results of quantitative analyses, the CASAC advice, and public comments, the Administrator concludes that the current 1-hour and annual $NO_2$ primary standards, together, are requisite to protect public health with an adequate margin of safety. Therefore, in this review, the EPA is retaining the current 1-hour and annual $NO_2$ primary standards, without revision.

## 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

[1] The 2016 $NO_X$ ISA defines short-term exposures as those with durations of minutes up to 1 month, with most studies examining effects related to exposures in the range of 1 hour to 1 week (U.S. EPA, 2016a, p. 1–15).

''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, [is] requisite to protect the public health.'' [2] 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.'' [3]

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 (D.C. Cir. 1980); *American Petroleum Institute* v. *Costle,* 665 F.2d 1176, 1186 (D.C. Cir. 1981); *American Farm Bureau Federation* v. *EPA,* 559 F.3d 512, 533 (D.C. Cir. 2009); *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 Association,* 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,[4] 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 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).[5]

*B. Related $NO_2$ Control Programs*

States are primarily responsible for ensuring attainment and maintenance of ambient air quality standards once the EPA has established them. Under section 110 of the Act, 42 U.S.C. 7410, and related provisions, states are to submit, for the EPA's 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 the EPA, also administer the Prevention of Significant Deterioration permitting 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; 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 for the $NO_2$ NAAQS (see 77 FR 9532 (February 17, 2012)). In addition, there are currently no monitors where there are design values (DVs) [6] above either the 1-hour or annual standard (U.S. EPA, 2017a, Figure 2–5), with the maximum DVs in 2015 being 30 ppb (annual) and 72 ppb (hourly) (U.S. EPA, 2017a Section, 2.3.1).

While $NO_X$ [7] is emitted from a wide variety of source types, the top three categories of sources of $NO_X$ emissions are highway vehicles, off-highway vehicles, and stationary fuel combustion sources.[8] The EPA anticipates that $NO_X$

[2] 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).

[3] 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, 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.''

[4] As used here and similarly throughout this document, 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 lifestage.

[5] Lists of the CASAC members and members of the $NO_2$ Review Panel are available at: *http://yosemite.epa.gov/sab/sabproduct.nsf/WebCASAC/CommitteesandMembership?OpenDocument.*

[6] The metric used to determine whether areas meet or exceed the NAAQS is called a design value (DV). In the case of the primary $NO_2$ 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 $NO_2$ concentrations. The requirements for calculating DVs for the primary $NO_2$ NAAQS from valid monitoring data are further specified in Appendix S to Part 50.

[7] In this context, $NO_X$ refers to the sum of NO and $NO_2$, as is common within air pollution research and control communities. However, in the larger context of this NAAQS review, the terms ''oxides of nitrogen'' and ''nitrogen oxides'' generally refer more broadly to gaseous oxides of nitrogen, which include $NO_2$ and NO, as well as their gaseous reaction products.

[8] Highway vehicles include all on-road vehicles, including light duty as well as heavy duty vehicles,

emissions will continue to decrease over the next 20 years. For example, 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 $NO_X$, with Tier 3 standards phasing in from model year 2017 to model year 2025. For heavy-duty engines, new $NO_X$ standards were phased in between the 2007 and 2010 model years, following the introduction of ultra-low sulfur diesel fuel. More stringent $NO_X$ standards for non-road diesel engines, locomotives, and certain marine engines are becoming effective throughout the next decade. In future decades, these vehicles and engines meeting more stringent $NO_X$ standards will become an increasingly large fraction of in-use mobile sources, leading to large $NO_X$ emission reductions.[9]

*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). Based on these air quality criteria, the EPA promulgated the $NO_2$ NAAQS (36 FR 8186, April 30, 1971). Both primary and secondary standards were set at 53 ppb,[10] annual average. Since then, the Agency has completed multiple reviews of the air quality criteria and primary $NO_2$ standards. In the last review, the EPA made revisions to the primary $NO_2$ NAAQS in order to provide requisite protection of public health. Specifically, the EPA supplemented the existing primary annual $NO_2$ 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 $NO_2$ 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 $NO_2$ 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 $NO_2$ 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 the 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 $NO_2$ 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 $NO_X$ ISA and subsequently 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 $NO_2$ and the review of the primary $NO_2$ NAAQS. The draft plan for the $NO_X$ 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 $NO_X$ 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 recommendations on the second draft ISA and the draft REA planning document 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 the CASAC 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 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.[11]

both gasoline- and diesel-powered, and on-highway motorcycles. Off-highway engines, vehicles and equipment include aircraft, marine vessels, locomotives, off-highway motorcycles, recreational vehicles and other non-road products (*e.g.,* lawnmowers, portable generators, chainsaws, forklifts). Fuel combustion sources includes electric power generating units (EGUs), which derive their power generation from all types of fuels.

[9] Reductions in ambient $NO_2$ concentrations could also result from the implementation of NAAQS for other pollutants (*e.g.,* ozone, PM), to the extent $NO_X$ emissions are reduced as part of the implementation of those standards.

[10] In 1971, primary and secondary $NO_2$ NAAQS were set at levels of 100 micrograms per cubic meter ($\mu g/m^3$), which equals 0.053 parts per million (ppm) or 53 ppb.

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

On July 14, 2017, the proposed decision to retain the $NO_2$ NAAQS was signed, and it was published in the **Federal Register** on July 26 (82 FR 34792). The 60-day comment period ended on September 25, 2017, and comments were received from various government, industry, and environmental groups, as well as members of the general public.

In addition, in July 2016, a lawsuit was filed against the EPA that included a claim that EPA had failed to complete its review of the primary $NO_2$ 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 the EPA should withhold consent.[12] The parties to the 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 [13] and the protection afforded by the primary $NO_2$ standards. The gaseous oxides of nitrogen include $NO_2$ 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).[14] The EPA is separately reviewing the welfare effects associated with $NO_X$ and $SO_X$ and the ecological welfare effects associated with PM. (U.S. EPA, 2017a).[15]

*D. Summary of Proposed Decisions*

For reasons discussed in the proposal and summarized in section II.B.1 below, the Administrator proposed to retain the current primary standards for $NO_2$, without revision.

*E. Organization and Approach to Final Decisions*

This action presents the Administrator's final decision in the current review of the primary $NO_2$ standards. The final decision addressing the primary $NO_2$ standards is based on a thorough review in the 2016 $NO_X$ ISA of scientific information on known and potential human health effects associated with exposure to $NO_2$ associated with levels typically found in the ambient air. This final decision also takes into account the following: (1) Staff assessments in the PA of the most policy-relevant information in the ISA, as well as quantitative exposure and risk information; (2) the CASAC advice and recommendations, as reflected in its letters to the Administrator and its discussions of drafts of the ISA and PA at public meetings; (3) public comments received during the development of these documents, both in connection with the CASAC meetings and separately; and (4) public comments received on the proposal. The primary $NO_2$ standards are addressed in section II below. Section III addresses statutory and executive order reviews.

## II. Rationale for Decision on the Primary Standards

This section presents the rationale for the Administrator's decision to retain the existing primary $NO_2$ standards. This rationale is based on a thorough review in the 2016 $NO_X$ ISA of the latest scientific information, generally published through August 2014, on human health effects associated with $NO_2$ and pertaining to the presence of $NO_2$ in the ambient air. This decision also takes into account: (1) The PA's staff assessments of the most policy-relevant information in the ISA and staff analyses of air quality, human exposure and health risks, upon which staff conclusions regarding appropriate considerations in this review are based; (2) the CASAC advice and recommendations, as reflected in discussions of drafts of the ISA and PA at public meetings, in separate written comments, and in the CASAC letters to the Administrator; (3) public comments received during the development of these documents, either in connection with the CASAC meetings or separately; and (4) public comments received on the proposal. Section II.A provides background on the general approach for review of the primary $NO_2$ standards and brief summaries of key aspects of the currently available air quality information, as well as health effects and exposure/risk information. Section II.B presents the Administrator's conclusions on the adequacy of the current primary $NO_2$ standards, drawing on consideration of this information, advice from the CASAC, and comments from the public. Section II.C summarizes the Administrator's decision on the primary $NO_2$ standards.

*A. Introduction*

The Administrator's approach to reviewing the current primary $NO_2$ standards is based, most fundamentally, on using the EPA's assessment of the current scientific evidence and associated quantitative analyses to inform his judgment regarding primary $NO_2$ standards that protect public health with an adequate margin of safety. 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 final decision draws 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 approach to informing these judgments is based on the recognition that the available health effects evidence generally reflects a continuum, consisting of levels at which scientists generally agree that health effects are likely to occur, through lower levels at which the likelihood and magnitude of the response become increasingly uncertain. This approach is consistent with the requirements of the NAAQS provisions of the Act and with how the EPA and the courts have historically interpreted the Act. These provisions require the Administrator to establish primary standards that, in the judgment of the Administrator, are requisite to protect public health with an adequate margin of safety. In so doing, the Administrator seeks to establish standards that are neither more nor less stringent than necessary for this purpose. The Act does not require that primary standards be set at a zero-risk

[12] One comment was received from the American Petroleum Institute (API) and one was received from an anonymous commenter. These comments are available in the docket for the proposed consent decree (EPA–HQ–OGC–2016–0719).

[13] These gaseous oxides of nitrogen can also be referred to as ''nitrogen oxides'' and include a broad category of gaseous oxides of nitrogen (*i.e.,* oxidized nitrogen compounds), including $NO_2$, NO, and their various reaction products.

[14] Additional information on the PM NAAQS is available at: *https://www.epa.gov/naaqs/particulate-matter-pm-air-quality-standards.*

[15] Additional information on the ongoing and previous review of the secondary $NO_2$ and $SO_2$ NAAQS is available at: *https://www.epa.gov/naaqs/nitrogen-dioxide-no2-and-sulfur-dioxide-so2-secondary-air-quality-standards.*

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.

To evaluate whether it is appropriate to consider retaining the current primary $NO_2$ standards, or whether consideration of revision is appropriate, the EPA has adopted an approach in this review that builds upon the general approach used in the last review and reflects the broader body of evidence and information now available. The Administrator's decisions in the prior review were based on an integration of information on health effects associated with exposure to $NO_2$ with information on the public health significance of key health effects, as well as on policy judgments as to when the standard is requisite to protect public health with an adequate margin of safety and advice from the CASAC and public comments. These considerations were informed by air quality and related analyses and quantitative exposure and risk information. Similarly, in this review, as described in the PA, the proposal, and elsewhere in this document, we draw on the current evidence and quantitative assessments of exposure pertaining to the public health risk of $NO_2$ in ambient air. In considering the scientific and technical information here, as in the PA, we consider both the information available at the time of the last review and information newly available since the last review, including most particularly that which has been critically analyzed and characterized in the current ISA. In considering the entire body of evidence presented in the current ISA, as in the PA and as in the last review, we focus particularly on those health endpoints for which the ISA finds associations with $NO_2$ to be causal or likely causal. The evidence-based discussions presented below draw upon evidence from both controlled human exposure studies and epidemiologic studies. Sections II.A.1 through II.A.3 below provide an overview of the current $NO_2$ air quality, health effects, and quantitative exposure and risk information with a focus on the specific policy-relevant questions identified for these categories of information in the PA (U.S. EPA, 2017a, Chapter 3).

### 1. Characterization of $NO_2$ Air Quality

This section presents information on $NO_2$ atmospheric chemistry and ambient concentrations, with a focus on information that is most relevant for the review of the primary $NO_2$ standards. This section is drawn from the more detailed discussion of $NO_2$ air quality in the PA (U.S. EPA, 2017a, Chapter 2) and the 2016 $NO_X$ ISA (U.S. EPA, 2016a, Chapter 2).[16] It presents a summary of $NO_2$ atmospheric chemistry (section II.A.1.a), trends in ambient $NO_2$ concentrations (section II.A.1.b), ambient $NO_2$ concentrations measured at monitors near roads (section II.A.1.c), the relationships between hourly and annual ambient $NO_2$ concentrations (section II.A.1.d), and background concentrations of $NO_2$ (section II.A.1.e).

#### a. Atmospheric Chemistry

Ambient concentrations of $NO_2$ are influenced by both direct $NO_2$ emissions and by emissions of NO, with the subsequent conversion of NO to $NO_2$ primarily though reaction with ozone ($O_3$). The initial reaction between NO and $O_3$ to form $NO_2$ occurs fairly quickly during the daytime, with reaction times on the order of minutes. However, $NO_2$ can also be photolyzed to regenerate NO, creating new $O_3$ 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 $NO_2$. These include nitrate radicals ($NO_3$), nitrous acid (HONO), nitric acid ($HNO_3$), dinitrogen pentoxide ($N_2O_5$), nitryl chloride ($ClNO_2$), peroxynitric acid ($HNO_4$), peroxyacetyl nitrate and its homologues (PANs), other organic nitrates, such as alkyl nitrates (including isoprene nitrates), and $pNO_3$. The sum of these reactive oxidation products and NO plus $NO_2$ comprise the oxides of nitrogen.[17] [18]

Due to the close relationship between NO and $NO_2$, and their ready interconversion, these species are often grouped together and referred to as $NO_X$. The majority of $NO_X$ emissions are in the form of NO. For example, 90% or more of tail-pipe $NO_X$ emissions are in the form of NO, with only about 2% to 10% emitted as $NO_2$ (Itano et al., 2014; Kota et al., 2013; Jimenez et al., 2000; Richmond-Bryant et al., 2016). $NO_X$ emissions require time and sufficient $O_3$ concentrations for the conversion of NO to $NO_2$. Higher temperatures and concentrations of reactants result in 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 $NO_2$ concentrations occur. In particular, while ambient $NO_2$ concentrations are often elevated near important sources of $NO_X$ emissions, such as major roadways, the highest measured ambient concentrations in a given urban area may not always occur immediately adjacent to those sources.[19]

#### b. National Trends in $NO_X$ Emissions and Ambient $NO_2$ Concentrations

Ambient concentrations of $NO_2$ in the U.S. are due largely to $NO_X$ emissions from anthropogenic sources. Background $NO_2$ is estimated to make up only a small fraction of current ambient concentrations (U.S. EPA, 2016a, Section 2.5.6; U.S. EPA, 2017a, Section 2.3.4).[20] Nationwide estimates indicate that there has been a 61% reduction in total $NO_X$ 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, 2017a, Section 2.1.2, Figure 2–3).

Long-term trends in $NO_2$ DVs across the U.S. show that ambient concentrations of $NO_2$ 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 $NO_2$

[16] The focus is on $NO_2$ in this document, 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 2016 $NO_X$ ISA (U.S. EPA, 2016a, Chapter 2).

[17] This follows usages in 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 $NO_X$ are often restricted to refer only to the sum of NO and $NO_2$.

[18] See Figure 2–1 of the $NO_2$ PA for additional information (U.S. EPA, 2017a).

[19] Ambient $NO_2$ concentrations around stationary sources of $NO_X$ emissions are similarly impacted by the availability of $O_3$ and by meteorological conditions, although surface-level $NO_2$ concentrations can be less impacted in cases where stationary source $NO_X$ emissions are emitted from locations elevated substantially above ground level.

[20] Background concentrations of a pollutant can be defined in various ways, depending on context and circumstances. Background concentrations of $NO_2$ are discussed in the 2016 $NO_X$ ISA (U.S. EPA, 2016a, Section 2.5.6) and the PA (U.S. EPA, 2017a, Section 2.3.4).

concentrations (U.S. EPA, 2017a, Figure 2–5).[21] The annual and hourly DVs trended upward in less than 4% of the sites.[22] Even considering the fact that there are a handful of sites where upward trends in $NO_2$ 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).

c. Near-Road $NO_2$ Air Quality

The largest single source of $NO_X$ emissions is on-road vehicles, and emissions are primarily in the form of NO, with $NO_2$ formation requiring both time and sufficient $O_3$ concentrations. Depending on local meteorological conditions and $O_3$ concentrations, ambient $NO_2$ concentrations can be higher near roadways than at sites in the same area but farther removed from the road (and from other sources of $NO_X$ emissions).

When considering the historical relationships between $NO_2$ concentrations at monitors near roadways and monitors farther away from roads, $NO_2$ 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 $NO_2$ 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[23] of dedicated near-road $NO_2$ monitors indicate that daily maximum 1-hour $NO_2$ 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 1-hour standard) were highest at near-road monitors (*i.e.,* higher than all non-near-road monitors 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).[24]

d. Relationships between Hourly and Annual $NO_2$ Concentrations

Control programs have resulted in substantial reductions in $NO_X$ emissions since the 1980s. These reductions in $NO_X$ emissions have decreased both short-term peak $NO_2$ concentrations and annual average concentrations (U.S. EPA, 2017a, Section 2.3.1). Since the 1980s, the median annual $NO_2$ 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 $NO_2$ monitors located at area-wide monitoring sites; data from the new near-road monitoring network were not included the analysis of the relationship between hourly and annual $NO_2$ concentrations due to the limited amount of data available.[25] 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 indicates that 1-hour DVs at or below 100 ppb generally correspond to annual DVs below 35 ppb, with many monitors recording annual concentrations around 30 ppb. (U.S. EPA, 2017a, p. 2–21, Figure 2–11). Based on this, an area meeting the 1-hour standard with its level of 100 ppb would be expected to maintain annual average $NO_2$ concentrations well below the 53 ppb level of the annual standard (U.S. EPA, 2017a, Figure 2–11). It will be important to re-evaluate the relationship between 1-hour and annual standards as more data become available from recently deployed near-road monitors.

2. Overview of the Health Effects Evidence

This section summarizes the available scientific evidence on the health effects of $NO_2$ exposures. These summaries are based primarily on the assessment of the evidence in the 2016 $NO_X$ 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 $NO_2$ standards (U.S. EPA, 2017a).

In the current review of the primary $NO_2$ NAAQS, the 2016 $NO_X$ ISA uses frameworks to characterize the strength of the available scientific evidence for health effects attributable to $NO_2$ exposures and to classify the evidence for factors that may increase risk in some populations[26] or lifestages (U.S. EPA, 2016a, 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 2016 $NO_X$ 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, 2016a, Preamble, Table II).[27] As discussed further below, in evaluating the public health protection provided by the current standards, the EPA's focus is on health effects determined to have a ''causal'' or a ''likely to be causal'' relationship with $NO_2$ exposures. 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 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

[21] Based on an analysis of data from sampling sites with sufficient data to produce at least five valid DVs.

[22] It is not clear what specific sources may be responsible for the upward trends in ambient $NO_2$ concentrations at these sites. (*See* U.S. EPA, 2017a, Section 2.1.2).

[23] Prior to the 2010 rulemaking, monitors were ''not sited to measure peak roadway-associated $NO_2$ concentrations . . . .'' (75 FR 6479).

[24] 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.

[25] Area-wide sites are intended to characterize ambient $NO_2$ concentrations at the neighborhood and larger spatial scales.

[26] 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.

[27] 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 2016 $NO_X$ ISA (U.S. EPA, 2016a).

variety of factors such as age, genetic background, nutritional status, immune competence, and social factors (U.S. EPA, 2017a, Preamble, Section 5.b). Thus, exposure to $NO_2$ 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 $NO_2$ exposures, the 2016 $NO_X$ 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 2016 $NO_X$ ISA judges there is ''adequate'' evidence (U.S. EPA, 2016a, Table 7–27).

The sections below summarize the evidence for effects related to short-term $NO_2$ exposures (*e.g.,* minutes up to 1 month) and the evidence for effects related to long-term $NO_2$ exposures (*e.g.,* months to years).[28] The final section discusses the potential public health implications of $NO_2$ exposures, based on the evidence for populations and lifestages at increased risk of $NO_2$-related effects. The focus of these sections is on health effects that the 2016 $NO_X$ ISA has determined to have a ''causal'' or ''likely to be causal'' relationship with $NO_2$. Health effects whose causal determinations have changed since the last review are also briefly addressed. More information on health effects for which causal determinations are suggestive of, but not sufficient to infer a causal relationship or inadequate to infer a causal relationship (*i.e.,* health effects for which the evidence is weaker) may be found in section II.C of the proposal (87 FR 34792, July 26, 2017).

a. Health Effects With Short-Term Exposure to $NO_2$

This section discusses the evidence for health effects following short-term $NO_2$ exposures. Section II.B.2.a.i discusses the nature of the health effects that have been shown to occur following short-term $NO_2$ exposures and the strength of the evidence supporting various effects, based on the assessment of that evidence in the 2016 $NO_X$ ISA. Section II.B.2.a.ii discusses the $NO_2$ concentrations at which health effects have been demonstrated to occur, based on the considerations and analyses included in the PA. Section II.B.2.a.iii discusses $NO_2$ concentrations in controlled human exposure studies, while section II.B.2.a.iv. discusses $NO_2$ concentrations in locations of epidemiologic studies.

i. Nature of Effects

Across previous reviews of the primary $NO_2$ NAAQS (U.S. EPA, 1993; U.S. EPA, 2008a), evidence has consistently demonstrated respiratory effects attributable to short-term $NO_2$ exposures. In the last review, the 2008 $NO_X$ ISA concluded that evidence was ''sufficient to infer a likely causal relationship between short-term $NO_2$ 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 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 $NO_2$ 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 $NO_X$ ISA noted an overarching uncertainty in determining the extent to which $NO_2$ is independently associated with effects or whether $NO_2$ 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 that was critically evaluated in the 2016 $NO_X$ ISA as part of the full body of evidence informing the nature of the relationship between health effects and short-term exposures to $NO_2$ (U.S. EPA, 2016a).[29] Chapter 5 of the 2016 $NO_X$ ISA presents a detailed assessment of the evidence for health effects associated with short-term $NO_2$ exposures (U.S. EPA, 2016a). In considering the available evidence and the causal determinations presented in the 2016 $NO_X$ ISA, consistent with the PA (U.S. EPA, 2017a), this action focuses on respiratory effects described below. Cardiovascular effects and mortality are also briefly addressed.

Respiratory Effects

The 2016 $NO_X$ ISA concludes that evidence supports a causal relationship between respiratory effects and short-term $NO_2$ exposures, primarily based on evidence for asthma exacerbation. In reaching this conclusion, the 2016 $NO_X$ 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 $NO_2$ exposure can trigger an asthma exacerbation'' (U.S. EPA, 2016a, p. 1–17). In the last review, the 2008 $NO_X$ 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 $NO_2$ could be disentangled from effects related to other traffic-related pollutants. In contrast to the current review, the 2008 $NO_X$ 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 2016 $NO_X$ 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).[30]

Strong evidence supporting this causal determination in the 2016 $NO_X$ ISA comes from a meta-analysis of controlled human exposure studies that evaluate the potential for increased AR[31] following 20-minute to 1-hour $NO_2$ exposures (Brown, 2015).[32] While

[28] Short-term exposures are defined as those with durations of minutes up to 1 month, with most studies examining effects related to exposures in the range of 1 hour to 1 week (2016 $NO_X$ ISA, p. 1–15).

[29] A list of causal determinations from the 2016 $NO_X$ 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 $NO_2$ PA (U.S. EPA, 2017a).

[30] Experimental studies, such as controlled human exposure studies, provide support for effects of exposures to $NO_2$ itself, and generally do not reflect the complex atmospheres to which people are exposed. Thus, unlike epidemiologic studies, experimental studies that evaluate exposures to $NO_2$ itself are not subject to uncertainties related to the potential for copollutant confounding.

[31] The 2016 $NO_X$ ISA states that AR is ''inherent responsiveness of the airways to challenge by bronchoconstricting agents'' (U.S. EPA, 2016a, p. 5–9). 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 ($FEV_1$), but some studies report the change in $FEV_1$ for a specified dose of challenge agent. The change in specific airways resistance (sRaw) is also used to quantify AR.

[32] These studies evaluate the effect of inhaled $NO_2$ on the inherent responsiveness of the airways to challenge by bronchoconstricting agents.

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.[33] AR has been the key respiratory outcome from controlled human exposures in the previous and the current review of the primary $NO_2$ NAAQS. The 2016 $NO_X$ 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 $NO_2$ exposures in subjects with asthma across the large body of controlled human exposure studies,[34] most of which were available in the last review (U.S. EPA, 2017a, Tables 3–2 and 3–3). More specifically, the meta-analysis identified the fraction of individuals having an increase in AR following $NO_2$ exposure, compared to the fraction having a decrease, across studies.[35] 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.[36]

The results from the meta-analysis demonstrate that the majority of study volunteers with asthma experienced increased AR following resting exposure to $NO_2$ 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 asthma. These controlled human exposure studies, the meta-analysis, and uncertainties in this body of evidence are discussed in greater detail below.

The 2016 $NO_X$ 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 2016 $NO_X$ ISA considered a halving of the provocative dose (PD) to indicate responses that may be clinically relevant.[37] [38] With regard to this approach, the 2016 $NO_X$ 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).

Studies considered for inclusion into the meta-analyses by Brown (2015) were identified from the meta-analysis by Goodman et al. (2009), the 2016 $NO_X$ ISA, and a literature search for controlled human exposure studies of individuals with asthma exposed to $NO_2$ that were published since the 2008 $NO_X$ ISA. In one analysis, Brown (2015) showed that $NO_2$ 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) in about a quarter of study volunteers. While these results support the potential for clinically relevant increases in AR in some individuals with asthma following $NO_2$ exposures within the range of 100 to 530 ppb, uncertainty remains given that the analysis of PD is limited to a subset of the studies in which non-specific AR was assessed in individuals following resting exposures to $NO_2$ and air.[39] In addition, compared to conclusions based on the entire range of $NO_2$ 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 $NO_2$ exposure concentration within this range.

Controlled human exposure studies discussed in the 2016 $NO_X$ 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 $NO_2$ concentrations at or near those found in the ambient air in the U.S. However, a subset of studies using $NO_2$ 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 $NO_2$ exposures ranging from 300–1,000 ppb (U.S. EPA, 2016a, Section 5.2.2.5).

In addition to this evidence for $NO_2$-induced increases in AR and allergic inflammation in controlled human exposure studies, the 2016 $NO_X$ ISA also describes evidence from epidemiologic studies for positive associations between short-term $NO_2$ 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 2016 $NO_X$ ISA indicates that epidemiologic studies consistently demonstrate $NO_2$-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 $NO_2$ concentrations in subjects' location(s). Epidemiologic studies also demonstrated associations between short-term $NO_2$ exposures and respiratory symptoms, lung function decrements, and pulmonary inflammation, particularly for measures of personal total and ambient $NO_2$ exposures and $NO_2$ measured outside schools. This is important because there is considerable spatial variability in $NO_2$

[33] A meta-analysis synthesizes data from multiple studies using statistical analyses.

[34] These controlled human exposure studies were conducted in people with asthma, a group at increased risk for $NO_2$-related effects. The severity of asthma varied across studies, ranging from inactive asthma up to severe asthma, with the majority of study participants having a mild form of asthma. (Brown, 2015).

[35] More information on the distribution of study subjects across $NO_2$ concentrations can be found below (section II.A.2.ii). Information on the fraction of individuals who experienced an increase versus a decrease stratified by concentration can also be found in that section.

[36] ''Bronchial challenge agents can be classified as nonspecific (*e.g.,* histamine; $SO_2$; 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).

[37] PD is the dose of challenge agent required to elicit a specified change in a measure of lung function, typically a 20% decrease in $FEV_1$ or a 100% increase in specific airway resistance (sRaw).

[38] The 2016 $NO_X$ 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 AR 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 2016 $NO_X$ ISA to represent an increase in AR that indicates a clinically relevant response.

[39] Section 3.2.2.1 of the PA (U.S. EPA, 2017a) includes additional discussion of these uncertainties.

concentrations, and measurements in subjects' locations may better represent variability in ambient $NO_2$ 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 $NO_2$-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 2016 $NO_X$ 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 2016 $NO_X$ ISA notes that $NO_2$ associations with asthma-related effects persist with adjustment for temperature; humidity; season; long-term time trends; and $PM_{10}$, $SO_2$, or $O_3$. Recent studies also add findings for $NO_2$ associations that generally persist with adjustment for a key copollutant, including $PM_{2.5}$ 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 rarely studied, but $NO_2$ associations with asthma exacerbation tend to persist in the few available copollutant models. The 2016 $NO_X$ ISA recognizes, however, that copollutant models have inherent limitations and cannot conclusively rule out confounding (U.S. EPA, 2015a, Preamble, Section 4.b).

The 2016 $NO_X$ ISA also notes that results based on personal exposures or pollutants measured at people's locations provide support for $NO_2$ associations that are independent of $PM_{2.5}$, EC/BC, organic carbon (OC), or UFPs. Compared to ambient $NO_2$ concentrations measured at central-site monitors, personal $NO_2$ exposure concentrations and indoor $NO_2$ 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 $NO_2$ 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 2016 $NO_X$ ISA comes from controlled human exposure studies demonstrating $NO_2$-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 2016 $NO_X$ 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 2016 $NO_X$ 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 $NO_2$ 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 fundamental understanding of the respiratory effects related to ambient $NO_2$ exposures. New epidemiologic evidence does, however, reduce some uncertainty from the last review regarding the extent to which effects may be independently related to $NO_2$, 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.,* $NO_2$ and traffic-related pollutants).

Cardiovascular Effects

The evidence for a causal relationship between cardiovascular health effects and short-term $NO_2$ exposures in the 2016 $NO_X$ ISA was judged ''suggestive of, but not sufficient to infer, a causal relationship'' (U.S. EPA, 2016a, Section 5.3.11), which reflects a conclusion that the evidence for a causal relationship is stronger in the last review, when the conclusion was that the evidence was ''inadequate to infer the presence or absence of a causal relationship.'' The 2016 determination was primarily supported by consistent epidemiologic evidence from multiple new studies indicating associations between $NO_2$ concentrations and myocardial infarction. More information on these health effects may be found in section II.C.1.a.ii of the proposal (87 FR 34792, July 26, 2017).

Mortality

The 2016 $NO_X$ ISA concludes that the evidence for a causal relationship between short-term $NO_2$ 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). More information on these health effects may be found in section II.C.1.a.iii of the proposal (87 FR 34792, July 26, 2017).

ii. Short-Term $NO_2$ 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 $NO_2$ concentrations that have been associated with various effects. The PA explicitly considers these $NO_2$ 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 $NO_2$ 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 type of effect for which there is the strongest evidence supporting a causal relationship, as discussed in the section above). The PA specifically considers to what extent the evidence indicates adverse asthma-related effects attributable to short-term exposures to $NO_2$ 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 $NO_2$-induced effects have been reported over the ranges of $NO_2$ exposure concentrations evaluated in controlled human exposure studies and the extent to which $NO_2$-associated effects have been reported for distributions of ambient $NO_2$ concentrations in epidemiologic study locations that meet existing standards. These considerations are discussed below for controlled human exposure studies and epidemiologic studies.

iii. $NO_2$ 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 $NO_2$ 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, the evidence does not indicate respiratory symptoms or lung function decrements following $NO_2$ 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).[40] 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 $NO_2$ 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 $NO_2$ concentrations as low as 100 ppb. In contrast, controlled human exposure studies evaluated in the 2016 $NO_X$ ISA do not provide consistent evidence for respiratory symptoms, lung function decrements, or pulmonary inflammation in adults with asthma following exposures to $NO_2$ 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 in these studies make it difficult to interpret the likelihood that these effects could potentially occur following $NO_2$ exposures at or below the level of the current standards.[41]

Thus, in considering the exposure concentrations evaluated in controlled human exposure studies, the PA focuses on the body of evidence for $NO_2$-induced increases in AR in adults with asthma. In evaluating the $NO_2$ 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 $NO_2$ exposures, rather than to chance alone, having the advantage of being based on the same exposure conditions. The meta-analysis by Brown (2015) can also provide insight into the extent to which observed changes are due to $NO_2$ exposures, with the additional benefit of aiding in the identification of trends in individual-level responses across studies and the advantage of increased power to detect effects, even in the absence of statistically significant effects in individual studies, although each study in the meta-analysis may not be based on the exact same exposure conditions.[42]

Consideration of Group Mean Results From Individual Studies

Individual controlled human exposure studies have generally not reported statistically significant increases in AR following resting exposures to $NO_2$ concentrations from 100 to 200 ppb. In considering such studies, the PA notes that the lowest $NO_2$ concentration to which individuals with asthma have been exposed is 100 ppb, with an exposure duration of 60 minutes in all studies at this concentration. Of the five studies conducted at 100 ppb, a statistically significant increase in AR following exposure to $NO_2$ 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 $NO_2$, 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 $NO_2$ 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 its results were not statistically significant (n = 4, Orehek et al., 1976). Thus, as noted above, individual controlled human exposure studies have generally not reported statistically significant increases in AR following resting exposures to $NO_2$ 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 $NO_2$, while trends in the direction of group mean responses were inconsistent following exposures to 100 ppb $NO_2$.

In considering studies in individuals with asthma conducted with exercise and at lower concentrations, the PA notes that three studies evaluated $NO_2$ 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 $NO_2$ 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 $NO_2$, respectively. Thus, as with studies of resting exposures, studies that evaluated exposures to 150 to 200 ppb $NO_2$ with exercise report trends toward increased AR, though results are generally not statistically significant.

Several studies evaluated exposures of individuals with asthma to $NO_2$ concentrations above 200 ppb. Of the five studies that evaluated 30-minute resting exposures to $NO_2$ concentrations from 250 to 270 ppb, $NO_2$-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 $NO_2$, 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 $NO_2$ concentrations from 300 to 600 ppb (U.S. EPA, 2017a, Table 3–3).[43]

Consideration of Results From the Brown (2015) Meta-Analysis

As discussed above, the 2016 $NO_X$ ISA assessment of the evidence for AR

[40] 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.

[41] Despite the difficulty in interpreting the likelihood that these effects would occur at concentrations closer to the current standards, as described later (section II.A.3) the current standards are expected to protect against exposures at the exposure concentrations used in these studies.

[42] Tables 3–2 and 3–3 in the $NO_2$ PA (adapted from the 2016 $NO_X$ 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 $NO_2$ exposure, average PD: The dose of challenge agent required to elicit a particular magnitude of change in $FEV_1$ or other measure of lung function) across subjects, and the statistical significance of the change in AR following $NO_2$ exposures.

[43] There are eight additional studies with exercising exposures to 300–350 ppb $NO_2$ as presented in Table 3–3 of the $NO_2$ PA, with exposure durations ranging from 30–240 minutes. Results across these studies are inconsistent, with only two of eight reporting statistically significant results. Only one of four studies with exercising exposures of 400 or 600 ppb reported statistically significant increases in 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 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 $NO_2$ exposure compared to exposure to filtered air.[44] 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 2016 $NO_X$ 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)), which informed the 2016 $NO_X$ ISA's emphasis on studies of resting exposures and non-specific challenge agents. Overall, the Brown meta-analysis presents the fraction of individuals having an increase in AR following exposure to various $NO_2$ 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).[45]

When evaluating results from the meta-analysis, the PA first considers results across all exposure conditions combined (*i.e.,* resting, exercising, non-specific challenge, and specific challenge). For 100 ppb $NO_2$ exposures, Brown (2015) reported that, of the study participants who experienced either an increase or decrease in AR following $NO_2$ exposures, 61% experienced an increase ($p = 0.08$). For 100 to < 200 ppb $NO_2$ exposures, 62% of study subjects experienced an increase in AR following $NO_2$ exposures ($p = 0.014$). For 200 to 300 ppb $NO_2$ exposures, 58% of study subjects experienced an increase in AR following $NO_2$ exposures ($p = 0.008$). For exposures above 300 ppb $NO_2$, 57% of study subjects experienced an increase in AR following $NO_2$ exposures, though this fraction was not statistically significantly different from 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 (*i.e.,* specific, non-specific). For exposures conducted at rest, across all exposure concentrations (*i.e.,* 100–530 ppb $NO_2$, 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 non-specific AR following $NO_2$ 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 $NO_2$, 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.[46] For non-specific challenge agents, the differences between the fraction of individuals who experienced increased AR following resting $NO_2$ exposures and the fraction who experienced decreased AR reached statistical significance for all of the ranges of exposure concentrations evaluated ($p < 0.001$).

In contrast to the results from studies conducted at rest, the fraction of individuals having an increase in AR following $NO_2$ exposures with exercise was not consistently greater than 50%, particularly when looking at the allergen challenge group, and none of the results were statistically significant (Brown, 2015). Across all $NO_2$ exposures with exercise, measures of non-specific AR were available for 241 individuals, 54% of whom experienced an increase in AR following $NO_2$ 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 non-specific 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 $NO_2$ exposures. The results do not indicate statistically significant fractions of individuals having an increase in specific AR following exposure to $NO_2$ 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 $NO_2$ exposures (Brown, 2015, Table 4). In contrast, for exposures during exercise, most study subjects did not experience $NO_2$-induced increases in specific AR. In contrast, for exposures during exercise, most study subjects did not experience $NO_2$-induced increases in specific AR.[47] Overall, results across studies are less consistent for increases in specific AR following $NO_2$ exposures.

Uncertainties in Evidence for AR

When considering the evidence for $NO_2$-induced increases in AR in individuals with asthma, there are important uncertainties that should be considered. One uncertainty is that available studies of $NO_2$ and AR have generally evaluated adults with mild asthma, while people with more severe asthma could experience more serious effects and/or effects following exposures to lower $NO_2$ concentrations.[48] 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 600 ppb $NO_2$ 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, and can be used to inform the characterization of the magnitude of the effects; however, the lack of an apparent dose-response relationship does not necessarily

[44] More specifically, the Brown (2015) meta-analysis combined information from the studies presented in Tables 3–2 and 3–3 of the PA. It compared the number of study participants who experienced an increase in AR following $NO_2$ 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.

[45] 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 $NO_2$ PA.

[46] 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.

[47] 48% 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) $NO_2$.

[48] Brown (2015) notes, however, that disease status varied in the studies included in the meta-analysis, ranging from ''inactive asthma up to severe asthma in a few studies.''

indicate that there is no relationship between the exposure and effect, particularly in these analyses based largely on between-subject comparisons (*i.e.,* as opposed to comparisons within the same subject exposed to multiple concentrations). As discussed in the 2016 $NO_X$ ISA, there are a number of methodological differences across studies that could contribute to between-subject differences and that could obscure or complicate a dose-response relationship between $NO_2$ and AR (U.S. EPA, 2016a, section 5.2.2.1).[49] These include subject activity level (rest versus exercise) during $NO_2$ exposure, asthma medication usage, choice of airway challenge agent, method of administering the bronchoconstricting agents, and physiological endpoint used to assess AR. Such methodological differences across studies likely contribute to the variability and uncertainty in results across studies and complicate interpretation of the overall body of evidence for $NO_2$-induced AR. Thus, while the lack of an apparent dose-response relationship adds uncertainty to the interpretation of controlled human exposure studies of AR and reduces the ability to fully characterize the health risks associated with these exposures, it does not indicate the lack of an $NO_2$ effect.

An additional uncertainty in interpreting these studies within the context of considering the adequacy of the protection provided by the current primary $NO_2$ NAAQS is the potential adversity of the reported $NO_2$-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 2016 $NO_X$ 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.[50]

Five studies provided data for each individual's PD. These five studies provided individual-level data for a total of 72 study participants (116 AR measurements) and eight $NO_2$ exposure concentrations, for resting exposures and non-specific bronchial challenge agents. Across exposures to 100, 140, 200, 250, 270, 480, 500, and 530 ppb $NO_2$, 24% of study participants experienced a halving of the PD (indicating increased AR) while 8% showed a doubling of the PD (indicating decreased AR). The relative distributions of the PDs 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 $NO_2$ exposures within the range of 100 to 530 ppb, uncertainty remains given that this analysis is limited to a subset of studies. In addition, compared to conclusions based on the entire range of $NO_2$ 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 $NO_2$ exposure concentration within this range.

PA Conclusions on Short-Term $NO_2$ 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 $NO_2$ concentrations from 100 to 530 ppb, particularly for resting exposures and measures of non-specific AR (n = 33 to 70 for various ranges of $NO_2$ 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 $NO_2$-induced increases in AR following exposures to $NO_2$ concentrations at or above 250 ppb. Individual studies (n = 4 to 20) generally do not report statistically significant increases in AR following exposures to $NO_2$ concentrations at or below 200 ppb, though the evidence suggests a trend toward increased AR following $NO_2$ 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 $NO_2$. Important limitations in this evidence include the lack of an apparent dose-response relationship between $NO_2$ and AR and uncertainty in the adversity of the reported increases in AR. These limitations become increasingly important at the lower $NO_2$ exposure concentrations (*i.e.,* at or near 100 ppb), where the evidence for $NO_2$-induced increases in AR is not consistent across studies. The PA placed weight on that lack of consistency, when considered in light of the lack of an apparent dose-response relationship between $NO_2$ and increased AR, as well as the uncertainty in the adversity of the reported effect.

iv. Consideration of $NO_2$ 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 $NO_2$ concentrations in locations where epidemiologic studies have examined $NO_2$ 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 2016 $NO_X$ 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 standards, the PA emphasizes those studies conducted in the U.S. and Canada.[51] For short-term exposures to $NO_2$, the PA emphasizes studies reporting associations with effects judged in the 2016 $NO_X$ 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 $NO_2$-health effect associations may be larger. These considerations help inform the range of ambient $NO_2$ concentrations where there is the most confidence for $NO_2$-associated health effects and the range of concentrations over which confidence in such effects is appreciably

[49] For instance, Brown (2015) notes that the few studies evaluating effects at multiple $NO_2$ concentrations and at resting exposures may indicate some support for a dose-response relationship, as they show increasing AR with increasing exposure concentrations.

[50] As noted above, the degree to which populations in U.S. urban areas have the potential for such $NO_2$ exposures is evaluated in Chapter 4 of the PA and described in Section II.A.3 below.

[51] 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 are 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 2016 $NO_X$ ISA's assessment of the weight of the evidence that informs the causal determinations.

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 $NO_2$ concentrations in study areas that would have met the current 1-hour $NO_2$ standard during the study period?

Addressing this question can provide important insights into the extent to which $NO_2$-associated health effects are present for distributions of ambient $NO_2$ 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 $NO_2$-associated effects indicated by epidemiologic studies. To the degree studies have not reported associations in locations meeting the current $NO_2$ standards, there is greater uncertainty regarding the potential for the reported effects to occur following the $NO_2$ exposures associated with air quality meeting those standards.

The emphasis that the proposal and this final action place on studies to inform the question above is discussed in more detail in the proposal for this action (82 FR 34792, July 26, 2017, section II.F.4). Briefly, 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 (CI)) health effect associations. In evaluating whether such associations are likely to reflect $NO_2$ concentrations meeting the existing 1-hour standard, the PA considers the 1-hour ambient $NO_2$ concentrations measured at monitors in study locations during study periods. The PA also considers what additional information is available regarding the ambient $NO_2$ 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 $NO_2$ health effect associations have been reported for $NO_2$ air quality concentrations that likely would have met the current 1-hour $NO_2$ 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).[52] For each $NO_2$ 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 $NO_2$ concentrations.[53] These concentrations approximate the DVs that are used when determining whether an area meets the 1-hour primary $NO_2$ NAAQS.[54] Thus, these estimated DVs can provide perspective on whether study areas would likely have met or exceeded the primary 1-hour $NO_2$ 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 $NO_2$ DV estimates is that currently required near-road $NO_2$ 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 $NO_2$ concentrations near the most heavily trafficked roadways. In addition, mobile source $NO_X$ 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 $NO_2$ concentration gradients around major roads could have been more pronounced than indicated by data from recently deployed near-road monitors.[55] This information suggests that if the current near-road monitoring network had been in operation during study periods, $NO_2$ 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 about whether an area would have met the current 1-hour standard during the study period can be reached based on study areas with DV estimates that are at or just below 100 ppb.[56]

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 $NO_2$ exposures. To this end, the PA highlights the epidemiologic studies examining associations between asthma hospitalizations or ED visits and short-term exposures to ambient $NO_2$ that were conducted in the U.S. and Canada (U.S. EPA, 2017a, Figure 3–1). These studies were identified and evaluated in the 2016 $NO_X$ 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 multicity studies tend to have greater power to detect associations. The one multicity 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).[57] Associations in these studies

[52] 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).

[53] All study locations had maximum annual DVs below 53 ppb (U.S. EPA, 2017a, Appendix A).

[54] As described in section I.B., 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 $NO_2$ 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 $NO_2$ standard, the DV for a monitor is based on the 3-year average of the 98th percentile of the annual distribution of daily maximum 1-hour $NO_2$ concentrations. For more information on these studies and the calculation of the study area DVs estimates, see Appendix A of the $NO_2$ PA (U.S. EPA, 2017a).

[55] Recent data indicate that, for most near-road monitors, measured 1-hour $NO_2$ concentrations are higher than those measured at all of the non-near-road monitors in the same CBSA (Section II.A.1.d).

[56] Epidemiologic studies that evaluate potential $NO_2$ health effect associations during time periods when near-road monitors are operational could reduce this uncertainty in future reviews.

[57] 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 the 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

Continued

were generally not statistically significant, were less precise (*i.e.,* wider 95% CI), 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 $NO_2$ primary 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 $NO_2$, 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 $PM_{2.5}$ and $PM_{10}$ (U.S. EPA, 2016a, Section 3.5).[58] Of the studies 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 $PM_{2.5}$, $SO_2$, CO, or $O_3$, $NO_2$ consistently had the strongest effect estimates that were robust to the inclusion of other pollutants. Villeneuve et al. (2007) utilized a model including $NO_2$ and CO ($r = 0.74$) for ED visits in the warm season and reported that associations for $NO_2$ were robust to CO. Strickland et al. (2010) found that the relationship between ambient $NO_2$ and asthma ED visits in Atlanta, GA, was robust in models including $O_3$, but copollutant models were not analyzed for other pollutants, and the correlations between $NO_2$ and other pollutants were not reported. Taken together, these studies provide some evidence for independent effects of $NO_2$ for asthma-related hospital admissions and 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, section 3.5).

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 $NO_2$ and ED visits (Stieb et al., 2009). In addition, of the single-city studies reporting positive and relatively precise associations between $NO_2$ and asthma hospital admissions and ED visits, most locations likely had $NO_2$ concentrations above the current 1-hour $NO_2$ standard over at least part of the study period. Although maximum estimated DVs for the studies conducted in Atlanta were 100 ppb (Peel et al., 2005; Strickland et al., 2010), 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 lack precision and are not statistically significant, indicating that associations between $NO_2$ 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 $NO_2$-associated hospital admissions and ED visits at ambient $NO_2$ 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 $NO_2$-associated outcomes in locations with $NO_2$ concentrations that would have clearly met that standard.

b. Health Effects With Long-Term Exposure to $NO_2$

This section discusses the evidence for health effects associated with long-term $NO_2$ exposures. Section II.A.2.b.i discusses the nature of the health effects that have been shown to be associated with long-term $NO_2$ exposures and the strength of the evidence supporting various effects, based on the assessment of that evidence in the 2016 $NO_X$ ISA. Sections II.A.2.b.ii and II.A.2.b.iii discuss the $NO_2$ concentrations at which health effects have been demonstrated to occur based on the considerations and analyses included in the PA.

i. Nature of Effects

In the last review of the primary $NO_2$ NAAQS, evidence for health effects related to long-term ambient $NO_2$ 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 effects 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 $NO_2$ is more robust than in previous reviews, there are still a number of uncertainties limiting understanding of the role of long-term $NO_2$ exposures in causing health effects.

Chapter 6 of the 2016 $NO_X$ ISA presents a detailed assessment of the evidence for health effects associated with long-term $NO_2$ exposures (U.S. EPA, 2016a). This evidence is summarized briefly below for respiratory effects. Cardiovascular effects and diabetes, reproductive and developmental effects, premature mortality, and cancer are also briefly addressed.

Respiratory Effects

The 2016 $NO_X$ ISA concluded that there is ''likely to be a causal relationship'' between long-term $NO_2$ exposure and respiratory effects, based primarily on evidence integrated across disciplines for a relationship with asthma development in children.[59] 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

contracted for and sponsored by the New York State Energy Research and Development Authority and the ATSDR.

[58] In this case, differential exposure measurement error occurs when exposure measurement error varies by pollutant (*e.g.,* within a model exposure to $PM_{2.5}$ may be estimated with higher accuracy than exposure to $SO_2$).

[59] Asthma development is also referred to as ''asthma incidence'' in this document and elsewhere. Both asthma development and asthma incidence refer to the onset of the disease rather than the exacerbation of existing disease.

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 $NO_2$ exposure (U.S. EPA, 2016a, Section 6.2.9). As noted above, $NO_2$ 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 causal relationship'' in the current review represents a change from 2008 $NO_X$ 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, 2016a, Table 1–1). This expanded evidence includes several recently published longitudinal studies that indicate positive associations between asthma incidence in children and long-term $NO_2$ exposures, with improved exposure assessment in some studies based on $NO_2$ modeled estimates for children's homes or $NO_2$ 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 2016 $NO_X$ ISA notes several other strengths of the evidence base including the general timing of asthma diagnosis and relative confidence that the $NO_2$ 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 $NO_2$ concentrations estimated from land use regression models with good $NO_2$ prediction in some studies.

While the causal determination has been strengthened in this review, important uncertainties remain. For example, the 2016 $NO_X$ 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 $NO_2$ 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 2016 $NO_X$ ISA states that ''[e]pidemiologic studies of asthma development in children have not clearly characterized potential confounding by $PM_{2.5}$ or traffic-related pollutants [*e.g.,* CO, BC/EC, volatile organic compounds (VOCs)]'' (U.S. EPA, 2016a, p. 6–64). The 2016 $NO_X$ ISA further notes that ''[i]n the longitudinal studies, correlations with $PM_{2.5}$ 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 $NO_2$'' (U.S. EPA, 2016a, p. 6–64). High correlations between $NO_2$ and other traffic-related pollutants were based on modeling, and studies of asthma incidence that used monitored $NO_2$ 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 $NO_2$ is independently related to asthma development.

The 2016 $NO_X$ 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 $NO_2$ and traffic-related copollutants and found them to be relatively high in many cases, ranging from 0.54–0.95 for $PM_{2.5}$, 0.54–0.93 for BC/EC, 0.2–0.95 for $PM_{10}$, 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 $PM_{2.5}$ and EC) (U.S. EPA, 2016a, Table 6–3). Additionally, three studies (McConnell et al., 2003; MacIntyre et al., 2014; Gehring et al., 2013) [60] evaluated copollutant models with $NO_2$ and $PM_{2.5}$, and some findings suggest that associations for $NO_2$ 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 $NO_2$ 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 $NO_2$ 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 2016 $NO_X$ ISA explains 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 $NO_2$ (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 $NO_2$ exposure and increased pulmonary inflammation in healthy humans. The 2016 $NO_X$ ISA also points to supporting evidence from studies demonstrating that short-term exposure repeated over several days (260–1,000 ppb) and long-term $NO_2$ 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 $NO_2$ 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 provides support for a role of $NO_2$ in asthma development by describing a potential role for repeated exposures to lead to recurrent inflammation and allergic responses.

To summarize, the 2016 $NO_X$ ISA notes that there is new evidence available that strengthens conclusions from the last review regarding respiratory health effects attributable to long-term ambient $NO_2$-exposure. The

[60] 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 (forced expiratory volume in 1 second) −0.98 (−1.70, −0.26), (FVC) −2.14 (−4.20, −0.04), (peak expiratory flowF) −1.04 (−1.94, −0.13).

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 $NO_2$ 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, 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 $NO_2$, 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 $NO_2$ itself may be causing the development of asthma versus serving as a surrogate for the broader traffic-pollutant mix.

Cardiovascular Effects and Diabetes

In the previous review, the 2008 $NO_X$ ISA stated that the evidence for cardiovascular effects attributable to long-term ambient $NO_2$ 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 $NO_2$ and cardiovascular effects and diabetes, as the 2016 $NO_X$ ISA judged the evidence to be ''suggestive, but not sufficient to infer'' a causal relationship (U.S. EPA, 2016a, Section 6.3). More information on these health effects may be found in section II.C.2.a.ii of the proposal (87 FR 34792, July 26, 2017).

Reproductive and Developmental Effects

In the previous review, a limited number of epidemiologic and toxicological studies had assessed the relationship between long-term $NO_2$ exposure and reproductive and developmental effects. The 2008 $NO_X$ ISA concluded that there was not consistent evidence for an association between $NO_2$ 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 2016 $NO_X$ 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 2016 $NO_X$ ISA found the evidence to be ''suggestive of, but not sufficient to infer, a causal relationship'' between long-term exposure to $NO_2$ and birth outcomes and ''inadequate to infer the presence or absence of a causal relationship'' between long-term exposure to $NO_2$ and fertility, reproduction and pregnancy as well as postnatal development. More information on these health effects may be found in section II.C.2.a.iii of the proposal (87 FR 34792, July 26, 2017).

Total Mortality

In the 2008 $NO_X$ ISA, a limited number of epidemiologic studies assessed the relationship between long-term exposure to $NO_2$ and mortality in adults. The 2008 $NO_X$ 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 2016 $NO_X$ ISA for the current review concludes that evidence is ''suggestive of, but not sufficient to infer, a causal relationship'' between long-term exposure to $NO_2$ and mortality among adults (U.S. EPA, 2016a, Section 6.5.3). More information on these health effects may be found in section II.C.2.a.iv of the proposal (87 FR 34792, July 26, 2017).

Cancer

The evidence evaluated in the 2008 $NO_X$ 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 $NO_2$ exposure and lung cancer incidence but lack of toxicological evidence demonstrating that $NO_2$ induces tumors. In the current review, the conclusion drawn from the integration of evidence is ''suggestive of, but not sufficient to infer, a causal relationship'' (U.S. EPA, 2016a, Section 6.6.9). More information on cancer outcomes may be found in section II.C.2.a.v of the proposal (87 FR 34792, July 26, 2017).

ii. Long-Term $NO_2$ 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, the EPA considers the long-term $NO_2$ concentrations that have been associated with various effects. The PA explicitly considers these $NO_2$ 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 $NO_2$ 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 type of effect for which there is 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 $NO_2$ exposures and asthma development for distributions of ambient $NO_2$ 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 $NO_2$ exposure concentrations examined in experimental studies. These considerations are discussed below for epidemiologic studies and experimental studies.

Ambient $NO_2$ Concentrations in Locations of Epidemiologic Studies

As discussed above for short-term exposures (Section II.A.2.a), when considering epidemiologic studies of long term $NO_2$ exposures within the context of evaluating the adequacy of the current $NO_2$ 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 $NO_2$ 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 study periods.

The epidemiologic studies available in the current review that evaluate associations between long-term $NO_2$ exposures and asthma incidence are summarized in Table 6–1 of the 2016

$NO_X$ ISA (U.S. EPA, 2016a, p. 6–7). In evaluating the adequacy of the current $NO_2$ standards, the PA places the greatest emphasis on the three U.S. and Canadian studies identified in the 2016 $NO_X$ ISA as providing key supporting evidence for the causal determination.[61] However, the PA also considers what the additional three U.S. and Canadian studies not identified as key studies in the 2016 $NO_X$ ISA can indicate about the adequacy of the current standards, while noting the increased uncertainty in these studies related to exposure measurement and copollutant confounding (Table 6–5 of the 2016 $NO_X$ ISA).

While it is appropriate to consider what these studies can tell us with regard to the adequacy of the existing primary $NO_2$ standards (see below), the emphasis that is placed on these considerations reflects 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 $NO_2$ 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 $NO_2$ in locations likely to have met the current primary $NO_2$ standards?

As discussed above for short-term exposures (Section II.A.2.a), addressing this question can provide important insights into the extent to which $NO_2$-health effect associations are present for distributions of ambient $NO_2$ 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 $NO_2$-associated asthma development indicated by epidemiologic studies. To the degree studies have not reported associations in locations meeting the current primary $NO_2$ standards, there is greater uncertainty regarding the potential for the development of asthma to result from the $NO_2$ exposures associated with air quality meeting those standards.

To evaluate this issue, the PA compares $NO_2$ estimated DVs in study areas to the levels of the current primary $NO_2$ standards. In addition to comparing annual DVs to the level of the annual standard, support for consideration of 1-hour DVs comes from the 2016 $NO_X$ ISA's integrated mode of action information describing the biological plausibility for development of asthma (section II.B.1, below). In particular, studies demonstrate the potential for repeated short-term $NO_2$ exposures to induce pulmonary inflammation and development of allergic responses. The 2016 $NO_X$ ISA states that ''findings for short-term $NO_2$ 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 2016 $NO_X$ ISA states the following (U.S. EPA, 2016a, p. 4–64):

> The initiating events in the development of respiratory effects due to long-term $NO_2$ 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 $NO_2$-associated asthma development, the PA considers the combined protection afforded by the 1-hour and annual standards.[62]

To inform consideration of whether a study area's air quality could have met the current primary $NO_2$ standards during study periods, the PA presents DV estimates based on the $NO_2$ concentrations measured at existing monitors during the years over which the epidemiologic studies of long-term $NO_2$ exposures were conducted.[63] [64]

In interpreting these comparisons of DV estimates with the $NO_2$ standards, the PA also considers uncertainty in the extent to which identified DV estimates represent the higher $NO_2$ concentrations likely to have been present near major roads during study periods (section II.A.1, above). In particular, as discussed above for short-term exposures, study area DV estimates are based on $NO_2$ concentrations from the generally area-wide $NO_2$ 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 $NO_2$ concentrations near roadways and that recent air quality information from the new near-road $NO_2$ monitoring network generally indicates higher $NO_2$ concentrations at near-road monitoring sites than at non near-road monitors in the same CBSA (section II.A.c, above). In addition, mobile source $NO_X$ emissions were substantially higher during the majority of study periods (1986–2006) than they are today (section II.A.b, above), and $NO_2$ 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.[65]

In considering the epidemiologic studies looking at long-term $NO_2$ 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 2016 $NO_X$ 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

[61] 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 2016 $NO_X$ ISA identifies three as key studies supporting the causal determination (Carlsten et al., 2011; Clougherty et al., 2007; Jerrett et al., 2008).

[62] It is also the case that broad changes in $NO_2$ concentrations will affect both hourly and annual metrics. This is discussed in more detail in Section II.A.1 above, and in the CASAC letter to the Administrator on the draft PA (Diez Roux and Sheppard, 2017). Thus, as in the recent review of the $O_3$ NAAQS (80 FR 65292, October 26, 2015), it is appropriate here to consider the extent to which a short-term standard could provide protection against longer-term pollutant exposures.

[63] 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 $NO_2$ NAAQS (U.S. EPA, 2017a, Appendix A).

[64] 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 $NO_2$ PA (U.S. EPA, 2017a).

[65] As noted above for studies of short-term $NO_2$ exposures (II.A.2.a), epidemiologic studies that evaluate potential $NO_2$ health effect associations during time periods when near-road monitors are operational could reduce this uncertainty in future reviews.

Angeles estimated DVs) 53 ppb.[66] These seven communities also had 1-hour estimated DVs (maximum 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 et al., 2007) [67] or above (Carlsten et al., 2011) 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 2016 $NO_X$ ISA (Clark et al., 2010; McConnell et al., 2010; Nishimura et al., 2013). The multicity 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 $NO_2$ 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 $NO_2$ 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 $NO_2$ measurements that have well-recognized limitations in reflecting variability in ambient $NO_2$ concentrations in a community and variability in $NO_2$ exposure among subjects.

PA Conclusions on Ambient $NO_2$ Concentrations in Locations of Epidemiologic Studies

Based on the information discussed above, while epidemiologic studies provide support for $NO_2$-associated asthma development at ambient $NO_2$ concentrations likely to have been above those allowed by the current standards, these studies do not report such associations at ambient $NO_2$ concentrations that would have clearly met both of the current standards. Thus, in evaluating the adequacy of the public health protection provided by the current 1-hour and annual $NO_2$ standards, the PA concludes that epidemiologic studies do not provide a clear basis for concluding that ambient $NO_2$ 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, 2017a, section 3.3.2). This conclusion stems from consideration of the available evidence from U.S. and Canadian studies for $NO_2$-associated asthma incidence, the ambient $NO_2$ 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 $NO_2$ and long-term concentrations of other roadway-associated pollutants; and (2) the general lack of information from copollutant models on the potential for $NO_2$ 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 $NO_2$ standards.

Furthermore, the analysis of study area estimated DVs does not provide support for the occurrence of $NO_2$-associated asthma incidence in locations with ambient $NO_2$ 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 DVs 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 $NO_2$ exposures. Given this information and consideration of these uncertainties, the degree to which these epidemiologic studies can inform whether adverse $NO_2$-associated effects (*i.e.,* asthma development) are occurring below the levels of the current primary $NO_2$ standards is limited.

iii. $NO_2$ 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.[68] Experimental studies examining asthma-related effects attributable to long-term $NO_2$ exposures are largely limited to animals exposed to $NO_2$ concentrations well above those found in the ambient air (*i.e.,* ≥1,000 ppb). As discussed above, the 2016 $NO_X$ ISA indicates that evidence from these animal studies supports the causal determination by characterizing ''a potential mode of action linking $NO_2$ 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 $NO_2$ exposures of 500–2,000 ppb for 12 weeks. Despite providing support for the ''likely to be a causal'' relationship, these experimental studies, by themselves, do not provide insight into the occurrence of adverse health effects following exposures below the levels of the existing primary $NO_2$ standards.[69]

[66] 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, DV estimates for the Los Angeles and Riverside CBSAs were used to represent multiple study communities.

[67] 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 during the study period.

[68] While there are not controlled human exposure studies for long-term exposures, the 2016 $NO_X$ 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 (U.S. EPA 2016a, chapter 6; U.S. EPA, 2017a, section 3).

[69] In addition, the 2016 $NO_X$ ISA draws from experimental evidence for short-term exposures to support the biological plausibility of asthma development. Consideration of the $NO_2$ exposure concentrations evaluated in these studies is discussed in Section II.A.2 above.

Overall Conclusions for Long Term Exposures

Taking all of the evidence and information together, including important uncertainties, the PA revisits the extent to which the evidence supports the occurrence of $NO_2$-attributable asthma development in children at $NO_2$ 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 $NO_2$ concentrations that would clearly meet the existing annual and 1-hour primary $NO_2$ standards. This conclusion recognizes the $NO_2$ air quality relationships, which indicate that meeting the 1-hour $NO_2$ standard would be expected to limit annual $NO_2$ concentrations to well below the level of the current annual standard (Section II.A.2.d, 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 $NO_2$ exposures and asthma development do not provide a clear basis for concluding that ambient $NO_2$ concentrations allowed by the current primary $NO_2$ 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 $NO_2$-attributable effects that are plausibly related to asthma development, the relatively high $NO_2$ exposure concentrations used in these studies do not provide insight into whether such effects would occur at $NO_2$ exposure concentrations that would be allowed by the current standards.

c. Potential Public Health Implications

Evaluation of the public health protection provided against ambient $NO_2$ exposures requires consideration of populations and lifestages that may be at greater risk of experiencing $NO_2$-attributable health effects. In the last review, the 2008 $NO_X$ ISA noted that a considerable fraction of the U.S. population lives, works, or attends school near major roadways, where ambient $NO_2$ concentrations are often elevated (U.S. EPA, 2008a, Section 4.3). Of this population, the 2008 $NO_X$ ISA concluded that ''those with physiological susceptibility will have even greater risks of health effects related to $NO_2$'' (U.S. EPA, 2008a, p. 4–12). With regard to susceptibility, the 2008 $NO_X$ ISA concluded that ''[p]ersons with preexisting respiratory disease, children, and older adults may be more susceptible to the effects of $NO_2$ exposure'' (U.S. EPA, 2008a, p. 4–12).

In the current review, the 2016 $NO_X$ ISA again notes that because of the large populations attending school, living, working, and commuting on or near roads, where ambient $NO_2$ concentrations can be higher than in many other locations (U.S. EPA, 2016a, Section 7.5.6),[70] there is widespread potential for elevated ambient $NO_2$ exposures. For example, Rowangould (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 $NO_2$ exposures as a result of living, working, attending school, or commuting on or near roadways.

The impacts of exposures to elevated $NO_2$ 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 (U.S. EPA, 2017a, Section 3.4) draws from the 2016 $NO_X$ ISA's assessment of the evidence (U.S. EPA, 2016a, Chapter 7). The 2016 $NO_X$ 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 2016 $NO_X$ 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 2016 $NO_X$ ISA then uses a systematic approach for classifying the evidence for each potential at-risk factor (U.S. EPA, 2015a, 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.,* the recently completed review for ozone, 80 FR 65292, October 26, 2015), the PA focuses the consideration of potential at-risk populations on those factors for which the 2016 $NO_X$ ISA determines there is ''adequate'' evidence (U.S. EPA, 2016a, Table 7–27). For $NO_2$, the at-risk populations identified include people with asthma, children and older adults (U.S. EPA, 2016a, Table 7–27), and this information is based primarily on evidence for asthma exacerbation or asthma development as evidence for an independent relationship of $NO_2$ exposure with other health effects is more uncertain.

The PA's consideration of the evidence supporting conclusions regarding the populations at increased risk of $NO_2$-related effects 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 $NO_2$-related health effects? (U.S. EPA, 2017a, p. 3–40).

In addressing this question, the PA considers the evidence in the 2016 $NO_X$ ISA for effects in people with asthma, children, and older adults (U.S. EPA, 2016a, Chapter 7, Table 7–27), respectively, as described below.

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 $NO_2$-induced increases in AR provide key evidence that people with asthma are more sensitive than people without asthma to the effects of short-term $NO_2$ exposures. In particular, a meta-analysis conducted by Folinsbee et al. (1992)

[70] The 2016 $NO_X$ ISA specifically notes that a zone of elevated $NO_2$ concentrations typically extends 200 to 500 m from roads with heavy traffic (U.S. EPA, 2016a, Section 2.5.3).

demonstrated that $NO_2$ 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 $NO_2$ exposure concentrations greater than 1,000 ppb (U.S. EPA, 2016a, Section 7.3.1). The Brown (2015) meta-analysis showed that following resting exposures to $NO_2$ 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 differences in time spent outdoors to suggest differences in $NO_2$ exposure. However, the Folinsbee et al. (1992) meta-analysis of information from controlled human exposure studies, which supported the 2016 $NO_X$ ISA's determination of a causal relationship between short-term exposures and respiratory effects, clearly demonstrates that adults with asthma are at increased risk for $NO_2$-related respiratory health effects compared to healthy adults. Thus, consistent with observations made in the 2008 $NO_X$ ISA (U.S. EPA, 2008a), in the current review the 2016 $NO_X$ ISA determines that the ''evidence is adequate to conclude that people with asthma are at increased risk for $NO_2$-related health effects'' (U.S. EPA, 2016a, p. 7–7).

Children

According to the 2010 census, 24% of the U.S. population is less than 18 years of age, with 6.5% less than 6 years of age (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). Higher activity along with higher ventilation rates relative to lung volume and higher propensity for oronasal breathing could potentially result in greater $NO_2$ penetration to the lower respiratory tracts of children; however, this effect has not been examined for $NO_2$ (U.S. EPA, section 4.2.2.3). All of these factors could contribute to children being at higher risk than adults for effects attributable to ambient $NO_2$ exposures (U.S. EPA, 2016a, Section 7.5.1.1).

Epidemiologic evidence across diverse locations (U.S., Canada, Europe, Asia, Australia) consistently demonstrates $NO_2$-associated health effects with both short- and long-term exposures in children. In particular, short-term increases in ambient $NO_2$ 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 $NO_2$-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 in children has been reported to be associated with long-term $NO_2$ 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 $NO_2$ and asthma-related outcomes, including the larger associations with short-term exposures observed in children, the 2016 $NO_X$ ISA concludes the evidence ''is adequate to conclude that children are at increased risk for $NO_2$-related health effects'' (U.S. EPA, 2016a, p. 7–32).

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 $NO_X$ ISA that older adults may be at increased risk for $NO_2$-related health effects. (U.S. EPA, 2016a, Table 7–15). While it is not clear that older adults experience greater $NO_2$ exposures or doses, epidemiologic evidence generally indicates greater risk of $NO_2$-related health effects in older adults compared with younger adults. For example, comparisons of older and younger adults with respect to $NO_2$-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 $NO_2$ 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 2016 $NO_X$ 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 $NO_2$-related health effects'' (U.S. EPA, 2016a, p. 7–37).

PA Conclusions on At-Risk Populations

As described in the PA, and consistent with the last review, the 2016 $NO_X$ ISA determined that the available evidence is adequate to conclude that people with asthma, children, and older adults are at increased risk for $NO_2$-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% all children, 13% all older adults) underscores the potential for important public health impacts attributable to $NO_2$ 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 $NO_2$, including near heavily trafficked roadways.

3. Overview of Risk and Exposure Assessment Information

Beyond the consideration of the scientific evidence, discussed above in Section II.A.2, the EPA also considers the extent to which new or updated quantitative analyses of $NO_2$ air quality, exposures, or health risks could inform conclusions on the adequacy of the public health protection provided by the current primary $NO_2$ standards. Conducting such quantitative analyses, if appropriate, could inform judgments about the public health impacts of $NO_2$-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, 2015b) and in the PA (U.S. EPA, 2017a), the staff evaluated the extent to which the available evidence and information provide support for conducting new or updated analyses of $NO_2$ 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 $NO_2$ 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 $NO_2$ exposures and/or health risks. In

developing the final PA, staff also considered 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 $NO_2$ air quality concentrations (*i.e.,* as surrogates for potential $NO_2$ 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 on respiratory health effects associated with short and long-term exposure to $NO_2$ 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 on short-term $NO_2$ exposures in its review of the REA Planning document, and for long-term exposures they agreed but encouraged the EPA to consider the feasibility of such an assessment for long-term exposures (Diez Roux and Frey, 2015b, p. 5). In its review of the draft PA the CASAC agreed with the EPA's conclusions on the feasibility of an epidemiologic risk assessment based on evidence of long-term $NO_2$ exposures (Diez Roux and Sheppard, 2016, p. 2).[71]

a. Overview of Approach to Estimating Potential $NO_2$ Exposures

To provide insight into the potential occurrence of $NO_2$ air quality concentrations that may be of public health concern, the PA included new analyses comparing $NO_2$ 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,[72] CBSAs with the highest $NO_2$ design values, and CBSAs with a relatively large number of $NO_2$ monitors overall (*i.e.,* providing improved spatial characterization).[73]

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.[74] Upward adjustment was required because all locations in the U.S. meet the current $NO_2$ NAAQS.

In identifying the range of $NO_2$ 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 $NO_2$ benchmarks from 100 to 300 ppb, based largely on studies of non-specific AR in study participants exposed to $NO_2$ at rest.[75] [76] 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, the risks of these exposures cannot be fully characterized based on existing studies and caution is appropriate when interpreting the potential public health implications of 1-hour $NO_2$ concentrations at or around 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.A.2 above and U.S. EPA, 2017a, Section 4.2.1).

b. Results of Updated Analyses

In considering the results of these updated analyses, the EPA focuses on the number of days per year that 1-hour $NO_2$ concentrations at or above the respective benchmarks 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 $NO_2$ standard (U.S. EPA, 2017a, Section 4.2.1.2). For unadjusted air quality:

- One-hour ambient $NO_2$ 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 $NO_2$ 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 $NO_2$ concentrations in study areas, including those near major roadways, only rarely reached or exceeded 100 ppb. On average in all study areas, 1-hour $NO_2$ concentrations at or above 100 ppb occurred on less than one day per year.
  - Even in the worst-case years, most study areas had either zero or one day with 1-hour $NO_2$ 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 $NO_2$ standard:

- The current standard is estimated to allow no days in study areas with 1-hour ambient $NO_2$ 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 $NO_2$ concentrations at or above 150 ppb, based on both area-wide and

[71] After considering the factors discussed above, we conclude that a quantitative risk assessment based on epidemiologic studies of long-term $NO_2$ exposures is not warranted in this review because of a lack of U.S. epidemiologic studies identified by the 2016 $NO_X$ ISA as being key studies, lack of baseline incidence rates for the health effects of interest, uncertainty regarding the shape of the concentration-response function, and a lack of studies that have controlled for potential confounders, making it difficult to determine the true magnitude of effect (U.S. EPA, 2017a, sections 4.4.2.2 and 4.4.2.3).

[72] As discussed above, near-road monitors are required within 50 m of major roads in large urban areas that met certain criteria for population size or traffic volume. 40 CFR part 58, appendix E, Sec. 6.4(a). 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).

[73] 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 $NO_X$ emissions and mobile source $NO_X$ emissions in the U.S.; and they include a wide range of stationary source $NO_X$ emissions (U.S. EPA, 2017a, Appendix B, Figures B2–2 to B2–8).

[74] In all study areas, ambient $NO_2$ 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 $NO_2$ 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).

[75] Benchmarks from the upper end of this range are supported by the results of individual studies, the majority of which consistently reported statistically significant increases in AR following $NO_2$ 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 $NO_2$-induced increases in AR following exposures below 200 ppb.

[76] While benchmarks between 100 to 200 ppb were considered, analyses were only conducted on concentrations between 100 to 200 ppb as 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 $NO_2$ concentrations at or above 200 ppb.

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 $NO_2$ 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 $NO_2$ 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 $NO_2$ concentrations at or above 100 ppb (30 days in the single worst-case location and year).

c. Uncertainties

There are a variety of limitations and uncertainties in these comparisons of $NO_2$ air quality with health-based benchmarks. In particular, there are uncertainties in the evidence underlying the benchmarks themselves, uncertainties in the upward adjustment of $NO_2$ air quality concentrations, and uncertainty in the degree to which monitored $NO_2$ concentrations reflect the highest potential $NO_2$ concentrations. Each of these is discussed below.

i. Health-Based Benchmarks

The primary goal of this analysis is to inform conclusions regarding the potential for the existing primary $NO_2$ standards to allow exposures to ambient $NO_2$ concentrations that may be of concern for public health. As discussed in detail above (Sections II.A.2), the meta-analysis by Brown (2015) indicates the potential for increased AR in some people with asthma following $NO_2$ exposures from 100 to 530 ppb, while individual studies show more consistent results above 250 ppb. While it is possible that certain individuals could be more severely affected by $NO_2$ exposures than indicated by existing studies, which have generally evaluated adults with mild asthma,[77] there remains uncertainty in the degree to which the effects identified in individual studies within the Brown (2015) meta-analysis would be of public health concern, specifically at lower concentrations (*e.g.,* 100 ppb). In particular, the uncertainties regarding the potential for adverse effects following $NO_2$ exposures at lower concentrations when looking across individual studies complicate the interpretation of comparisons between ambient $NO_2$ concentrations and health-based benchmarks. When considered in the context of the less consistent results observed across individual studies following exposures to 100 ppb $NO_2$, in comparison to the more consistent results at higher exposure concentrations,[78] these uncertainties have the potential to be of particular importance for interpreting the public health implications of ambient $NO_2$ concentrations at or around the 100 ppb benchmark.[79]

With regard to the magnitude and clinical relevance of the $NO_2$-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.A.2), the meta-analysis evaluates the available individual-level data on the magnitude of the change in AR following resting $NO_2$ exposures. Brown (2015) reports that the magnitude of the increases in AR observed following resting $NO_2$ exposures from 100 to 530 ppb was 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 experienced a halving of the PD of challenge agent following $NO_2$ exposures. This magnitude of change has been recognized by the ATS and the ERS 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 $NO_2$ exposures from 100 to 530 ppb, it is based on a subset of volunteers for which non-specific AR was reported following exposures to $NO_2$ and air at rest, and the interpretation of these results for any specific exposure concentration within the range of 100 to 530 ppb is uncertain (see section II.A.2, above).

ii. Approach to Adjusting Ambient $NO_2$ Concentrations

These analyses use historical air quality relationships as the basis for adjusting ambient $NO_2$ concentrations to just meet the current 1-hour standard (U.S. EPA, 2017a, Appendix B). The approach to adjusting ambient $NO_2$ concentrations was supported by the CASAC, who found the approach both suitable and appropriate (Diez Roux and Frey, 2015b, p.1). This approach is meant to illustrate a hypothetical scenario and does not represent expectations regarding future air quality trends. There are, however, some uncertainties in this approach. If ambient $NO_2$ 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 $NO_2$ concentrations over much of the U.S. (*i.e.,* reductions beyond the ''unadjusted'' air quality used in these analyses). Thus, if ambient $NO_2$ concentrations were to increase to the point of just meeting the existing 1-hour $NO_2$ 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 $NO_2$ 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.[80] In locations where near-road monitors

[77] 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.''

[78] As discussed previously, while the meta-analysis indicates that a statistically significant majority of study volunteers experienced increased non-specific AR following exposures to 100 ppb $NO_2$, results were only 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 $NO_2$.

[79] Sensitivity analyses included in Appendix B of the PA (U.S. EPA, 2017a, Section 3.2, table B3–1) also evaluated 1-hour $NO_2$ benchmarks below 100 ppb (*i.e.,* 85, 90, 95 ppb), though the available health evidence does not provide a clear a basis for determining what exposures to such $NO_2$ concentrations might mean for public health.

[80] However, 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).

measure the highest $NO_2$ DVs, reliance on those near-road monitors to identify air quality adjustment factors would likely 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 $NO_2$ concentrations at or above benchmarks. Given that near-road monitors in most areas measure higher 1-hour $NO_2$ 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 $NO_2$ concentrations at or above benchmarks in some study areas.

iii. Degree to Which Monitored $NO_2$ Concentrations Reflect the Highest Potential $NO_2$ Exposures

To the extent there are unmonitored locations where ambient $NO_2$ concentrations exceed those measured by monitors in the current network, the potential for $NO_2$ exposures at or above benchmarks could be underestimated. In the last review, this uncertainty was determined to be particularly important for potential exposures on and around roads. The 2008 REA estimated that the large majority of modeled exposures to ambient $NO_2$ concentrations at or above benchmarks occurred on or near roads (U.S. EPA, 2008b, Figures 8–17 and 8–18). When characterizing ambient $NO_2$ concentrations, the 2008 REA attempted to address this uncertainty by estimating the elevated $NO_2$ concentrations that can occur on or near the road. These estimates were generated by applying literature-derived adjustment factors to $NO_2$ concentrations at monitoring sites located away from the road.

In the current review, given that the 23 selected study areas have among the highest $NO_X$ emissions in the U.S., and given the siting characteristics of existing $NO_2$ 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 $NO_X$ emissions within most CBSAs, and the 23 study areas evaluated have among the highest mobile source $NO_X$ emissions in the U.S. (U.S. EPA, 2017a, Appendix B, Section B2.3.2). Most study areas have near-road $NO_2$ 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, and Los Angeles in the EPA's database of metadata for near-road monitors).[81] Thus, as explained in the PA, even though the location of highest $NO_2$ concentrations around roads can vary (U.S. EPA, 2017a, Section 2.1), the near-road $NO_2$ monitoring network, with monitors sited from 2 to 50 m away from heavily trafficked roads, is likely to effectively capture the types of locations around roads where the highest $NO_2$ concentrations can occur.[82]

This conclusion is consistent with the 2016 $NO_X$ ISA's analysis of available data from near-road $NO_2$ 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 $NO_2$ concentrations (U.S. EPA, 2016a, Section 2.5.3.2). The 2016 $NO_X$ 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 $NO_2$ exposures near non-roadway sources of $NO_X$ emissions. As noted in the PA, the 23 selected study areas include CBSAs with large non-roadway sources of $NO_X$ emissions. This includes study areas with among the highest $NO_X$ emissions from electric power generation facilities (EGUs) and airports, the two types of non-roadway sources that are associated with the highest $NO_X$ emissions in the U.S (U.S. EPA, 2017a, Appendix B, Section B2.3.2).

While it is difficult to isolate non-road impacts from certain non-road sources like ports and airports, looking at monitors that are influenced by non-road emissions can help characterize the potential for such exposures. As discussed below, several study areas have non-near-road $NO_2$ monitors sited to better characterize the impacts of such sources.

As described in the PA (U.S. EPA, 2017a, Section 4.1.2.3), table 2–12 in the 2016 $NO_X$ ISA (U.S. EPA, 2016a) summarizes $NO_2$ 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 $NO_2$ concentration measured in 2014 (105 ppb) occurred at the Schiller Park, IL monitoring site, located adjacent to O'Hare International Airport, and very close to a major rail yard (*i.e.,* Bedford Park Rail Yard) and to a four-lane arterial road (US 12 and US 45) (U.S. EPA, 2016a, Section 2.5.3.2). Thus, beyond the $NO_2$ near-road monitors, some $NO_2$ monitors in study areas are also sited to capture high ambient $NO_2$ concentrations around important non-roadway sources of $NO_X$ emissions. In addition, one of the highest 1-hour daily maximum $NO_2$ concentrations recorded in recent years (136 ppb) was observed at a Denver, CO, site that is not part of the near-road monitoring network. 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 commercial heating and other activities, as well as local traffic (U.S. EPA, 2016a, Section 2.5.3.2).

d. Conclusions

As discussed above and in the REA Planning document (U.S. EPA, 2015b, Section 2.1.1), an important uncertainty identified in the 2008 REA was the characterization of 1-hour $NO_2$ concentrations around major roadways. In the current review, data from recently deployed near-road $NO_2$ monitors improves understanding of such ambient $NO_2$ concentrations.

As discussed in Section I.B, recent $NO_2$ concentrations measured in all U.S.

[81] This database is found at *http://www3.epa.gov/ttn/amtic/nearroad.html.*

[82] In the current review, 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'' $NO_2$ 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 $NO_2$ concentrations, and in the degree to which they may differ. Therefore, in evaluating the potential for roadway-associated $NO_2$ exposures, the PA focuses on the concentrations at locations of near-road monitors (U.S. EPA, 2017a, Chapter 4). However, it remains possible that some areas (*e.g.,* street canyons in urban environments) could have higher ambient $NO_2$ concentrations than indicated by near-road monitors. Sensitivity analyses estimating the potential for on-road $NO_2$ exposures are described in Appendix B of the PA (U.S. EPA, 2017a).

locations meet the existing primary $NO_2$ NAAQS. Based on these recent (*i.e.,* unadjusted) ambient measurements, analyses estimate almost no potential for 1-hour exposures to $NO_2$ 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 $NO_2$ concentrations at or above the 200 ppb benchmark, and virtually none for exposures at or above 150 ppb. This is the case for all years, including worst-case years and 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 $NO_2$ concentrations at or above 100 ppb on some days (*e.g.,* in most study areas, about one to 10 days per year, on average).[83]

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 $NO_2$ concentrations at or above 100 ppb.[84] These results are similar to the results presented in the REA from the last review (U.S. EPA, 2008b, tables 7–23 through 7–25), based on $NO_2$ 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 $NO_2$ concentrations at or above these benchmarks, though there is some uncertainty as to whether these results fully characterize on and near-road exposures, in part because most near-road monitors do not yet have three years of data. (U.S. EPA, 2017a, Appendix B, Section B5.9, Table B5–66).[85]

When these results and associated uncertainties are taken together, the current 1-hour $NO_2$ standard is expected to allow virtually no potential for exposures to the $NO_2$ 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 $NO_X$ emissions in the U.S. Such $NO_2$ 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 $NO_2$ concentrations at or above 100 ppb on some days, there is uncertainty regarding the adversity of the reported $NO_2$-induced increases in AR following exposures to 100 ppb $NO_2$. However, by limiting exposures to $NO_2$ concentrations at or above 100 ppb, the current standard provides protection against exposures to higher $NO_2$ concentrations, for which the evidence of potentially adverse $NO_2$-attributable effects is more consistent, as well as against exposures to $NO_2$ concentrations at 100 ppb, for which the evidence of potentially adverse $NO_2$-attributable effects is less consistent, but where the meta-analysis indicates that a marginally significant majority of study participants experienced an increase in AR following exposures (Brown, 2015).

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 $NO_2$ concentrations that would be of clear public health concern in locations meeting the current 1-hour standard. Additionally, while a lower level for the 1-hour standard (*i.e.,* lower than 100 ppb) would be expected to further limit the potential for exposures to 100 ppb $NO_2$, the public health implications of such reductions are unclear, particularly given that no additional protection would be expected against exposures to $NO_2$ concentrations at or above the higher benchmarks (*i.e.,* 200 ppb and above), as the REA analyses already estimate no days with 1-hour $NO_2$ concentrations at or above the 200 ppb benchmark in areas just meeting the current 1-hour standard. Thus, the PA concludes that these analyses comparing ambient $NO_2$ concentrations to health-based benchmarks do not provide support for considering potential alternative standards that provide a different degree of public health protection. Additionally, in its review of the PA, 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 $NO_2$'' (Diez Roux and Sheppard, 2017).

### *B. Conclusions on the Primary Standards*

In drawing conclusions on the adequacy of the current primary $NO_2$ standards, in view of the advances in scientific knowledge and additional information now available, the Administrator considers the evidence base, information, and policy judgments that were the foundation of the last review and reflects upon the body of evidence and information newly available in this review. In so doing, the Administrator has taken into account both evidence-based and exposure- and risk-based considerations, advice from the CASAC, and public comment. Evidence-based considerations draw upon the EPA's assessment and integrated synthesis of the scientific evidence from epidemiological studies and controlled human exposure studies evaluating health effects related to exposures to $NO_2$ as presented in the ISA, with a focus on policy-relevant considerations as discussed in the PA. The exposure- and risk-based considerations draw from the results of the quantitative analyses presented in the 2008 REA and the additional updated analyses presented in the PA (as summarized in section II.D of the proposal and section II.A.3 above) and consideration of these results in the PA. As described in section II.A.2 of the proposal, consideration of the evidence and exposure/risk information in the PA and by the Administrator is framed by consideration of a series of key policy-relevant questions. Section II.B.1 below summarizes the rationale for the Administrator's proposed decision, drawing from section II.E.4 of the proposal. Advice received from the CASAC in this review is briefly summarized in section II.B.2 below. A fuller presentation of PA considerations and conclusions, and advice from the CASAC, which were all taken into account by the Administrator, is provided in sections II.E.1 through II.E.3 of the proposal. Public comments on the proposed decision are addressed in section II.B.3 below. The Administrator's conclusions in this review regarding the current primary standards are described in section II.B.4 below.

#### 1. Basis for the Proposed Decision

At the time of the proposal, the Administrator carefully considered the

[83] Because the results show almost no days with 1-hour ambient $NO_2$ concentrations above 150 ppb, the results for the 100 ppb benchmark are due primarily to 1-hour $NO_2$ concentrations that are closer to 100 ppb than 200 ppb.

[84] The 98th percentile generally corresponds to the 7th or 8th highest 1-hour concentration in a year.

[85] On-/near-road simulations in the last review estimated that a 1-hour $NO_2$ standard with a 98th percentile form and a 100 ppb level could allow about 20 to 70 days per year with 1-hour $NO_2$ 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 B5–66).

assessment of the current evidence and the conclusions reached in the 2016 $NO_X$ ISA; the currently available exposure/risk information, including associated limitations and uncertainties; considerations and staff conclusions and associated rationales presented in the PA; the advice and recommendations from the CASAC; and public comments that had been offered up to that point. In reaching his proposed conclusion on the primary standard, the Administrator took note of evidence-based considerations (as summarized in section II.B.1.a below) and exposure- and risk-based considerations (as summarized in section II.B.1.b below).

a. Evidence-Based Considerations

In considering the evidence available in the current review with regard to adequacy of the current 1-hour and annual $NO_2$ standards, the first topic of consideration was the nature of the health effects attributable to $NO_2$ exposures, drawing upon the integrated synthesis of the health evidence in the 2016 $NO_X$ ISA and the evaluations in the PA (Chapter 3). The following questions guided this consideration: (1) To what extent does the currently available scientific evidence alter or strengthen conclusions from the last review regarding health effects attributable to ambient $NO_2$ exposures? (2) Are previously identified uncertainties reduced or do important uncertainties remain? (3) Have new uncertainties been identified? These questions were addressed in the proposal for both short-term and long-term $NO_2$ exposures, with a focus on health endpoints for which the 2016 $NO_X$ ISA concludes that the evidence indicates there is a ''causal'' or ''likely to be a causal'' relationship.

With regard to short-term $NO_2$ exposures, the proposal noted that, as in the last review, the strongest evidence continues to come from studies examining respiratory effects. In particular, the 2016 $NO_X$ ISA concludes that evidence indicates a ''causal'' relationship between short-term $NO_2$ 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. The proposal further noted that 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 $NO_2$ exposures and respiratory effects.

The strongest evidence supporting this ISA causal determination comes from controlled human exposure studies demonstrating $NO_2$-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 $NO_2$ concentrations as low as 100 ppb, while individual studies most consistently report such increases following exposures to $NO_2$ concentrations at or above 250 ppb. Most of the controlled human exposure studies assessed in the 2016 $NO_X$ 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 $NO_2$ exposures and AR and uncertainty in the potential adversity of $NO_2$-induced increases in AR.[86]

Supporting evidence for a range of $NO_2$-associated respiratory effects also comes from epidemiologic studies. In this regard, the proposal placed particular focus on studies that have examined $NO_2$ associations with asthma-related hospital admissions or ED visits, outcomes which are clearly adverse. 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 fundamentally alter the understanding of the respiratory effects associated with ambient $NO_2$ exposures. Due to limitations in the available epidemiologic methods, uncertainty remains in the current review regarding the extent to which findings for $NO_2$ are confounded by traffic-related copollutants (*e.g.,* $PM_{2.5}$, EC/BC, CO), as well as regarding the potential for exposure measurement error and the extent to which near-road $NO_2$ concentrations are reflected in the available air quality data.

Thus, while some new evidence is available in this review, the proposal noted that that new evidence did not substantially alter the understanding of the respiratory effects that occur following short-term $NO_2$ exposures. This evidence is summarized in Section II.C.1 of the proposal, as well as in Section II.A.2 above, and is discussed in detail in the 2016 $NO_X$ ISA (U.S. EPA, 2016a, section 5.2.2).

With regard to long-term $NO_2$ exposures, the 2016 $NO_X$ ISA concludes that there is ''likely to be a causal relationship'' between long-term $NO_2$ 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 $NO_2$ exposures in the development of asthma. Uncertainties in interpreting associations with asthma development include high correlations between long-term average ambient concentrations of $NO_2$ 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. Specifically, the extent to which $NO_2$ 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 $NO_2$ 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 of the proposal, as well as in Section II.A.2 above, and is discussed in detail in the 2016 $NO_X$ ISA (U.S. EPA, 2016a, section 6.2.2).

Given the evaluation of the evidence in the 2016 $NO_X$ ISA, and the 2016 $NO_X$ ISA's causal determinations, the EPA's further consideration of the evidence in the proposal focused 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 $NO_2$ standards. In particular, the EPA considered the following question: To what extent does the available evidence for respiratory effects attributable to either short- or long-term $NO_2$ exposures support or call into question the basic elements of the

[86] This is particularly true at low concentrations (*i.e.,* 100 ppb).

current primary $NO_2$ standards? In addressing this question, the sections below summarize the proposal's consideration of the evidence in the context of the indicator, averaging times, levels, and forms of the current standards.

i. Indicator

The indicator for both the current annual and 1-hour NAAQS for oxides of nitrogen is $NO_2$. While the presence of gaseous species other than $NO_2$ has long been recognized (U.S. EPA, 2016a, Chapter 2), no alternative to $NO_2$ 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 $NO_2$. Similarly, the large majority of epidemiologic studies report health effect associations with $NO_2$, as opposed to other gaseous oxides of nitrogen. In addition, because emissions that lead to the formation of $NO_2$ generally also lead to the formation of other $NO_X$ oxidation products, measures leading to reductions in population exposures to $NO_2$ can generally be expected to lead to reductions in population exposures to other gaseous oxides of nitrogen. Therefore, an $NO_2$ 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 $NO_2$ indicator for standards meant to protect against exposures to gaseous oxides of nitrogen. In its review of the draft PA, the CASAC agreed with this conclusion (Diez Roux and Sheppard, 2017). In light of these considerations, EPA proposed to retain the indicator for the current standards.

ii. Averaging Time

The current primary $NO_2$ standards are based on 1-hour and annual averaging times. The proposal explained that, together, these standards can provide protection against short- and long-term $NO_2$ 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 $NO_2$ 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 $NO_2$ in people with asthma. In addition, epidemiologic studies had reported health effect associations with both 1-hour and 24-hour $NO_2$ 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 $NO_2$ exposures. Based on available analyses of $NO_2$ 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 $NO_2$ 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 $NO_2$ 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) $NO_2$ 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 the CASAC advice in the last review to establish a short-term primary standard for oxides of nitrogen based on using 1-hour maximum $NO_2$ concentrations and to retain the current annual standard (Samet, 2008, p. 2; Samet, 2009, p. 2).

The proposal explained that, 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 2016 $NO_X$ ISA continue to provide evidence that $NO_2$ exposures from less than one 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 2016 $NO_X$ ISA's determination that ''[a] causal relationship exists between short-term $NO_2$ 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 2016 $NO_X$ 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). As in the last review, the 2016 $NO_X$ ISA concludes that there is no indication of a stronger association for any particular short-term duration of $NO_2$ 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 2016 $NO_X$ 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). Thus, in the PA, staff reached the conclusion that, when taken together, the combined evidence from experimental and epidemiologic studies continues to support an $NO_2$ standard with a 1-hour averaging time to protect against health effects related to short-term $NO_2$ 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). In light of these considerations, EPA proposed to retain the averaging time for the current 1-hour standard.

With regard to protecting against long-term exposures, the proposal explained that 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 $NO_2$. 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 $NO_2$ concentrations (*e.g.,* above 8,000 ppb) (U.S. EPA, 1995, section 7).

As described above, evidence newly available in the current review demonstrates associations between long-term $NO_2$ exposures and asthma development in children, based on $NO_2$ concentrations averaged over year of birth, year of diagnosis, or entire lifetime. Supporting evidence indicates that repeated short-term $NO_2$ exposures could contribute to this asthma development. In particular, the 2016

$NO_X$ ISA states that ''findings for short-term $NO_2$ 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, pp. 6–64 and 6–65). Taken together, the evidence supports the potential for recurrent short-term $NO_2$ 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 $NO_2$ exposures, the evidence supports the consideration of both 1-hour and annual averaging times. In its review of the draft PA, the CASAC supported this approach of considering the protection provided against long-term $NO_2$ exposures by considering the combination of the annual and 1-hour $NO_2$ standards. With reference to the current annual standard, the 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). In light of these considerations, EPA proposed to retain the averaging time for the current annual standard.

iii. Level and Form

In evaluating the extent to which evidence supports or calls into question the levels or forms of the current $NO_2$ standards, the EPA considered the following question: To what extent does the evidence indicate adverse respiratory effects attributable to short- or long-term $NO_2$ exposures lower than previously identified or below the existing standards? In addressing this question, it is useful to consider the range of $NO_2$ exposure concentrations that have been evaluated in experimental studies (controlled human exposure and animal toxicology) and the ambient $NO_2$ concentrations in locations where epidemiologic studies have reported associations with adverse outcomes. The proposal's consideration of these issues is discussed below for short-term and long-term $NO_2$ exposures.

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 $NO_2$ concentrations near those in the ambient air (U.S. EPA, 2017a, Section 3.2.2).[87] In evaluating the $NO_2$ exposure concentrations at which increased AR has been observed, the proposal considered both the group mean results reported in individual studies and the results from a recent meta-analysis evaluating individual-level data (Brown, 2015; U.S. EPA, 2016a, Section 5.2.2.1).[88]

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 $NO_2$ 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 $NO_2$ specifically, the lowest exposure concentration evaluated, a marginally statistically significant majority of study participants experienced increased AR.[89] As discussed in more detail in Section II.C.1 of the proposal, and in Section II.A.2 above, individual studies consistently report statistically significant $NO_2$-induced increases in AR following resting exposures to $NO_2$ concentrations at or above 250 ppb but have generally not reported statistically significant increases in AR following resting exposures to $NO_2$ concentrations from 100 to 200 ppb. Limitations in this evidence include the lack of an apparent dose-response relationship between $NO_2$ and AR and remaining uncertainty in the adversity of the reported increases in AR. These uncertainties become increasingly important at the lower $NO_2$ exposure concentrations (*i.e.,* at or near 100 ppb), as the evidence for $NO_2$-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 and summarized in the proposal, provided information about the ambient $NO_2$ concentrations in locations where such studies have examined associations with asthma-related hospital admissions or ED visits (short-term) or with asthma incidence (long-term). In particular, these studies informed consideration of the extent to which $NO_2$-health effect associations are consistent, precise, statistically significant, and present for distributions of ambient $NO_2$ concentrations that likely would have met the current standards. To the extent $NO_2$-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 $NO_2$-associated effects indicated by those studies. In the absence of studies reporting associations in locations meeting the current $NO_2$ standards, there would be greater uncertainty regarding the potential for reported effects to be caused by $NO_2$ exposures that occur with air quality meeting those standards. There are also important uncertainties in the epidemiologic evidence which warrant consideration, including the potential for copollutant confounding and exposure measurement error and the extent to which near-road $NO_2$ concentrations are reflected in the available air quality data.

With regard to epidemiologic studies of short-term $NO_2$ exposures conducted in the U.S. or Canada, the proposal noted 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 $NO_2$ 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 $NO_2$ and asthma hospital admissions and ED visits, most locations had $NO_2$ concentrations likely to have violated the current 1-hour $NO_2$ 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 $NO_2$ monitors been in place during study periods, DVs would likely have been higher. Thus, it is likely that even

[87] As discussed in Section II.C of the proposal and Section II.A.2 above, experimental studies have not reported other respiratory effects following short-term exposures to $NO_2$ concentrations at or near those found in the ambient air.

[88] As noted earlier in this section, 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 $NO_2$ exposures, rather than to chance alone, allowing us to evaluate the strength of the $NO_2$ and AR relationship across different concentrations of $NO_2$ in each study, and these studies have the advantage of being based on the same exposure conditions. The meta-analysis by Brown (2015) can also provide insight into the extent to which observed changes are due to $NO_2$ exposures, but has the additional benefit of aiding in the identification of 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, though each study in the meta-analysis may not be based on the exact same exposure conditions.

[89] 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 $NO_2$, 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 $NO_2$, the majority of study participants did not experience increased AR (U.S. EPA, 2016a; Brown 2015).

the one study location with a maximum DV of 100 ppb (Atlanta) would have violated the existing 1-hour standard during study periods.[90] 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 proposal also considered the potential for copollutant confounding as ambient $NO_2$ concentrations are often highly correlated with other pollutants. This can complicate attempts to distinguish between independent effects of $NO_2$ 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 $PM_{2.5}$, EC/BC, and CO). Taken together, while available U.S. and Canadian epidemiologic studies report $NO_2$-associated hospital admissions and ED visits in locations likely to have violated the current 1-hour $NO_2$ standard, the proposal placed weight on the PA's conclusion that these studies do not indicate the occurrence of such $NO_2$-associated effects in locations and time periods with $NO_2$ concentrations that would clearly have met the current 1-hour $NO_2$ standard (*i.e.,* with its level of 100 ppb and 98th percentile form).

In giving further consideration specifically to the form of the 1-hour standard, the proposal noted 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 $NO_2$ concentrations based, in part, on evidence for health effects associated with short-term $NO_2$ exposures from experimental studies which provided information on specific exposure concentrations that were linked to respiratory effects (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.[91] In addition, the proposal noted that a 98th percentile form is consistent with the EPA'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 $NO_2$.[92] In light of these considerations, EPA proposed to retain the level and form for the current 1-hour standard.

Long-Term

With regard to health effects related to long-term $NO_2$ exposures, the proposal first considered the basis for the current annual standard. It was originally set to protect against $NO_2$-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 $NO_2$ 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 $NO_2$, the evidence for adverse health effects attributable to long-term $NO_2$ exposures did not support changing the level of the annual standard (75 FR 6474, February 9, 2010).

In the current review, the strengthened ''likely to be causal'' relationship between long-term $NO_2$ 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 uncertainties resulting from the methods used to assign $NO_2$ exposures, the high correlations between $NO_2$ and other traffic-related pollutants, and the lack of information regarding the extent to which reported effects are independently associated with $NO_2$ rather than the overall mixture of traffic-related pollutants. The potential for such confounding is particularly important to consider when interpreting epidemiologic studies of long-term $NO_2$ exposures given: (1) The relatively high correlations observed between measured and modeled long-term ambient concentrations of $NO_2$ and long-term concentrations of other roadway-associated pollutants; (2) the general lack of information from copollutant models on the potential for $NO_2$ 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 $NO_2$ concentrations near those in the ambient air. Thus, it remains unclear the degree to which the observed effects in these studies are independently related to exposure to ambient concentrations of $NO_2$. 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 $NO_2$ standards.

While the proposal recognized the above uncertainties, it considered what studies of long-term $NO_2$ and asthma development indicate with regard to the adequacy of the current primary $NO_2$ standards. As discussed above for short-term exposures, the proposal considered the degree to which the evidence indicates adverse respiratory effects associated with long-term $NO_2$ exposures in locations that would have met the current NAAQS. As summarized in Section II.C.2 of the proposal, and in Section II.A.2 above, the causal determination for long-term exposures is supported both by studies of long-term $NO_2$ exposures and by studies indicating a potential role in asthma development for repeated short-term exposures to high $NO_2$ concentrations.[93]

As such, when considering the ambient $NO_2$ concentrations present during study periods, the proposal considered these concentrations within

[90] Based on recent air quality information for Atlanta, 98th percentiles of daily maximum 1-hour $NO_2$ 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 $NO_x$ emissions from traffic sources were higher (U.S. EPA, 2017a, Section 2.1.2).

[91] 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).

[92] The 98th percentile typically corresponds to about the 7th or 8th highest daily maximum 1-hour $NO_2$ concentration in a year.

[93] There remains some uncertainty as to whether the health effects associated with long term exposure to $NO_2$ are due to repeated higher short term exposures, a longer, cumulative exposure, or some mixture of both.

the context of both the 1-hour and annual $NO_2$ standards. Analyses of historical data indicate that 1-hour DVs at or below 100 ppb generally correspond to annual DVs below 35 ppb.[94] The CASAC noted this relationship, stating that ''attainment of the 1-hour standard corresponds with annual design value averages of 30 ppb $NO_2$'' (Diez Roux and Sheppard, 2017). Thus, meeting the 1-hour standard with its level of 100 ppb would be expected to maintain annual average $NO_2$ concentrations below the 53 ppb level of the current annual standard.

As discussed in Section II.C.1 of the proposal, and in Section II.A.2 above, 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 $NO_2$ monitors in place during study periods, they do not reflect the $NO_2$ 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 $NO_2$ 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) (U.S. EPA, 2016a, section 2.5.3.1, *e.g.,* Tables 2–6 and 2–8, Figures 2–16 and 2–17).

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 proposal placed weight on the PA's conclusion that the epidemiologic evidence does not provide support for $NO_2$-attributable asthma development in children in locations with $NO_2$ concentrations that would have clearly met the current annual and 1-hour $NO_2$ 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 proposal noted the PA's evaluation indicating that most of the locations included in epidemiologic studies of long-term $NO_2$ exposure and asthma incidence would likely have violated either one or both of the current $NO_2$ standards, over at least parts of the study periods. In light of these considerations, EPA proposed to retain the level and form for the current annual standard.

b. Exposure- and Risk-Based Considerations

Exposure- and risk-based considerations were also important to the proposed decision and its rationale, like the consideration of the health evidence discussed in section II.B.1.a above. As described in greater detail in Section II.A.3 above, and in the REA Planning document (U.S. EPA, 2015b, Section 2.1.1) and the PA (U.S. EPA, 2017a, Chapter 4), the EPA conducted updated analyses comparing ambient $NO_2$ 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. These analyses were presented in the PA. The staff further concluded in the PA 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 $NO_2$'' (Diez Roux and Sheppard, 2017).

When considering analyses comparing $NO_2$ air quality with health-based benchmarks, the proposal began by noting the PA's focus on the following specific questions: (1) To what extent are ambient $NO_2$ concentrations that may be of public health concern estimated to occur in locations meeting the current $NO_2$ standards? (2) What are the important uncertainties associated with those estimates?

As discussed in section II.A.3 above, and in section II.D.1 of the proposal, benchmarks are based on information from controlled human exposure studies of $NO_2$ exposures and AR. In identifying specific $NO_2$ benchmarks, and considering the weight to place on each, the updated analyses in the PA consider 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 $NO_2$ benchmarks between 100 and 300 ppb, based largely on studies of non-specific AR in people with asthma exposed to $NO_2$ at rest. As discussed in more detail in section II.D of the proposal, 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 $NO_2$ 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 $NO_2$-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 $NO_2$ (Brown, 2015), individual studies have not generally reported statistically significant increases in AR following resting exposures to 100 ppb $NO_2$.[95]

In further considering the potential public health implications of exposures to $NO_2$ concentrations at or around benchmarks, there are multiple uncertainties, as discussed in section II.C.I of the proposal and section II.A.3 above. As discussed in more detail in those sections, these uncertainties include the lack of an apparent a dose-response relationship between $NO_2$ and AR in people with asthma, and uncertainty in the potential adversity of the reported $NO_2$-induced increases in AR.

As discussed in section II.D.2 of the proposal, and in section II.A.3 above, analyses of unadjusted air quality, which meets the current standards in all locations, indicate almost no potential for 1-hour exposures to $NO_2$ 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[96] indicate virtually no potential for 1-hour exposures to $NO_2$ concentrations at or above 200 ppb (or 300 ppb) and almost none for exposures

[94] As noted in the PA, near-road monitors were not included in this analysis due to the limited amount of data available (U.S. EPA, 2017a, Figure 2–11).

[95] Meta-analysis results for exposures to 100 ppb $NO_2$ were statistically significant when analyses were restricted to non-specific AR, but not when analyses were restricted to specific AR (Brown, 2015).

[96] In all study areas, ambient $NO_2$ 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 $NO_2$ NAAQS, the adjustment needed to just meet the 1-hour standard was applied (U.S. EPA, 2017a, Section 4.2.1).

at or above 150 ppb.[97] 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 $NO_2$ 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 $NO_2$ concentrations of 100 ppb.

Section II.D.2 of the proposal noted that these analyses indicate that the current 1-hour $NO_2$ standard is expected to allow virtually no potential for exposures to the $NO_2$ 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 $NO_X$ emissions in the U.S. Such $NO_2$ 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 $NO_2$ exposures that have the potential to exacerbate asthma symptoms, but for which the evidence indicates greater uncertainty in the risk of such effects occurring (*i.e.,* at or near 100 ppb). Given the results of these analyses, and the uncertainties inherent in their interpretation, the proposal placed weight on the PA's conclusion that there is little potential for exposures to ambient $NO_2$ concentrations that would be of public health concern in locations meeting the current 1-hour standard.

2. The CASAC Advice in This Review

In the current review of the primary $NO_2$ standards the CASAC has provided advice and recommendations based on its review of drafts of the 2016 $NO_X$ ISA (Frey, 2014a; 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 $NO_2$ standards to protect the public health.

Briefly, with regard to the strength of the evidence for respiratory effects, the CASAC agreed with the 2016 $NO_X$ ISA conclusions. In particular, the CASAC concurred ''with the finding that short-term exposures to $NO_2$ 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 2016 $NO_X$ ISA conclusions on long-term exposures and respiratory effects, specifically stating the following (Diez Roux and Sheppard, 2017, p. 7):

> Long-term exposures to $NO_2$ 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 $NO_2$ 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.[98] 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 $NO_2$,'' noting ''that existing uncertainties in the epidemiologic literature limit the ability to properly estimate and interpret population risk associated with $NO_2$, 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 agreed with its conclusion that the available evidence, taken together, does not support the need for increased protection against short- or long-term $NO_2$ exposures, beyond that provided by the existing standards, 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). Further, the CASAC concurred with the draft PA's preliminary conclusion that it is appropriate to consider retaining the current primary $NO_2$ standards without revision, stating that, ''the CASAC recommends retaining, and not changing the existing suite of standards'' (Diez Roux and Sheppard, 2017). The CASAC further 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 $NO_2$ 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 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 ''a scientific rationale for this form is there is uncertainty regarding the severity of adverse effects at a level of 100 ppb $NO_2$, 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).

[97] Comparisons of $NO_2$ air quality to health-based benchmarks that estimated occurrences of $NO_2$ concentrations exceeding the 150 and 200 ppb health-based benchmarks are found in Figure 4–1 of the PA (U.S. EPA, 2017a).

[98] 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).

• *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, 2017, p. 8). However, the CASAC recognized that these studies ''are also subject to uncertainty, including possible confounding with other traffic-related pollutants'' (Diez Roux and Sheppard, 2017, p. 8). The 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, the CASAC recognized the causal associations between long-term exposures, or repeated short-term exposures, and asthma development (Diez Roux and Sheppard, 2017, p. 7) and the appropriateness of considering the protection provided by the current suite of standards together (Diez Roux and Sheppard, 2017, p. 9). Therefore, the CASAC advice on the annual standard takes into account the degree of protection provided by that standard, in combination with the current 1-hour standard. In particular, the CASAC recognized that meeting the 1-hour $NO_2$ standard can limit long-term $NO_2$ concentrations to below the level of the annual standard, observing that ''an hourly DV of 100 ppb $NO_2$ is associated with DV values that average approximately 30 ppb $NO_2$'' and that ''there is insufficient evidence to make a scientific judgment that adverse effects occur at annual DVs less than 30 ppb $NO_2$'' (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, the 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, the CASAC stated that ''[t]here is an ongoing need for research in multipollutant exposure and epidemiology to attempt to distinguish the contribution to $NO_2$ exposure to human health risk'' (Diez Roux and Sheppard, 2017, p. 10). More specifically, the CASAC pointed to the importance of further understanding the effects of co-pollutant exposures and the variability in ambient $NO_2$ 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, the 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).

3. Comments on the Proposed Decision

This section presents the responses of the EPA to the public comments received on the 2017 $NO_2$ NAAQS proposal (82 FR 34792, July 26, 2017). All significant issues raised in timely public comments have been addressed in this document, as the EPA is not preparing a separate Response to Comments document. We have additionally considered comments submitted after the close of the public comment period, to the extent practicable.

Overall, the EPA received 17 sets of comments, with the majority expressing support for the Administrator's proposed decision to retain the current primary standards, without revision. Comments supporting the Administrator's proposed decision were received from various industry groups,[99] individuals, and state environmental or health agencies.[100] These commenters generally note their agreement with the Administrator's rationale provided in the proposal and many note the CASAC concurrence with the EPA that the current evidence does not support revision to the standards. Some of the commenters also agree with the EPA and the CASAC statements that the information in this review has not substantially altered our previous understanding of the concentrations at which effects can occur, and that the scientific evidence does not support standards more protective than the current 1-hour and annual standards.

Several groups, including some that support the Administrator's proposed decision to retain the current standards, provided additional comments, including on the EPA's causal determinations in the 2016 $NO_X$ ISA, the margin of safety provided by the current standards, and the potential for the scientific information to support alternative standards that are less stringent than the current standards. In addition, one organization (The American Lung Association) argues for more stringent primary $NO_2$ standards, noting the strong evidence for respiratory effects following both short- and long-term $NO_2$ exposures.

The following sections discuss the public comments on the proposal and the EPA's responses to those comments. Section II.B.3.a discusses comments on the EPA's assessment of the scientific evidence. Section II.B.3.b discusses comments on the degree of protection provided by the current standards and on the potential for the available scientific information to support standards that are less stringent than the current standards. Section II.B.3.c discusses comments recommending that the EPA revise the current standards to be more stringent. Section II.B.3.d briefly explains the EPA's approach to comments related to implementation of the NAAQS, which are outside the scope of this action.

a. Comments on the Assessment of the Scientific Evidence

There were several comments submitted related to the EPA's assessment of the scientific evidence. Some commenters agree with the causal framework used in the 2016 $NO_X$ ISA and with the ISA's conclusions regarding the strength of the evidence for various health outcomes and for at-risk populations. Other commenters, while agreeing with the overall proposed decision to retain the existing primary standards, assert that the ISA framework for causal determinations does not result in a systematic, balanced, and rigorous evaluation of the evidence. As discussed below, these commenters generally claim that the 2016 $NO_X$ ISA does not adequately address uncertainties and biases in the evidence and recommend that the EPA should strengthen its causal framework.

Some comments received on the proposed decision express an overall

[99] Comments were received from the following industry groups: The NAAQS Implementation Coalition, the Utility Air Regulatory Group, Edison Electric Institute, Interstate National Gas Associations of America, Cleco Power, the American Fuel and Petrochemical Manufacturers, the American Petroleum Institute, The Tri-state Generation and Transmission Association, and the Class of '85 Regulatory Response Group.

[100] Comments were received from the following state environmental or health agencies: Texas Commission on Environmental Quality (TCEQ) and Arkansas Department of Environmental Quality (ADEQ).

objection to ISA conclusions that the evidence linking $NO_2$ exposures with a variety of health effects has become stronger in this review. A subset of these comments further imply that the 2016 $NO_X$ ISA's conclusions on the strength of evidence, and the corresponding discussions in the PA, are not entirely consistent with the uncertainties noted by the Administrator throughout the discussion of his proposed decision on the primary $NO_2$ standards.

In responding to these comments, the EPA notes that the ISA's causal framework has been implemented and refined over multiple NAAQS reviews, drawing from extensive interactions with the CASAC and from the public input received as part of the CASAC review process. Based on application of that framework in the current review, the 2016 $NO_X$ ISA has made causal determinations for a variety of health outcomes. The ISA provides a careful and detailed rationale for all of its causal determinations, explicitly characterizing the key evidence, the reason for the change from the 2008 $NO_X$ ISA (if a change occurred), and the uncertainties remaining in the body of evidence (see, *e.g.,* U.S. EPA, 2016a, Table 1–1). In most cases where the causal determination has changed since the 2008 $NO_X$ ISA, the change has been due to the availability, in the current review, of additional studies that reduce uncertainty or bias in the evidence (U.S. EPA, 2016a, Table 1–1).[101] The causal determinations in the $NO_X$ ISA underwent extensive CASAC review, which included multiple opportunities for public input. The EPA considered the CASAC advice and the public input in making final causal determinations. The CASAC concurred with the 2016 $NO_X$ ISA's causal determinations and explained the reasons for its concurrence (Diez Roux and Frey, 2015a, p.1; Diez Roux and Sheppard, 2017, p. 7).

For example, in concluding that a ''causal relationship exists between short-term $NO_2$ exposure and respiratory effects based on evidence for asthma exacerbation'' (U.S. EPA, 2016a, p. 1–17), the ISA cites ''epidemiologic evidence for $NO_2$-associated asthma exacerbation and biological plausibility from $NO_2$-induced increases in [AR] and allergic inflammation in adults with asthma'' (U.S. EPA, 2016a, p. 5–247). In agreement with this causal determination, the CASAC states the following (Diez Roux and Sheppard, 2017, p. 7):

> The CASAC concurs with the finding that short-term exposures to $NO_2$ are causal for respiratory effects based on evidence for asthma exacerbation. The strongest evidence is for an increase in airway responsiveness based on controlled human exposure studies, with supporting evidence from epidemiologic studies.

In addition, in concluding that ''[t]here is likely to be a causal relationship between long-term $NO_2$ exposure and respiratory effects based on evidence for the development of asthma'' (U.S. EPA, 2016a, p. 1–20), the ISA notes that ''[r]ecent epidemiologic studies consistently indicate increases in asthma incidence in children particularly in association with $NO_2$ exposures estimated at or near children's homes or schools'' and that experimental evidence ''provides biological plausibility by characterizing a potential mode of action by which long-term $NO_2$ exposure may lead to asthma development'' (U.S. EPA, 2016a, p. 6–67). In agreement with this causal determination, the CASAC states the following (Diez Roux and Sheppard, 2017, p. 7):

> Long-term exposures to $NO_2$ 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 co-pollutants on the association between $NO_2$ and asthma incidence.

Thus, based on the evidence considered in the 2016 $NO_X$ ISA, and consistent with the CASAC advice, we disagree with comments that the strengthening of the causal determinations in the 2016 $NO_X$ ISA is not justified.

The EPA further disagrees with comments claiming that, in his consideration of the levels of the primary standards, the Administrator's discussion of uncertainties and limitations in the scientific evidence is inconsistent with the conclusions of the 2016 $NO_X$ ISA that the evidence for several health endpoints is stronger now than in the last review. As an initial matter, we note that the issues faced by the EPA in drawing causal determinations in the 2016 $NO_X$ ISA differ from EPA's considerations in evaluating the public health protection provided by the standards. In drawing the causal determinations, the ISA focuses on the degree to which the available evidence indicates that $NO_2$ exposures can cause specific health effects. These causal determinations reflect the ISA's assessment of studies spanning a relatively wide range of exposure concentrations, encompassing the full body of evidence relevant for the review. In contrast, in the proposal and in this final action, the EPA is additionally tasked with determining what the evidence can tell us about the adequacy of the public health protection provided by a particular standard or standards. This step typically involves focusing on the subset of studies that, together with risk and exposure information, can best inform the EPA's consideration of the public health impacts associated with particular air quality concentrations. Consideration of uncertainties is important for both tasks, but the nature of those uncertainties, and exactly how the various uncertainties factor into each aspect of the review, may differ. For example, strengthening of a causal determination in the ISA may be based on studies that clarify a proposed mode of action linking exposures with an observed effect, despite being conducted at exposure concentrations that would not be allowed by the current standards. Such studies may reduce uncertainties in a way that supports strengthening a causal determination, but not revising the standard. Thus, the Administrator's consideration of uncertainties in the evidence when reaching conclusions on the standards is not inconsistent with the ISA conclusions that the evidence supports strengthening some causal determinations in this review.

We further note that, in reaching his proposed and final decisions, the Administrator's consideration of the evidence, including its limitations and uncertainties, draws directly from the 2016 $NO_X$ ISA's assessment of that evidence and from the PA's considerations and conclusions related to the adequacy of the public health protection provided by the current standards. Both the ISA and PA include extensive discussion and consideration of the scientific evidence and its uncertainties. As noted above, Table 1–1 in the ISA summarizes the key evidence for various $NO_2$-related health

[101] The exception to this is the 2016 $NO_X$ ISA determination that a causal relationship exists between short-term $NO_2$ exposure and respiratory effects. This conclusion is strengthened from the ''likely to be causal'' relationship determined in the 2008 $NO_X$ ISA for Oxides of Nitrogen. Rather than new evidence, the 2016 $NO_X$ ISA notes that integrated experimental and epidemiologic evidence for asthma exacerbation, with due weight to controlled human exposure studies, supports a causal relationship between short-term $NO_2$ exposure and respiratory effects. Specifically, the 2016 $NO_X$ ISA explains that the conclusion is strengthened from the previously determined ''likely to be causal'' relationship because the combined controlled human exposure and epidemiologic evidence can be linked in a coherent and biologically plausible pathway to explain how $NO_2$ exposure can trigger an asthma exacerbation. (U.S. EPA, 2016a, pp. 1–17 to 1–19).

outcomes, including the remaining uncertainties inherent in that evidence. In addition, drawing from the ISA, the PA includes extensive consideration of uncertainties and limitations in the evidence as they relate to conclusions on the adequacy of the public health protection provided by the current primary $NO_2$ NAAQS (U.S. EPA, 2017a, sections 3.2.2.1, 3.2.2.2, 3.3.2.1). Contrary to the comments noted above, the Administrator's proposed and final decisions draw from the characterization in those documents of uncertainties and limitations in the evidence (*e.g.,* sections II.A.2, II.A.3, II.B.4 of this final action). The Administrator's proposed and final decisions to retain the current primary $NO_2$ standards are consistent with the PA's conclusions (U.S. EPA, 2017a, section 5.4). Moreover, these decisions are consistent with recommendations of the CASAC to retain the current standards (Diez Roux and Sheppard, 2017).

Some comments further criticize the Agency's characterization of the evidence by asserting that the EPA places too much emphasis on epidemiologic studies that are methodologically flawed and insufficient for determining a standard. While we agree that there are uncertainties inherent in epidemiologic studies, these uncertainties, which have been extensively considered as part of the assessment of the evidence in the ISA and the evaluation of policy options in the PA, as well as in the proposal and this final action (*e.g.,* summarized in sections II.A.2 and II.B.1 above), do not make the epidemiologic evidence insufficient for informing decisions on the primary $NO_2$ standards. Rather, conclusions in this review draw from the consideration of scientific evidence from a range of disciplines, each with its own strengths and limitations.[102] In particular, the 2016 $NO_X$ ISA's causal determinations are based on the integration of evidence across controlled human exposure, epidemiologic, and animal toxicological studies. The focus of the ISA's integration is on evaluating the consistency and inconsistency in the pattern of effects across studies and endpoints as well as the strengths and limitations of the evidence across the various disciplines (U.S. EPA, 2016a, p. 1). For each study, the 2016 $NO_X$ ISA systematically evaluates study design, populations evaluated, approach to exposure assessment/assignment, approach to outcome assessment, potential for confounding, and statistical methodology (U.S. EPA, 2016a, Table A–1). As described below, and more fully in the ISA (see *e.g.,* U.S. EPA, 2016a, Table 1–1), uncertainties and limitations in the evidence, including in the evidence from epidemiologic studies, are explicitly considered in the ISA's causal determinations and can affect how various aspects of the evidence are weighed in making those determinations.

For example, while the ISA concludes that epidemiologic studies do indicate the occurrence of $NO_2$-associated asthma exacerbation, it further concludes that ''epidemiologic evidence on its own does not rule out the influence of other traffic-related pollutants'' (U.S. EPA, 2016a, p. 1–18). The ISA further concludes that ''[t]he key evidence that $NO_2$ exposure can independently exacerbate asthma are the findings from previous controlled human exposure studies for increases in airway responsiveness in adults with asthma'' (U.S. EPA, 2016a, p. 1–18). Thus, based in part on uncertainties in the available epidemiologic evidence, the ISA's conclusion that ''[a] causal relationship exists between short-term $NO_2$ exposure and respiratory effects'' (U.S. EPA, 2016a, p. 1–17) places the greatest emphasis on information from controlled human exposure studies (*e.g.,* U.S. EPA, 2016a, p. 5–247). As noted above, the CASAC endorsed this emphasis, stating 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). In fact, the CASAC recommended that the controlled human exposure studies, alone, are sufficient to justify the causal determination for short term $NO_2$ exposures and respiratory effects (Diez Roux and Frey, 2015a, cover letter at p. 2).[103] Consistent with this, information from controlled human exposure studies is emphasized in the PA's conclusions on the public health protection provided by the current standards against short-term $NO_2$ exposures (U.S. EPA, 2017a, sections 3.2 and 5.4) and in the Administrator's conclusion to retain those standards in this final decision (section II.B.4, below).

In addition, the 2016 $NO_X$ ISA's conclusion on long-term $NO_2$ exposure and respiratory effects recognizes uncertainty in epidemiologic studies due to potential confounding by other traffic-related pollutants. The ISA specifically concludes that uncertainty remains ''in identifying an independent effect of $NO_2$ exposure from traffic-related copollutants because evidence from experimental studies for effects related to asthma development is limited, and epidemiologic analysis of confounding is lacking'' (U.S. EPA, 2016a, p. 1–32).[104] However, in making its overall determination that ''there is likely to be a causal relationship between long-term $NO_2$ exposure and respiratory effects'' the ISA also notes that support for biological plausibility comes from experimental studies in animals (*e.g.,* U.S. EPA, 2016a, Table 1–1). While recognizing remaining uncertainties in the evidence, the CASAC agreed with this ISA causal determination, observing that ''[t]he strongest evidence is for asthma incidence in children in epidemiologic studies, with supporting evidence from experimental animal studies'' (Diez Roux and Sheppard, 2017, p. 7).

Thus, the 2016 $NO_X$ ISA's conclusions reflect the consideration of information from all lines of evidence, not only epidemiologic studies, including appropriate consideration of the uncertainties and limitations in that evidence. The CASAC reviewed and endorsed the 2016 $NO_X$ ISA's approach to assessing the evidence, including uncertainties and limitations in that evidence, and its key conclusions based on the application of that approach (*e.g.,* Diez Roux and Frey, 2015a; Diez Roux and Sheppard, 2017, p. 7). Additionally, the ISA's careful consideration of scientific evidence from multiple disciplines, and the uncertainties and limitations in that evidence, including in epidemiologic studies, informed the PA's conclusions on the public health protection provided by the current standards and the Administrator's decision to retain those standards, without revision, in this review. Thus, the EPA does not agree with comments that undue emphasis was placed on epidemiologic studies.

Several comments further contend that the 2016 $NO_X$ ISA overstates the consistency of results across

[102] In fact, relative to other types of evidence, strengths of epidemiologic studies can include providing information on the most serious pollutant-associated effects in human populations, including populations with pre-existing conditions, or at particular life stages, that put them at increased risk of such effects.

[103] Specifically, the CASAC recommended that ''the evidence supporting changes to the causal determination status for oxides of nitrogen for associations with short-term exposures be based primarily on the findings from the controlled human exposure studies, as they alone are sufficient to justify the change'' (Diez Roux and Frey, 2015a, cover letter at p.2).

[104] Such uncertainties also informed the PA's conclusions on the public health protection provided by the current standards (U.S. EPA, 2017a, section 5.4).

epidemiologic studies and that it does not adequately capture uncertainties in the epidemiologic evidence. The EPA disagrees with these comments. As noted above, the 2016 $NO_X$ ISA appropriately characterizes the uncertainties and limitations in the epidemiologic evidence, including uncertainties resulting from inconsistent results across studies (*e.g.,* U.S. EPA, 2016a, Tables 5–39 and 6–5). For endpoints where the epidemiologic evidence is not consistent, the 2016 $NO_X$ ISA discusses the inconsistencies. For example, the ISA states that ''[e]pidemiologic evidence for $NO_2$-related decreases in lung function in populations with asthma is inconsistent as a whole'' (U.S. EPA, 2016a, p. 5–241). In contrast, the ISA appropriately characterizes the consistent results of epidemiologic studies that evaluate asthma-related outcomes. In particular, the 2016 $NO_X$ ISA notes that ''[r]ecent studies that examined the association between short-term $NO_2$ exposure and asthma hospital admissions and ED visits consistently report positive associations and support the results of U.S. and Canadian studies evaluated in the 2008 ISA for Oxides of Nitrogen.'' (U.S. EPA, 2016a, p. 5–91). Figures 5–16 and 5–17 in the 2016 $NO_X$ ISA illustrate the consistent, positive associations reported in studies that have evaluated the potential for confounding of the $NO_2$ association by co-occurring pollutants, a key potential uncertainty in $NO_2$ epidemiologic studies (U.S. EPA, 2016a, pp. 5–248 to 5–249). Based on its assessment of such studies of short-term $NO_2$ exposure and asthma-related effects, the 2016 $NO_X$ ISA concludes that ''the pattern of association observed for $NO_2$ supports the consistency of evidence and does not indicate a high probability of associations found by chance alone'' (U.S. EPA, 2016a, p. 5–241).

Some comments criticizing the 2016 $NO_X$ ISA's characterization of consistency of results across epidemiologic studies, and the ISA's consideration of uncertainties in those studies, focus specifically on studies of long-term $NO_2$ exposures. Such comments claim that the EPA overstates the consistency of the epidemiologic evidence, particularly given the potential for copollutant confounding and exposure measurement error in studies of long-term $NO_2$ exposures. As discussed below, the EPA disagrees with these comments.

Figure 6–1 in the 2016 $NO_X$ ISA illustrates the consistently positive associations between long-term exposures and asthma incidence in children. Based on such studies, the ISA concludes the following (U.S. EPA, 2016a, p. 6–63):

> Multiple longitudinal studies demonstrate associations between higher ambient $NO_2$ concentrations measured in the first year of life, in the year of diagnosis, or over a lifetime and asthma incidence in children. Results are consistent across locations based on various study designs and cohorts.

In reaching this conclusion, the 2016 $NO_X$ ISA also thoroughly discusses the uncertainties and limitations in these studies, including uncertainties and limitations stemming from the potential for copollutant confounding and exposure measurement error (U.S. EPA, 2016a, section 6.2.2.1). For example, with respect to studies of long-term exposures, the ISA notes that ''[e]pidemiologic studies of asthma development in children have not clearly characterized potential confounding by $PM_{2.5}$ or traffic-related pollutants'' (U.S. EPA, 2016a, p. 6–64). Drawing from this discussion in the ISA, the potential for such confounding is a key consideration in the PA's conclusions on the adequacy of the public health protection provided by the current primary $NO_2$ NAAQS (U.S., EPA, 2017, section 5.4). The Administrator has further considered such uncertainty in reaching his proposed and final decisions in this review (82 FR 34792, July 26, 2017, section II.F.4; and see section II.B.4 below). The 2016 $NO_X$ ISA also characterizes the potential for exposure measurement error in these studies and uncertainties related to reliability of asthma diagnosis and age of children and temporality between diagnosis and exposures (U.S. EPA, 2016a, section 6.2). Based on the broader body of evidence (*i.e.,* including controlled human exposure and animal toxicological studies), the 2016 $NO_X$ ISA concludes that uncertainty in the epidemiologic evidence base ''is partly reduced by the biological plausibility provided by findings from experimental studies'' (U.S. EPA, 2016a, p. 6–64). When taken together, the 2016 $NO_X$ ISA concludes that the evidence supports a relationship between long-term $NO_2$ exposure and respiratory effects that is ''likely to be causal,'' and the CASAC supported this conclusion in its review of drafts of the 2016 $NO_X$ ISA and the PA (Diez Roux and Frey, 2015a; Diez Roux and Sheppard, 2017, p. 7).

Some comments additionally contend that the ISA provides a skewed and unbalanced picture of the scientific record by failing to discuss null associations in epidemiologic studies and by focusing on results at the lag that had the most positive and statistically significant association. These comments assert that the ISA ignores temporal differences in the lag at which the strongest association was found.

With regard to reporting null associations, the EPA agrees that the assessment of the scientific evidence should consider all relevant, well-conducted studies that meet the ISA's criteria for inclusion, regardless of whether results are positive, null, or negative. Accordingly, the EPA employs a comprehensive approach to ensure that all of the relevant literature is identified for consideration and evaluation in the ISA (U.S. EPA, 2015a, Figure III, p. 6). As an initial step in the development of the 2016 $NO_X$ ISA, a call for information was published in the **Federal Register** (77 FR 7149, February 2, 2012). This call for information invited members of the public to provide information relevant to the assessment, including the identification of publications that evaluate potential relationships between pollutant exposures and health effects or data from the fields of atmospheric or exposure science. Subsequent to this call for information, the EPA conducted a comprehensive literature search and an evaluation and integration of evidence from the identified studies. As part of this process, the EPA evaluated study quality according to predefined criteria that are consistent with widely established methods in the field (U.S. EPA, 2016a, Table A–1, p. A2). This evaluation and assessment of the evidence, which included studies that reported null or negative results, was presented in two drafts of the ISA, each of which was reviewed by the CASAC at a public meeting where there were opportunities for members of the public to provide comments. As discussed above, in its advice to the Administrator, the CASAC concurred with key conclusions in the ISA regarding the strength of the evidence linking $NO_2$ exposures with various health outcomes (Diez Roux and Frey, 2015a, cover letter at p. 1; Diez Roux and Sheppard, 2017, p. 7).

In addition, we note that there is ample discussion throughout the ISA of null and negative results when they are reported in the studies, including epidemiologic studies (*e.g.,* U.S. EPA, 2016a, Figures 5–7 and 6–1, and accompanying text).[105] Summary tables

[105] The 2016 $NO_X$ ISA also recognizes the potential for publication bias, stating that ''[p]ublication bias is another source of uncertainty that can impact the magnitude of estimated health or welfare effects. It is well understood that studies reporting non-null findings are more likely to be published than reports of null findings'' (U.S. EPA, 2016a p. li).

of key evidence in the ISA for each causal determination discuss outcomes for which negative or inconsistent results are observed (see Table ES–1 of the 2016 $NO_X$ ISA for a comprehensive list of summary tables included in the ISA). Additionally, the EPA notes that while these comments criticized the EPA's assessment of the evidence, they did not identify well-conducted studies, regardless of association observed, or lack thereof, that were not included in the 2016 $NO_X$ ISA. Thus, given the extensive public process that the EPA has used to identify and assess the relevant scientific evidence, including multiple opportunities for CASAC to provide advice and for members of the public to provide input, together with the ISA's discussion of all relevant, well-conducted studies, regardless of results, we do not agree with comments claiming that the ISA provides an unbalanced picture of the scientific record by failing to account for studies reporting null or negative associations.

Additionally, the EPA does not agree with comments criticizing the 2016 $NO_X$ ISA's approach to identifying the most appropriate lags in epidemiologic studies of short-term $NO_2$ exposures. We note that lag structure can vary within the population according to differences among individuals in time-activity patterns, pre-existing disease, or other factors that influence exposure and responses to exposure. The ISA specifically notes that ''[t]he lag structure for associations with $NO_2$ exposure may vary among health effects depending on differences in the time course by which underlying biological processes occur'' (U.S. EPA, 2016a, p. 1–39). In addition, differences in associations among exposure lags may be influenced by ''differences in the extent to which single-day and multiday average ambient $NO_2$ concentrations represent people's actual exposures'' (U.S. EPA, 2016a, p. 1–39).

In assessing the support for specific lags in epidemiologic studies of short-term $NO_2$ exposures and asthma-related effects, the ISA notes support for same-day exposures and for exposures averaged over multiple days (U.S. EPA, 2016a, section 1.6.2). The ISA further notes support for these lags from experimental studies (U.S. EPA, 2016a, section 1.6.2). Specifically, controlled human exposure studies found airway responsiveness in adults with asthma to increase immediately after, or 20 minutes to 4 hours after, a single $NO_2$ exposure and over 4 days of repeated exposure (U.S. EPA, 2016a, section 5.2.2.1). In experimental studies, $NO_2$ exposure enhanced allergic inflammation 30 minutes up to 19 hours after a single- or 2-day exposure in humans and 7 days after exposure in rats (U.S. EPA, 2016a, section 5.2.2.5). Thus, based on its assessment of the evidence, the ISA concludes that ''findings from experimental studies provide biological plausibility for the asthma-related effects observed in epidemiologic studies in association with 2- or 5-hour exposures, same-day $NO_2$ exposures, as well as exposures averaged over multiple days'' (U.S. EPA, 2016a, p. 1–40). Accordingly, when assessing epidemiologic studies of short-term $NO_2$ exposures, the ISA focuses on the lags that are best supported in the evidence, with a recognition that the most appropriate lag can vary according to the specific endpoint evaluated, time-activity patterns of members of the study population, the prevalence of pre-existing disease in the study population, and other factors that influence pollutant exposures or the responses to those exposures.

Some comments recommend that the EPA conduct quantitative analyses of uncertainty whenever possible. As discussed above and elsewhere in this document (*e.g.,* sections II.A.2, II.A.3, II.B.1, II.B.4), the EPA has thoroughly considered uncertainties in the evidence and in available quantitative analyses throughout this review of the primary $NO_2$ NAAQS. Uncertainties have been evaluated through a combination of qualitative and quantitative approaches, with the specific approach depending on the uncertainty being evaluated and the data available for its evaluation. For example, the 2016 $NO_X$ ISA's conclusions are based on an evaluation of the strengths and weaknesses in the overall collection of studies across disciplines. The ISA's approach to evaluating the evidence and drawing causal determinations generally involves qualitative consideration of uncertainties in the various lines of evidence (U.S EPA, 2016a, preamble). As noted above, this framework has been implemented and refined over multiple NAAQS reviews, drawing from extensive interactions with the CASAC and from the public input received as part of the CASAC review process. The CASAC has reviewed the causal determinations in the $NO_X$ ISA, including the ISA's consideration of uncertainties in the evidence, and has concurred with those determinations (Diez Roux and Frey, 2015a, cover letter at p.1; Diez Roux and Sheppard, 2017, p. 7).

With regard to analyses comparing $NO_2$ air quality and health-based benchmarks, the PA includes both quantitative and qualitative evaluation of uncertainties. For example, quantitative sensitivity analyses were used to evaluate the degree to which study areas adequately reflect influential factors that could contribute to variability in $NO_2$ concentrations and potential exposures (U.S. EPA, 2017a, Appendix B, section 2.3.2) and to examine the potential impacts of $NO_2$ exposures on or near roadways (U.S. EPA, 2017a, Appendix B, section 2.4.2). In addition, the PA includes extensive qualitative discussion of uncertainties in air quality-benchmark comparisons, and the implications of these uncertainties for the interpretation of analysis results (U.S. EPA, 2017a, section 4.2.1.3). This includes consideration of uncertainties in evidence underlying the health-based benchmarks, in the approach to adjusting ambient $NO_2$ concentrations to simulate just meeting the current standard, and in the degree to which monitored $NO_2$ concentrations reflect the highest potential $NO_2$ exposures. Thus, as part of this review, the EPA has thoroughly considered uncertainties in the evidence and in available quantitative analyses, with the specific approach depending on the uncertainty being evaluated and the data available for its evaluation.

b. Comments Relating to Consideration of Less Stringent Standards

Though most commenters express support for the proposed decision to retain the current primary $NO_2$ standards, some of these commenters additionally encourage the identification and consideration of less stringent standards. Such comments are often based on criticisms of the EPA's approach to assessing the scientific evidence, as discussed in section II.B.3.a above, with some comments contending that the proposal understates the margin of safety provided by the current 1-hour and annual standards. Some comments further conclude that limitations and uncertainties in the body of scientific evidence support the possibility that the current standards are more protective than is requisite, claiming that, in its consideration of the adequacy of the protection provided by the current standards, the EPA failed to consider whether the $NO_2$ NAAQS should be made less stringent. One comment additionally asserts that the failure to identify alternative, less stringent standards is arbitrary and capricious, stating that the EPA has not adequately examined whether the uncertainties in the evidence call into question the proposed decision to retain the current standards or whether the standard level(s) should be less stringent. This

comment contends that the EPA must examine the possibility that the current standards may be too stringent and that, without such an examination, there is not adequate foundation in the record to support the proposed decision to retain those standards.

The Administrator has carefully considered whether standards less stringent than the current standards would be sufficient to protect public health with an adequate margin of safety and, thus, whether retaining the current standards would not be requisite (see discussion in proposal at 82 FR 34792, July 26, 2017, section II.F.4, and below). This consideration is informed by the thorough discussions of the uncertainties in the scientific evidence in the 2016 $NO_X$ ISA, the PA, and elsewhere in this document (U.S. EPA, 2016a, table 1–1; U.S. EPA, 2017a, section 3; and section II.A.3, above). The Administrator is not required to identify or evaluate specific alternative standards in order to make a determination than an existing standard or suite of standards provide the requisite protection. To the contrary, where the record supports a judgment that the current standards are requisite to protect public health with an adequate margin of safety, and that more or less stringent standards would not be requisite, the EPA may conclude, as it has here, that detailed evaluation of specific alternative standards is not warranted.[106]

Further, we disagree with the suggestion that, by focusing on whether the current standards adequately protect public health, the EPA has failed to consider the possibility that those standards should be revised to be less stringent in order to provide the requisite level of protection. Comments making this claim mistakenly presume that, in considering the adequacy the current primary $NO_2$ NAAQS and the public health protection they provided, the EPA has not considered whether the current standards should be revised to be less stringent. In fact, the EPA's consideration of the adequacy of the current standards and the public health protection they provide is intended to inform, and therefore substantively overlaps with, the Administrator's consideration of whether more or less stringent standards would, in his judgment, be requisite under the Clean Air Act. Accordingly, in considering the adequacy of the current standards to satisfy the CAA's requirements, the EPA also evaluates whether identification of potential alternative standards, either more or less stringent, is warranted. As described below, several considerations support the EPA conclusion in this review that standards less stringent than the current standards would not be requisite.

First, compared to the current standards, less stringent standards would be more likely to allow $NO_2$ exposures that could exacerbate respiratory effects in people with asthma. The current $NO_2$ standards are expected to allow virtually no potential for exposures to the $NO_2$ concentrations that have been shown most consistently to increase AR in people with asthma (*i.e.,* 250 ppb and above). In addition, the current standards provide a margin of safety, in part by limiting the potential for exposures to 1-hour $NO_2$ concentrations at or above 100 ppb, an exposure concentration with the potential to exacerbate asthma symptoms but for which the evidence indicates uncertainty in the risk of such effects occurring (U.S. EPA, 2017a, sections 5.2, 5.4). Although limitations in this evidence take on increased importance when considering the potential public health implications of such exposures to 100 ppb, as discussed in greater detail below (e.g, sections II.B.3.c and II.B.4), the CAA requires that a primary NAAQS protect the public health even where, as here, the risks from the pollutant cannot be quantified or ''precisely identified as to nature or degree.'' *API* v. *EPA,* 684 F.3d at 1350 (internal citation omitted). Further, in setting a standard with an adequate margin of safety, the EPA is to ''err on the side of caution.'' *Id.* at 1352. Thus, EPA places weight on the consideration that less stringent standards would be expected to be less effective than the current standards at protecting against these short-term exposures to $NO_2$ concentrations at or above health-based benchmarks.

Second, less stringent standards would be more likely to allow the ambient $NO_2$ concentrations that have been reported in epidemiologic studies to be associated with clearly adverse effects. For example, such standards would be more likely to allow the short-term ambient $NO_2$ concentrations that have been shown in epidemiologic studies conducted in the U.S. or Canada to be associated with asthma-related hospitalizations. In addition, recognizing that the current 1-hour standard contributes substantially to protection against long-term $NO_2$ exposures, less stringent standards would also be more likely to allow the long-term ambient concentrations that have been reported in epidemiologic studies to be associated with asthma development in children. While the EPA recognizes the limitations and uncertainties in these studies, they provide evidence for associations with asthma-related effects in locations likely to have violated the current standards (U.S. EPA, 2017a, sections 3.2.2.2 and 3.3.2.1). Therefore, the EPA also places weight on the consideration that, compared to the current standards, less stringent standards would allow greater risk of the serious health effects reported in these studies.

Finally, the CASAC advice also supports the EPA conclusion that a detailed evaluation of less stringent potential alternative standards is not warranted in the current review. Specifically, the CASAC advised that the current primary $NO_2$ standards, but not less stringent standards, provide protection against adverse effects associated with both short- and long-term $NO_2$ exposures. Based on its consideration of the evidence, the CASAC concluded 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 p. 9) 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, for the reasons discussed above, we disagree with comments advocating for a detailed evaluation of potential alternative standards that would be less stringent than the current standards and with comments contending that EPA has not considered whether the current standards are too stringent and, thus, should not be retained.

Comments advocating for the identification of less stringent standards often focus on specific uncertainties in the available health evidence, claiming that, because of these uncertainties, the margin of safety provided by the current primary $NO_2$ standards is larger than acknowledged in the proposal. For example, some comments question the EPA's interpretation of controlled human exposure studies examining AR, claiming that these studies do not demonstrate adverse effects at exposure concentrations below 300 ppb. Such comments contend that the EPA should clearly articulate the limitations in controlled human exposure studies of AR following $NO_2$ exposures, and in the Brown (2015) meta-analysis of individual-level data from these studies.

The EPA agrees that there are uncertainties in the evidence from

[106] For example, in the final decision in the recently completed review of the National Ambient Air Quality Standards for Lead (81 FR 71906, October 18, 2016), the standards were retained without consideration of potential alternative levels.

controlled human exposure studies of $NO_2$-induced changes in AR. These uncertainties have been discussed and considered extensively throughout this review, including in the 2016 $NO_X$ ISA and the PA (U.S. EPA, 2016a; U.S. EPA, 2017a), and in the Administrator's consideration of the evidence in both the proposal (82 FR 34792, July 26, 2017, section II.F.4) and this final action (section II.B.4, below). Specifically, important limitations in the evidence for increased AR following $NO_2$ exposures include the lack of an apparent dose-response relationship, which limits our ability to fully characterize the health risks associated with these exposures, and uncertainty in the adversity of the reported increases in AR (*e.g.,* see U.S. EPA, 2017a, section 3.2.2.1, and section II.A.2.a.iii above). While we agree that it is appropriate to consider these uncertainties in reaching decisions on the primary $NO_2$ NAAQS, as described below, we disagree that such uncertainties indicate that the reported effects do not have the potential to be adverse to public health.

In particular, as discussed in the ISA, increases in AR are considered to be a hallmark of asthma and can lead to poorer control of symptoms in people with the disease. Drawing on guidelines from the ATS and the ERS, analyses discussed in the 2016 $NO_X$ ISA indicate that the increases in AR reported following exposures to $NO_2$ concentrations from 100 to 530 ppb have the potential to be clinically relevant in some people with asthma (82 FR 34804, July 26, 2017; U.S., EPA, 2016a section 5.2.2.1). While there are no universally agreed upon criteria for determining whether such increases should be considered adverse, they represent respiratory effects that could be of particular concern for people with more severe cases of asthma than have typically been evaluated in the available studies of $NO_2$ exposures. These studies have generally evaluated people with mild asthma, while people with moderate or severe asthma could be more susceptible to $NO_2$-induced increases in AR, and thus more likely to exhibit adverse responses following $NO_2$ exposures (Brown, 2015).[107] Therefore, the uncertainty over the adversity of the response reported in controlled human exposure studies and the Brown (2015) meta-analysis does not mean that the $NO_2$-induced increase in AR is not adverse to any population. Rather, the evidence indicates a risk of adversity for some people, especially for those with more than mild asthma, though this risk cannot be fully characterized based on existing studies. When considered at a population level, these risks are amplified and take on public health significance.

In light of these observations, we disagree with the assertion that controlled human exposure studies do not demonstrate effects that could be adverse to public health following exposures to $NO_2$ concentrations below 300 ppb and with comments that the proposal overstates the margin of safety provided by the current standards. Rather, while acknowledging uncertainties in the evidence, and that the risk cannot be fully characterized based on existing studies, the EPA remains concerned about the potential for adverse respiratory effects following exposures to such $NO_2$ concentrations, particularly in people with more severe cases of asthma than have generally been evaluated in the available studies of $NO_2$ exposures. Further, given the large percentage of people with asthma that experienced an $NO_2$-induced increase in AR in these studies, including at exposures at and below 300 ppb,[108] and the large size of the asthmatic population in the United States, the EPA concludes that it is appropriate to place weight on $NO_2$-induced increases in AR in considering the potential for adverse public health effects following $NO_2$ exposures.

Additionally, some comments support placing more emphasis on a meta-analysis of information from controlled human exposure studies by Goodman et al. (2009). These comments assert that Goodman et al. concluded that exposures to $NO_2$ concentrations up to 600 ppb are not associated with clinically relevant effects.

The particular basis for these comments appears to be the conclusions reached by Goodman et al. (2009) that there is no dose-response relationship between $NO_2$ exposures and increased AR, and that the magnitude of any $NO_2$ effect on airway responsiveness is too small to be considered adverse. While the EPA acknowledges the lack of an apparent dose-response relationship between $NO_2$ exposures and increased AR, potentially due to differences in study protocols in the $NO_2$-airway response literature (U.S. EPA, 2016a, section 5.2.2.1), the EPA disagrees with the approach taken in the Goodman study to use existing data to attempt to evaluate whether a dose-response relationship exists. Specifically, the EPA notes that while Goodman et al., (2009) did not observe a dose-response relationship, this could be due to a variety of factors inherent to the study design rather than a true absence of a dose-response relationship.[109] Examples of such differences between studies include the $NO_2$ exposure method (*i.e.,* mouthpiece versus chamber), subject activity level (*i.e.,* rest versus exercise) during $NO_2$ exposure, choice of airway challenge agent, and physiological endpoint used to quantify airway responses.

As a result of these differences in study protocols, the 2016 $NO_X$ ISA judged it appropriate to assess only the fraction of study participants who experienced increased or decreased airway responsiveness following $NO_2$ exposures. The CASAC endorsed this approach of comparing the fractions of study participants, which was adopted in the meta-analysis by Brown (2015) and was the focus of discussion in the 2016 $NO_X$ ISA (U.S. EPA, 2016a, section 5.2.2.1). When commenting on Brown (2015) in the draft ISA, the CASAC noted that it was ''impressed with the meta-analysis of controlled human exposure studies'' and found that ''this analysis facilitates the inferences that can be drawn from the studies contained in the analysis'' (Diez Roux and Frey, 2015a, p. 2 of cover letter, p. 7 of consensus comments).

When the fraction of study participants who experienced increased or decreased airway responsiveness was analyzed, both Brown (2015) and Goodman et al. (2009) reported that exposures to $NO_2$ concentrations at and above 100 ppb increased airway responsiveness in the majority of people with asthma. Specifically, Table 4 of the Goodman et al. (2009) study reports that 64% (95% CI: 58%, 71%) of resting asthmatics exposed to $NO_2$ experienced an increase in airway responsiveness. Furthermore, Figure 2a of the Goodman et al. (2009) study reports that for exposures less than 200 ppb, 61%

[107] Furthermore, the potential for such effects in other at-risk populations that have generally not been evaluated in $NO_2$ controlled human exposure studies (*i.e.,* children and older adults) cannot be well-characterized based on the available studies.

[108] For example, as discussed elsewhere in this document (*e.g.,* section II.A.2 above), the Brown (2015) meta-analysis reported that following resting $NO_2$ exposure in the range of 200 ppb to 300 ppb, increased non-specific AR was reported in 78% of study participants.

[109] *CF. API* v. *EPA,* 684 F.3d at 1350 (nothing in the context of the last $NO_2$ NAAQSreview that ''the [Goodman] study did not establish there was 'no dose-response relationship'''). In a decision upholding the 2010 primary $NO_2$ NAAQS , the court held that EPA was ''justified in revising the NAAQS considering the evidence of a statistically significant relationship between relevant health conditions and $NO_2$ exposure at various concentrations, even if the agency did not know the precise dose-response relationship between V and airway responsiveness, among other health effects.'' *Id.* at 1351.

experienced an increase in AR (95% CI: 52%, 70%), while for exposures of 200 to 300 ppb, 66% experienced an increase (95% CI: 59%, 74%). These findings are consistent with those reported by Brown (2015) and discussed in the 2016 $NO_X$ ISA (U.S. EPA, 2016a, section 5.2.2.1).

Thus, both Goodman et al. (2009) and Brown (2015) report that the majority of study subjects experienced increased AR following resting $NO_2$ exposures. As discussed further above, increases in AR can lead to poorer control of symptoms in people with asthma and analyses in the 2016 $NO_X$ ISA indicate that the increases in AR reported following resting exposures to $NO_2$ concentrations from 100 to 530 ppb have the potential to be clinically relevant in some people with asthma. In addition, people with more severe cases of asthma than have typically been evaluated in the available studies of $NO_2$ exposures could be more likely to exhibit adverse responses following such exposures. Therefore, while we agree with comments that it is appropriate to consider the meta-analysis by Goodman et al. (2009), in addition to that by Brown (2015), we do not agree that such consideration supports the conclusion that exposures to $NO_2$ concentrations up to 600 ppb are not associated with clinically relevant effects.

Some comments assert that the EPA should place more emphasis on controlled human exposure studies that employ allergen challenge, rather than those that use non-specific challenge agents, because the commenters view such studies as more relevant to real world exposures. These comments claim that the lack of effects in studies that used allergen challenge increases the uncertainty that $NO_2$ in ambient air causes effects of concern.

As an initial matter, we note that the ATS and the ERS recognize increased AR following exposure to non-specific challenge agents (*e.g.,* methacholine) as a primary feature in the clinical definition and characterization of asthma severity (U.S. EPA, 2016a, section 5.2.2.1; Reddel et al., 2009). Thus, we do not agree with the implication of these comments that non-specific challenge agents are inherently less relevant to the evaluation of $NO_2$-induced changes in AR.

We further disagree that people would not have real world exposures to all of the non-specific challenge agents used in controlled human exposure studies. Specifically, both cold dry air and $SO_2$, which have been evaluated in studies of non-specific AR following $NO_2$ exposures, are nonspecific stimuli that people may encounter in the environment.[110] Thus, when viewed from a public health perspective, a member of the public has the potential to be exposed to a non-specific challenge agent just as they have the potential to be exposed to an allergen to which they have been sensitized.

In addition, while we agree with the potential public health significance of increased AR to allergen challenges (*e.g.,* see U.S. EPA 2016a, pp. 5–24 and 5–25), relatively little individual-level data on changes in AR following $NO_2$ exposures was available from studies using specific allergen challenges (*i.e.,* about 30% of the AR data). With regard to the allergen challenge studies that were available, the 2016 $NO_X$ ISA (U.S. EPA 2016a, p. 5–25) additionally notes that, ''. . . the response to an allergen is not only a function of the concentration of inhaled allergen, but also the degree of sensitization as measured by the level of allergen-specific IgE and responsiveness to nonspecific agents,'' making it difficult to predict the level of responsiveness to an allergen. The relatively small amount of individual-level data from allergen challenge studies, together with the greater difficulty in predicting allergen responsiveness, limits the degree to which these studies, by themselves, can inform conclusions on the potential public health implications of $NO_2$ exposures. Given this, in addition to considering results of individual studies, we consider the data from studies of allergen challenge, together with data from studies of non-specific challenge, as part of the meta-analysis by Brown (2015). When data from studies of non-specific challenge were combined with data from studies of allergen challenge, Brown (2015) reported that the majority of study participants experienced increased AR following resting exposures from 100 to 200 ppb, 200 to 300 ppb, and above 300 ppb (Table 5 in Brown, 2015). Thus, based on the larger body of information available, including information from studies that evaluated AR following allergen challenge, $NO_2$ exposures at and above 100 ppb have the potential to increase AR in people with asthma.

Some comments additionally point out the inconsistent results reported in controlled human exposure studies conducted in people who are exercising, claiming that such inconsistency calls into question the plausibility of a causal association between $NO_2$ and increased AR. With regard to these comments, the EPA agrees that individual studies conducted with exercise have not consistently reported $NO_2$-induced increases in AR. However, the EPA does not agree with commenters' conclusion that these inconsistencies call into question the causal association between $NO_2$ and increased AR.

As noted above, the 2016 $NO_X$ ISA has extensively considered all available studies that have evaluated the potential for $NO_2$ to increase AR in people with asthma. This includes studies conducted with participants at rest as well as studies with participants engaged in exercise (U.S. EPA, 2016a, section 5.2). As discussed in the ISA (U.S. EPA, 2016a, p. 5–23), the presence of a response in study participants at rest, but not while engaged in exercise, is not enough, in itself, to dismiss the causal association between $NO_2$ and airway responsiveness. This issue is discussed in detail in the Brown (2015) meta-analysis, and in other publications on $NO_2$ by Folinsbee (1992) and Bylin (1993), which were considered in the ISA. As discussed in those publications, the act of exercising may create a refractory period which may lead to diminished airway responsiveness to a challenge. Therefore, observing a response in participants at rest, but not exercising, does not indicate that there is no causal relationship between $NO_2$ exposures and increased airway responsiveness. The CASAC was aware of this difference in results across study protocols, but still agreed with EPA's determination that there was a causal relationship between $NO_2$ exposures and increased airway responsiveness, concluding that the Brown (2015) meta-analysis ''provides confirmation of causality for short-term effects'' (Diez Roux and Frey, 2015a, p. 6).

Some comments supporting the consideration of less stringent standards additionally focus on the epidemiologic evidence. Specifically, some industry groups comment that the EPA overstates the consistency of the epidemiologic evidence, particularly given the potential for co-pollutant confounding and exposure measurement error in studies of long-term $NO_2$ exposures, and given the results of a U.S. multicity study that reported no association between short-term $NO_2$ exposures and ED visits (Stieb et al., 2009).

As discussed in greater detail above (Section II.B.3.a), we do not agree with comments criticizing the 2016 $NO_X$ ISA's assessment of the epidemiologic evidence, including comments criticizing the ISA's characterization of the consistency of results across studies or comments criticizing the assessment

[110] Of the studies included in the meta-analysis by Brown (2015), $SO_2$ was used as a challenge agent in a study of resting exposures to 250 ppb $NO_2$ (Table 1 of Brown, 2015) and cold dry air was used in several studies of $NO_2$ exposures during exercise (Table 2 of Brown, 2015).

of uncertainties in those studies. Contrary to these comments, the ISA thoroughly considers uncertainties and limitations in the evidence, including the potential for co-pollutant confounding and exposure measurement error in epidemiologic studies (see *e.g.,* U.S. EPA, 2016a, sections 5.2.9.4 and 6.2.2.1). The PA additionally considers such uncertainties, and their implications for conclusions on the degree of public health protection provided by the current primary $NO_2$ standards (U.S. EPA, 2017a, sections 3.2.2.2, 3.3.2.1, 5.4).

With regard to comments on the study by Stieb et al. (2009) in particular, commenters correctly point out that this study reported no association between short-term $NO_2$ and ED visits. This lack of a positive association was discussed in the 2016 $NO_X$ ISA (U.S. EPA, 2016a, p. 5–84). However, the ISA's conclusion regarding the overall consistency of the broader body of available epidemiologic studies is based on the generally positive health effect associations reported in studies conducted across the U.S., Canada, Europe, and Asia (*e.g.,* U.S. EPA, 2016a, Figure 5–7). The relatively small number of studies in this group that did not report such positive associations, including the study by Stieb et al. (2009), were appropriately considered in reaching this broader ISA conclusion and do not call it into question. The lack of a positive association in the study by Stieb et al. (2009) was also specifically discussed in the PA (U.S. EPA, 2017a, p. 5–8), which noted that ''the only recent multicity study evaluated (Stieb et al., 2009) . . . did not report a positive association between $NO_2$ and ED visits'' (U.S. EPA, 2017a, p. 5–8). This observation, together with information from other key epidemiologic studies conducted in the U.S. or Canada,[111] informed the PA's conclusion that ''available U.S. and Canadian epidemiologic studies of hospital admissions and ED visits do not indicate the occurrence of $NO_2$-associated effects in locations and time periods with $NO_2$ concentrations that would clearly have met the current 1-hour $NO_2$ standard'' (U.S. EPA, 2017a, p. 5–9). Thus, the lack of a positive association with ED visits in the study by Stieb et al. (2009) was discussed in the ISA and informed the PA's conclusions on the adequacy of the public health protection provided by the current primary $NO_2$ NAAQS. Accordingly, we disagree with the comments arguing, based on Stieb et al. (2009) or on uncertainties and limitations in the epidemiologic evidence, as described more fully above (II.B.3.a), that EPA has overstated the consistency of the epidemiologic evidence.

Some comments additionally note that current ambient $NO_2$ concentrations are low, particularly compared to concentrations that would be of concern based on the health evidence, and are showing a downward trend. These comments contend that current monitoring, including available near-road monitoring, shows that $NO_2$ concentrations remain well below the levels of current standards, calling into question the EPA's analysis comparing $NO_2$ air quality with health-based benchmarks and its resulting impact on the Administrator's determinations in the proposed decision. They further assert that the lack of real-world exposures above benchmarks, together with the downward trend in $NO_2$ concentrations, contradicts EPA's rationale that the level of the current NAAQS must be maintained to protect against exposures at 100 ppb or 250 ppb. Based on current ambient $NO_2$ concentrations, these commenters argue that the EPA should consider how the monitoring data, including from near-road monitors, impacts its assessment of exposures and should also examine whether alternative, less stringent standards are appropriate.

Insofar as these comments are premised on the notion that exposure- and risk-related considerations in the NAAQS reviews should rely only on actual air quality, we disagree. We recognize that available monitoring data indicates that recent ambient $NO_2$ concentrations are below the $NO_2$ exposure concentrations shown in controlled human exposure studies to increase AR. For example, the PA notes that analyses based on recent $NO_2$ air quality ''estimate almost no potential for 1-hour exposures to $NO_2$ concentrations at or above benchmarks, even at the lowest benchmark examined (*i.e.,* 100 ppb)'' (U.S. EPA, 2017a, p. 4–19). However, the observation that recent $NO_2$ air quality concentrations, including from the near-road monitors, are lower than the exposure concentrations shown to cause effects does not, in and of itself, answer the question whether the current standards are more protective than necessary or whether the EPA should consider less stringent standards. Rather, it is important to consider the potential $NO_2$ exposures that would be permissible under the current standards to inform these questions.

In order to accomplish this, the PA further considers the potential for exposures to $NO_2$ concentrations at or above health-based benchmarks based on analyses where air quality has been adjusted upwards to simulate areas that would ''just meet'' the current primary $NO_2$ NAAQS. These analyses provide information on the public health protection associated with allowable $NO_2$ air quality under the current standards and, therefore, are clearly useful for informing a decision on the issue before the EPA. *See American Petroleum Institute* v. *EPA,* 684 F.3d at 1353 (upholding EPA's approach ''comparing the benefits of the one-hour standard against not only a scenario based upon existing air quality but also upon an alternate scenario in which areas just meet the [existing standard].''); *American Trucking Associations* v. *EPA,* 283 F.3d 355, 370–71 (D.C. Cir. 2002) (existence of evidence showing adverse effects occurring at levels allowed by the current standards justifies finding that it is appropriate to revise the existing NAAQS). This is a reasonable approach to informing judgments regarding the current standards, and it is consistent with section 109 of the CAA, which requires the EPA to review whether the current primary standards—not current air quality—are requisite to protect public health with an adequate margin of safety. CAA section 109(b)(1) and 109(d)(1); *see also NEDA/CAP* v. *EPA,* 686 F.3d 803, 813 (D.C. Cir. 2012) (rejecting the notion that it would be inappropriate for EPA to revise a NAAQS if current air quality does not warrant revision, stating ''[n]othing in the CAA requires EPA to give the current air quality such a controlling role in setting NAAQS''). Furthermore, although $NO_2$ air quality has been improving and is expected to continue improving, there are inherent uncertainties in predicting future air quality. Accordingly, it is reasonable to consider the $NO_2$ exposures that could occur under a pattern of air quality that just meets the current standards. *API* v. *EPA,* 684 F.3d at 1352.

In addition, the CASAC agreed with considering analyses based on adjusted air quality, stating that ''[t]he EPA has made a reasonable choice in looking both at the number of [benchmark] exceedances of the unadjusted data as well as the level of exceedance of the

[111] In considering the public health protection provided by the current standards, the PA focused on key studies assessed in the ISA that were conducted in the U.S. or Canada. Such studies are likely to reflect air quality and exposure patterns that are generally more 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 (U.S. EPA, 2017a, p. 3–20).

adjusted data'' (Diez Roux and Sheppard, 2017, p. 5). Therefore, for all of the reasons described above, relatively low recent ambient $NO_2$ concentrations, including those at near-road monitors, do not call into question analyses comparing $NO_2$ air quality to health-based benchmarks or the role those analyses play in the Administrator's decision to retain the existing standards.

c. Comments Supporting More Stringent Standards

One commenter argues that the current NAAQS do not protect public health with an adequate margin of safety, and that the standards should be revised to be more stringent. Specifically, these comments recommend that the level of the 1-hour $NO_2$ standard be set at 50 ppb, with a 99th percentile form, and that the level of the annual standard should be set at 30 ppb. These comments, and the EPA's responses, are discussed below. [112]

Comments asserting that the current 1-hour standard does not protect public health or provide any margin of safety cite the meta-analysis by Brown (2015) to support this position, arguing that this meta-analysis clearly shows that the majority of individuals with asthma were adversely affected by a concentration of $NO_2$ that would meet the current 1-hour standard. To support this point, these comments state that Brown (2015) reported increased AR following 1-hour exposures to 100 ppb $NO_2$, and they point to several uncertainties in the individual studies (*i.e.,* that no studies examined 1-hour concentrations below 100 ppb, that study subjects generally had mild asthma rather than more severe cases of disease, and that the studies do not provide information about potential effects of such exposures on children and seniors, two groups EPA recognizes as being particularly at risk). These comments disagree with the weight that EPA placed on the lack of consistency in the individual controlled human exposures studies at lower concentrations, contending that the Brown meta-analysis has greater statistical power than the individual studies. These comments further disagree with EPA's citation of uncertainties related to lack of exposures below 100 ppb as a rationale for retaining the current level of the 1-hour standard, contending that the CAA's requirement for an adequate margin of safety is intended to protect the population when information is limited.

As discussed above (Sections II.A.2, II.B.1), while the Brown meta-analysis shows that most study participants (*i.e.,* generally adults with mild asthma) experienced increased AR following resting $NO_2$ exposures from 100 to 530 ppb,[113] there are important limitations in the underlying studies, particularly in studies that evaluated $NO_2$ exposure concentrations at or near 100 ppb. Of the five studies included in the meta-analysis that evaluated resting exposures to 100 ppb $NO_2$, a statistically significant increase in AR following exposure to $NO_2$ was only observed in one (U.S. EPA, 2017a, section 3.2.2.1). Of the four studies that did not report statistically significant increases in AR following exposures to 100 ppb $NO_2$, three reported trends towards decreased AR (U.S. EPA, 2017a, section 3.2.2.1). Thus, individual controlled human exposure studies have generally not reported statistically significant increases in AR following resting exposures to $NO_2$ concentrations at 100 ppb (U.S. EPA, 2017a, section 3.2.2.1), indicating a greater uncertainty in the risk of such effects at 100 ppb.[114] When considering this general lack of consistent, statistically significant results across these five individual studies, limitations in the broader body of evidence from controlled human exposure studies (*i.e.,* uncertainty in adversity of reported responses and the lack of an apparent dose-response relationship), which are discussed above and have been considered throughout this review (*e.g.,* U.S. EPA, 2017a, section 3.2.2.1), take on increased importance when considering the risk of adverse effects and the potential public health implications of exposures to 100 ppb $NO_2$.

In light of the above information from the Brown (2015) meta-analysis and from the individual studies included in that meta-analysis, the Administrator's judgment in the proposal was that while it is appropriate to consider the degree of protection provided by the current 1-hour standard against exposures to $NO_2$ concentrations as low as 100 ppb,[115] emphasis should be placed on protecting against the potential for exposures to higher $NO_2$ concentrations, where individual studies generally report statistically significant increases in AR (*i.e.,* at or above 250 ppb, as discussed in U.S. EPA, 2017a, section 3.2.2.1). The more consistent results across studies at such higher exposure concentrations indicate greater concern for the risk of an $NO_2$-induced effect.

To this end, based on the results of the $NO_2$-air quality benchmark comparisons reported in the PA (U.S. EPA, 2017a, section 4.2.1), the current 1-hour standard is estimated to allow virtually no potential for 1-hour exposures to $NO_2$ concentrations at or above 200 ppb, even under worst-case conditions across a variety of study areas with among the highest $NO_X$ emissions in the United States. Such $NO_2$ concentrations were not estimated to occur, even at monitoring sites adjacent to some of the most heavily trafficked roadways. In addition, the current 1-hour standard limits, but does not eliminate, 1-hour exposures to $NO_2$ concentrations at or above 100 ppb (U.S. EPA, 2017a, section 4.2.1), an exposure concentration where uncertainties in the evidence take on increased importance. Despite the importance of uncertainties in the evidence for increased AR following exposures to $NO_2$ concentrations at or near 100 ppb, as summarized above, a focus on limiting such exposures gives weight to the results of Brown (2015) at 100 ppb and to the possibility that other at-risk groups (*e.g.,* people with more severe asthma, children, older adults) could experience more serious effects than reported in available studies. As such, the current 1-hour standard provides a margin of safety by virtually eliminating the potential for 1-hour exposures to $NO_2$ concentrations that have been consistently shown to increase AR in people with asthma and by limiting exposures to $NO_2$ concentrations that have the potential to exacerbate asthma

[112] These comments also refer, for the full discussion, to an attached comment letter submitted during the 2010 review of the primary $NO_2$ NAAQS. This reference suggests that the commenter believed the comments submitted as part of the 2010 review are still relevant in the current review, given that the 2016 $NO_X$ ISA focused much of its assessment on studies that were also included in the 2008 $NO_X$ ISA. We note that, to the extent a separate response to those comments is required, we have already responded to the prior comments in the 2010 final decision on the primary $NO_2$ NAAQS (75 FR 6474, February 9, 2010; U.S. EPA, 2010).

[113] As discussed above, the most consistent evidence for $NO_2$-induced increases in AR comes from studies of resting exposures.

[114] In addition, studies that evaluated resting exposures to 140 ppb and 200 ppb $NO_2$ did not generally report statistically significant increases in AR. Thus, individual controlled human exposure studies have generally not reported statistically significant increases in AR following resting exposures to $NO_2$ concentrations from 100 to 200 ppb, though this evidence suggests a trend toward increased AR following $NO_2$ exposures from 140 to 200 ppb (U.S. EPA, 2017a, section 3.2.2.1).

[115] Uncertainties in this evidence are of even greater concern for $NO_2$ exposure concentrations below 100 ppb, for which there are no data available in these studies. On this point, the CASAC noted that ''the lack of a clear dose-response model based on available data is another source of uncertainty that makes it difficult to extrapolate a dose-response relationship at levels lower than those measured in the controlled human studies.'' (Diez Roux and Sheppard, 2017, pp. 7–8).

symptoms, but for which the evidence indicates greater uncertainty in the risk of such effects.

While the EPA recognizes, as discussed in section I.A. above, that CAA section 109's requirement for a primary NAAQS to provide an adequate margin of safety is intended to address uncertainties associated with inconclusive scientific and technical information, it also notes that the CAA does not require a primary NAAQS to be established at a zero-risk level, or to protect the most sensitive individual, but rather at a level that avoids unacceptable risks to public health. *See Lead Industries Association* v. *EPA,* 647 F.2d at 1154, 1156 n.51. This approach to considering the degree of protection provided by the current NAAQS is consistent with the governing case law. The EPA further notes that under CAA section 109, a primary standard must be ''requisite''—*i.e.,* neither more nor less stringent than necessary—to protect public health with an adequate margin of safety. *See Whitman* v. *American Trucking Associations,* 531 U.S. at 465–472, 475–76. Additionally, the selection of any particular approach to providing an adequate margin of safety is a policy choice left to the Administrator's judgment. *See Lead Industries Association* v. *EPA,* 647 F.2d at 1161–62. As discussed above, the EPA's approach to the margin of safety in this review reasonably considers both the potential for adverse public health effects following exposures to 100 ppb $NO_2$ and the uncertainties in the public health implications of such exposures. Thus, the EPA's approach here comports with CAA section 109 and the case law described in section I.A above.

The EPA's approach to considering the degree of protection provided by the current $NO_2$ NAAQS is also consistent with advice from the CASAC, which recognized that ''there is uncertainty regarding the severity of adverse effects at a level of 100 ppb $NO_2$, 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). The CASAC additionally concluded that ''there is not a scientific basis for a standard lower than the current 1-hour standard'' (Diez Roux and Sheppard, 2017 p. 9). Thus, for the reasons discussed above, the EPA disagrees with comments claiming that the Brown (2015) meta-analysis indicates adverse effects at $NO_2$ concentrations meeting the current 1-hour standard and with comments claiming that the Brown (2015) meta-analysis shows that the 1-hour standard provides no margin of safety.

Comments advocating for a more stringent 1-hour standard further state that the current 98th percentile form allows too many days with $NO_2$ concentrations above 100 ppb, undermining protection for people with asthma, including children. These comments contend that the EPA's rationale that the 98th percentile provides more stability than the 99th percentile has no substantive evidence behind it.

In reviewing the NAAQS, the Administrator's foremost consideration is the adequacy of the public health protection provided by the combination of all of the elements of the standard, including the form. In particular, the EPA notes that the benchmark analysis presented in the PA, which informed the Administrator's proposed decision, evaluates the potential for $NO_2$ exposures with air quality just meeting the current 1-hour standard, including the 98th percentile form, and that analysis found that there were no exceedances of 200 ppb, and very few exceedances of 100 ppb (1 to 10 annually, on average). Thus, as described in more detail above, even under worst-case conditions across a variety of study areas with among the highest $NO_X$ emissions in the U.S., the current 1-hour standard, with its 98th percentile form, virtually eliminates the potential for exposures to the $NO_2$ concentrations that have been shown most consistently to increase AR in people with asthma and to which the Administrator gives most weight, and greatly limits the potential for exposures to lower $NO_2$ concentrations with the potential to exacerbate symptoms in some people with asthma, but for which uncertainties in the evidence take on increased importance.

In addition, the CASAC advice provides further support for the 98th percentile form. The CASAC accepted the protection provided by the current 98th percentile form, together with the other elements of the 1-hour standard, in recommending retention of the current standard without revision. In doing so, it provided the following advice (Diez Roux and Sheppard, 2017, p. 9):

> For the 1-hour current standard, the form is based on the 98th percentile of daily maximum 1-hour concentrations, which corresponds to the 7th or 8th highest daily maximum 1-hour concentration in a year. This form limits but does not eliminate exposures at or above 100 ppb $NO_2$. A scientific rationale for this form is there is uncertainty regarding the severity of adverse effects at a level of 100 ppb $NO_2$, and thus some potential for maximum daily levels to exceed this benchmark with limited frequency may nonetheless be protective of public health.

Thus, in providing its advice to retain the existing 1-hour standard, without revision, the CASAC clearly considered the implications of the 98th percentile form of that standard.

With regard to stability, the proposal explained that greater regulatory stability was one consideration supporting the selection of a 98th percentile form in the last review. In that review, the EPA established the 98th percentile form, noting ''the limited available information on the variability in peak $NO_2$ concentrations near important sources of $NO_2$ such as major roadways'' and ''the recommendation from the CASAC that the potential for instability in the 99th percentile concentration is cause for supporting a 98th percentile form'' (75 FR 6493, February 9, 2010).[116] However, in the proposal and in this final action, the Administrator's judgments focus primarily on his consideration of the public health protection provided by the current standards: A 1-hour standard with a level of 100 ppb and a 98th percentile form, and an annual average standard with a level of 53 ppb. The degree of public health protection provided by the current standards is a function of the combination of all elements of these standards (*i.e.,* indicator, averaging times, forms, levels). Thus, while judgments on stability can be a legitimate consideration, his decision to retain the current primary $NO_2$ NAAQS in this review (see below) reflects his judgments regarding public health protection provided by these standards. Given this, the EPA disagrees with comments contending that the form of the 1-hour standard should be revised to the 99th percentile.[117]

Comments advocating for more stringent standards also assert that the EPA should adopt an annual standard

[116] 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).

[117] These comments also note that EPA established a 99th percentile form when it revised the $SO_2$ primary NAAQS in 2010. The fact that EPA concluded that the 99th percentile was appropriate for one NAAQS, based on the combined elements of that revised standard and the evidence and information in the supporting record, does not mean that such a form should be used for a different NAAQS for a different pollutant. Rather, in reviewing each NAAQS, EPA makes a determination specific to the pollutant and standard in question, in the course of which it evaluates the public health protection it provides based on the combination of all the elements of the standard and based on the evidence and information in the record for that review.

level of 30 ppb. These comments note the strengthened evidence linking long-term $NO_2$ exposures with various health effects, particularly asthma development, arguing that it expands the range of potential effects and at-risk populations. They further note the recognition by the EPA and the CASAC, based on its review of analyses in the PA, that the current 1-hour standard and annual standard together are estimated to maintain annual $NO_2$ concentrations well below 53 ppb. These comments assert that both the EPA and the CASAC recognized that the annual standard was not sufficiently protective and, based on the degree of control associated with the 1-hour standard, in effect used 30 ppb as the effective standard for annual exposure. These comments thus conclude that EPA should lower the level of the annual standard level to 30 ppb.

We agree with comments that the evidence supporting associations between long-term $NO_2$ exposures and a variety of effects, particularly the development of asthma in children, has become stronger in this review.[118] While this evidence supports associations with a clearly adverse health outcome, given uncertainties in key studies and the protection provided by the 1-hour standard against long-term $NO_2$ exposures, we disagree with comments that this strengthened evidence supports a revised annual standard with a level of 30 ppb. Our consideration of these factors is described below.

As discussed in the proposal (82 FR 34792, July 26, 2017, section II.F.4), and in the Administrator's final decision below, uncertainties in studies of long-term $NO_2$ exposures, and in the $NO_2$ air quality present in the locations of those studies, limit their utility in identifying a specific revised annual standard that would provide the requisite protection. Important uncertainties in key U.S. and Canadian epidemiologic studies of long-term $NO_2$ exposures include the potential for confounding by highly correlated co-occurring pollutants and for exposure measurement error (see, *e.g.,* sections II.A.2, II.B.1, II.B.4 of this document).

With regard to potential confounding by co-occurring pollutants, the 2016 $NO_X$ ISA concludes that ''[e]pidemiologic studies of asthma development in children have not clearly characterized potential confounding by $PM_{2.5}$ or traffic-related pollutants [*e.g.,* CO, BC/EC, volatile organic compounds (VOCs)]'' (U.S. EPA, 2016a, p. 6–64). The 2016 $NO_X$ ISA further notes that ''[i]n the longitudinal studies, correlations with $PM_{2.5}$ and BC were often high (*e.g.,* $r = 0.7–0.96$), and no studies of asthma incidence evaluated copollutant models to address copollutant confounding, making it difficult to evaluate the independent effect of $NO_2$'' (U.S. EPA, 2016a, p. 6–64).

With regard to exposure measurement error, while some studies used well-validated estimates of $NO_2$ exposure (U.S. EPA, 2016a, section 6.2.2.1), most of the key epidemiologic studies conducted in the U.S. or Canada, which are the studies relevant for informing decisions on the standard, employed exposure models ''with unknown validation'' or used ''central-site measurements that have well-recognized limitations in reflecting variability in ambient $NO_2$ concentrations in a community and may not well represent variability in $NO_2$ exposure among subjects'' (U.S. EPA, 2017a, p. 3–35). Thus, it is unclear the extent to which most of the key studies conducted in the U.S. or Canada provide reliable estimates of asthma incidence for particular $NO_2$ concentrations that could be used in identifying a specific revised annual standard that would provide the requisite protection.

In addition, as discussed in detail in the PA, while epidemiologic studies conducted in the U.S. or Canada provide evidence for associations with asthma-related effects in locations likely to have violated the current standards, they do not indicate associations of asthma incidence with exposures to long-term $NO_2$ in locations that would have clearly met the current standards (U.S. EPA, 2017a, section 5.1). This is particularly the case given that $NO_2$ concentrations near the most heavily trafficked roadways are not likely reflected by monitors in operation during study years. Had such monitors been in place, $NO_2$ design values in these study areas may have been higher than indicated by the monitors that were in operation during study periods.

Thus, uncertainties in studies of long-term $NO_2$ exposures, together with uncertainties in the $NO_2$ air quality present in the study locations, limit the degree to which these studies can inform the identification of a specific revised annual standard that would provide the requisite protection. Taken together, these uncertainties limit what studies of long-term $NO_2$ and asthma development can tell us with regard to the adequacy of the public health protection provided by the current $NO_2$ standards.

Beyond the uncertainties discussed above, the EPA further recognizes that, as noted in comments, the current 1-hour standard is expected to provide substantial protection against long-term $NO_2$ exposures. Support for considering protection provided by the 1-hour standard against long-term $NO_2$ exposures comes from the ISA's integrated mode of action information describing the biological plausibility for development of asthma. In particular, the ISA states that ''findings for short-term $NO_2$ 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, pp. 6–66 and 6–64).[119] Given this, we note that meeting the 1-hour standard with its level of 100 ppb is expected to maintain annual average $NO_2$ concentrations well below the 53 ppb level of the current annual standard. With regard to this protection, the CASAC notes that the PA's analyses of historical data indicate that ''attainment of the 1-hour standard corresponds with annual design value averages of 30 ppb $NO_2$'' (Diez Roux and Sheppard, 2017). While the CASAC did not endorse the degree of public health protection provided by the annual standard alone (Diez Roux and Sheppard, 2017, p. 9), based on these air quality relationships it concluded 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). Thus, to the degree the evidence supports additional protection against long-term $NO_2$

[118] The ISA additionally concludes that, compared to the last review, stronger evidence is available in this review linking various non-respiratory effects with long-term $NO_2$ exposures (see, *e.g.,* U.S. EPA, 2016a, section 1.5.2). These include cardiovascular effects and diabetes, mortality, birth outcomes, and cancer. However, compared to the evidence linking $NO_2$ exposures with the development of asthma, there is greater uncertainty in the evidence for these non-respiratory effects. Therefore, in considering the public health protection provided by the current standards, the focus in this review is on respiratory effects (*e.g.,* see U.S. EPA, 2017a, section 5.1). More specifically, as noted in the PA ''we consider the full body of health evidence, 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 $NO_2$ exposures [*i.e.,* respiratory effects]'' (U.S. EPA, 2017a, p. 3–2).

[119] The ISA additionally recognizes that because the experimental evidence is limited, there remains some uncertainty as to whether long-term $NO_2$ exposures have an independent effect on asthma development or whether these health effects are due to repeated short-term exposures, or a mixture of long-term and short-term exposures (see U.S. EPA, 2016a, p. 6–67).

exposures, beyond that provided by the current annual standard alone, the 1-hour standard is expected to result in substantial additional protection against such exposures.

Based on the above information, when taken together, the EPA disagrees with comments that the level of the annual standard should be revised to 30 ppb. In particular, based on the uncertainties in the available key studies of $NO_2$ and asthma incidence conducted in the U.S. or Canada, uncertainty in the $NO_2$ concentrations present in locations of these key studies, and the substantial protection against long-term $NO_2$ exposures that is provided by the current 1-hour standard, we conclude that the evidence does not support a revised annual standard with a level of 30 ppb.

d. Other Comments

In addition to the comments presented above, the EPA received several comments related to implementation of the $NO_2$ NAAQS, including various comments on AERMOD and its use in permitting, as well as on the historical difficulty of facilities demonstrating compliance with the 1-hour $NO_2$ standard in permitting. As described in section I.A above, this action is being taken pursuant to CAA section 109(d)(1) and relevant case law. Consistent with this case law, the EPA has not considered costs, including the costs or economic impacts related to permitting or other implementation concerns, in this action. Under CAA section 109(d)(1) the EPA has the obligation to periodically review the air quality criteria and the existing primary NAAQS and make such revisions as may be appropriate. Thus, the scope of this action is to evaluate whether the existing $NO_2$ primary standards are requisite to protect public health with an adequate margin of safety, not to address concerns related to implementation of the existing standards. State and federal $NO_2$ control programs such as those discussed in section I.B may provide an opportunity for permitting and other implementation concerns to be addressed.

4. Administrator's Conclusions

Having carefully considered the public comments, as discussed above, and taking into consideration the large body of evidence concerning $NO_2$-related health effects and available estimates of the potential for $NO_2$ exposures, including the uncertainties and limitations inherent in the evidence and those estimates, the Administrator concludes that the current primary $NO_2$ standards are requisite to protect the public health, with an adequate margin of safety, and should be retained. The Administrator's conclusions are based on a careful consideration of the full body of information available in this review, giving weight to the assessment of the available policy-relevant scientific evidence and the conclusions contained in the 2016 $NO_X$ ISA; the PA's consideration of this evidence and of analyses comparing $NO_2$ air quality with health-based benchmarks; the PA's conclusions regarding the public health protection provided by the current primary $NO_2$ NAAQS and the rationale supporting those conclusions; the advice and recommendations from the CASAC; the scientific and policy judgments and conclusions discussed in the proposal; and public comments on the proposed action. The basis for the Administrator's conclusions on the current primary $NO_2$ standards is discussed further below.

As an initial matter, the Administrator takes note of the well-established body of scientific evidence supporting the occurrence of respiratory effects following $NO_2$ exposures, as described in detail in the 2016 $NO_X$ ISA (U.S. EPA, 2016a, chapter 5 and chapter 6) and summarized in the PA (U.S. EPA, 2017a, chapter 3). As in the last review, the clearest evidence indicates the occurrence of respiratory effects following short-term $NO_2$ exposures. The strongest support for this relationship comes from controlled human exposure studies demonstrating $NO_2$-induced increases in AR in individuals with asthma. As discussed above (section II.A.2), the Administrator notes that most of the controlled human exposure studies assessed in the 2016 $NO_X$ 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 $NO_2$ standard with its level of 100 ppb. Beyond the controlled human exposure studies, additional supporting evidence comes from epidemiologic studies reporting associations between short-term $NO_2$ exposures and 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, the results of these newer studies are generally consistent with the epidemiologic studies that were available in the last review.

With regard to respiratory effects of long-term $NO_2$ 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 $NO_2$ concentrations in these studies are serving as surrogates for exposures to the broader mixture of traffic-related pollutants (U.S. EPA, 2016a, table 1–1 and section 6.2.2). Supporting evidence also includes studies indicating a potential role for repeated short-term $NO_2$ exposures in the development of asthma (U.S. EPA, 2016a, pp. 6–64 and 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 2016 $NO_X$ ISA, he notes the stronger evidence for $NO_2$-associated cardiovascular effects (short- and long-term exposures), premature mortality (long-term exposures), and certain reproductive effects (long-term exposures) (U.S. EPA, 2016a, table 1–1). As detailed in the 2016 $NO_X$ 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, table 1–1 and section 6.2.2). Thus, as described above (section II.B.1), and consistent with CASAC advice (Diez Roux and Sheppard, 2017), the Administrator places the greatest emphasis on the evidence for respiratory effects attributable to either short- or long-term $NO_2$ exposures, which the ISA has determined demonstrates a ''causal'' and a ''likely to be causal'' relationship with $NO_2$ exposures, respectively.

The Administrator's evaluation of the public health protection provided against ambient $NO_2$ exposures also involves consideration of populations and lifestages that may be at greater risk of experiencing $NO_2$-attributable health effects. In the current review, the Administrator's consideration of potential at-risk populations draws from the 2016 $NO_X$ 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 places greatest weight on the potential effects of $NO_2$ 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 2016 $NO_X$ ISA, to directly inform his consideration of the adequacy of the public health protection provided by the current primary $NO_2$ standards. Adopting the approach taken in the PA, which has been reviewed by the CASAC (Diez Roux and Sheppard, 2017, pp. 6 to 9), 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 ED visits, and asthma development in children. He particularly emphasizes the results of controlled human exposure studies, which were identified in the 2016 $NO_X$ ISA as providing ''[t]he key evidence that $NO_2$ 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 advised 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, p. 7).

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 (Brown, 2015) and on the consistency of findings across individual studies. As discussed in sections II.A.2 and II.B.1 above, and consistent with the evidence in the last review, the Brown (2015) meta-analysis indicates that statistically significant majorities of study volunteers, generally with mild asthma, experienced increased AR following 30-minute to 1-hour resting exposures to $NO_2$ concentrations from 100 to 530 ppb. In some affected individuals, the magnitudes of these increases were large enough to have potential clinical relevance (sections II.A.2.a.i and II.B.3, above).[120] Based on these results, the Administrator notes the potential for people with asthma to experience $NO_2$-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 $NO_2$ concentrations at or above 250 ppb, with less consistent results across studies conducted at lower exposure concentrations, particularly 100 ppb (section II.A.2.a).[121]

Uncertainties in this evidence, discussed in sections II.A.2.a, II.A.3, and II.B.1 above, include the lack of an apparent dose-response relationship between $NO_2$ exposures and increased AR, which limits the degree to which the health risks of these exposures can be fully characterized, and uncertainty regarding the potential adversity of the reported responses. These uncertainties take on increased importance when considering the potential public health implications of exposures to lower $NO_2$ concentrations (*i.e.,* at and near 100 ppb), where individual studies generally do not report $NO_2$-induced increases in AR.

While the Administrator recognizes uncertainty in the extent to which $NO_2$-induced increases in AR may be adverse, he also notes the risk that such increases could be adverse for some people with asthma, particularly those with more severe asthma than have typically been evaluated in available studies. He further notes that this risk cannot be fully characterized based on existing studies. However, given that the majority of people with asthma experienced an $NO_2$-induced increase in AR in the controlled human exposure studies included in the Brown (2015) meta-analysis,[122] and given the large size of the asthmatic population in the United States, the Administrator recognizes the potential for effects that are adverse to public health following the types of $NO_2$ exposures evaluated in the studies analyzed by Brown (2015). Thus, while the Administrator is not able to definitively determine whether the increased AR reported in these studies would be adverse for a given individual, he concludes that, from a public health perspective, it is appropriate to provide protection from the risk of adversity associated with such increases. As noted above, this is especially true for people with more severe asthma and for other at-risk populations that have generally not been evaluated in available controlled human exposure studies of $NO_2$ and AR (*i.e.,* children and older adults).

Based on information from controlled human exposure studies, which is discussed in more detail in sections II.A.2, II.B.1, and II.B.3 of this final action, the Administrator is most concerned about the potential for people with asthma to experience adverse respiratory effects following exposures to $NO_2$ concentrations at or above 250 ppb. As noted above, 250 ppb is an exposure concentration where the potential for $NO_2$-induced respiratory effects is supported both by results of the meta-analysis and by consistent results reported across individual studies. Therefore, in reaching decisions on the primary $NO_2$ NAAQS, the Administrator emphasizes the importance of protecting against such exposures.

Because results are less consistent across individual studies that evaluated lower exposure concentrations, the Administrator places greater weight on the uncertainties in the evidence as he considers the potential public health implications of such exposures. However, the Administrator also recognizes the potential for adverse respiratory effects following exposures to $NO_2$ concentrations as low as 100 ppb, particularly in people with more severe cases of asthma than have generally been evaluated in the available $NO_2$ controlled human exposure studies. Available studies have generally evaluated people with mild asthma, while people with moderate or severe asthma could be more susceptible to $NO_2$-induced increases in AR, and thus more likely to exhibit adverse responses following $NO_2$ exposures (Brown, 2015). As discussed above, such effects have the potential to be adverse to public health, in light of the large size of the asthmatic population in the United States. Further, as noted above, the Administrator also recognizes the

[120] As discussed in section II.A.2.a.i of this final action, the consideration of clinical relevance by Brown (2015) is based on the fraction of exposed individuals who experienced a halving of the PD of challenge agent following $NO_2$ exposures. This magnitude of change has been recognized by the ATS and the ERS 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.

[121] In addition, studies that evaluated resting exposures to 140 ppb and 200 ppb $NO_2$ did not report statistically significant increases in AR, though group mean responses in these studies suggest a trend towards such an increase.

[122] As described above (II.A.2, II.B.1, II.B.3), this is the case for individuals exposed while at rest.

potential for such effects in other at-risk populations that have generally not been evaluated in $NO_2$ controlled human exposure studies (*i.e.,* children and older adults). Thus, when the evidence and uncertainties are taken together, the Administrator judges that, from a public health perspective, while it is appropriate to emphasize the degree of protection against the potential for exposures at or above 250 ppb, it is also appropriate to consider the degree of protection provided against potential exposures to $NO_2$ concentrations as low as 100 ppb.

In further considering the potential public health implications of the controlled human exposure studies, the Administrator looks to the results of quantitative comparisons between $NO_2$ air quality and health-based benchmarks. As discussed in the PA (U.S. EPA, 2017a, section 4.2 and section 5.2), 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 $NO_2$ air quality to specific health-based benchmarks, the Administrator first recognizes that all areas of the U.S. presently meet the current primary $NO_2$ standards. When based on recent unadjusted $NO_2$ air quality, these analyses estimate almost no days with the potential for 1-hour exposures to $NO_2$ concentrations at or above health-based benchmarks, including the lowest benchmark examined (*i.e.,* 100 ppb).

To inform his consideration of the public health protection associated with allowable $NO_2$ air quality under the current standards, the Administrator takes note of the analyses in the PA examining the potential for exposures to $NO_2$ concentrations at or above health-based benchmarks when air quality has been adjusted upwards to simulate areas that would ''just meet'' the current primary $NO_2$ NAAQS. Drawing on the discussion of these analyses in the PA (U.S. EPA, 2017a, section 5.2), the Administrator recognizes that, even when ambient $NO_2$ concentrations are adjusted upward to just meet the existing 1-hour standard, the analyses estimate no days with the potential for exposures to the $NO_2$ concentrations that have been shown most consistently to increase AR in people with asthma (*i.e.,* above 250 ppb [123]). Such $NO_2$ concentrations were not estimated to occur, even under worst-case conditions across a variety of study areas with among the highest $NO_X$ 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 $NO_2$ concentrations at or above 100 ppb (*i.e.,* about one to 10 days per year, on average) (U.S. EPA, 2017a, section 4.2.1). As discussed above, 100 ppb represents an exposure concentration with the potential to exacerbate asthma-related respiratory effects in some people, but for which uncertainties in the evidence take on increased importance.

Based on his consideration of these results, the Administrator concludes that evidence from controlled human exposure studies, together with analyses comparing ambient $NO_2$ concentrations to health-based benchmarks, supports his overall judgment that the current primary $NO_2$ NAAQS are requisite to protect public health with an adequate margin of safety. In particular, as discussed above, he is most concerned about exposures to $NO_2$ concentrations at and above 250 ppb, where the potential for $NO_2$-induced respiratory effects is supported both by results of the meta-analysis and by consistent results reported across individual studies. With regard to this, the Administrator notes that $NO_2$ air quality that just meets the current standards is estimated to allow no potential for exposures to such 1-hour $NO_2$ concentrations. The Administrator also recognizes the potential for effects that are adverse to public health with exposures to lower $NO_2$ concentrations, including as low as 100 ppb, although he places greater weight on the uncertainties in the evidence at these lower exposure concentrations. In light of these uncertainties, the Administrator judges it appropriate to limit, but not to eliminate, the potential for 1-hour exposures to $NO_2$ concentrations as low as 100 ppb. With regard to this, he notes that the current standard is estimated to restrict the potential for exposures to 1-hour $NO_2$ concentrations at or above 100 ppb to a limited number of days per year.

Thus, given that the current standards are estimated to allow no exposures to 1-hour $NO_2$ concentrations at or above 250 ppb, and only limited potential for such exposures to concentrations as low as 100 ppb, the Administrator concludes that the scientific evidence, together with the information from analyses comparing $NO_2$ air quality with health-based benchmarks, supports his judgment that that the current 1-hour and annual $NO_2$ primary standards, together, are requisite to protect public health with an adequate margin of safety. In reaching this conclusion, the Administrator finds that retaining the 1-hour $NO_2$ standard with the level of 100 ppb reflects a cautious approach, which is warranted given the CAA's requirement to for an adequate margin of safety. However, uncertainties in the evidence, especially those relating to the adversity of the effect and its likelihood to occur at exposures at or below 100 ppb, support the Administrator's conclusion that it is not necessary to eliminate the potential for exposures to 100 ppb $NO_2$.

The Administrator also considers what the available epidemiologic studies indicate with regard to the adequacy of the public health protection provided by the current $NO_2$ standards, noting that these studies often examine more serious health effects than the controlled human exposure studies. In particular, he considers analyses of $NO_2$ air quality in the locations, and during the time periods, of available U.S. or Canadian epidemiologic studies of asthma-related hospital admissions or ED visits. Although the $NO_2$ epidemiologic evidence is subject to greater uncertainty than the controlled human exposure studies of $NO_2$-induced changes in AR, as discussed in section II.B.1 above, these analyses can provide insights into the extent to which $NO_2$-health effect associations are present for distributions of ambient $NO_2$ 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 $NO_2$-associated effects indicated by epidemiologic studies. To the degree studies have not reported associations in locations meeting the current $NO_2$ standards, there is greater uncertainty regarding the potential for reported effects to occur following the $NO_2$ exposures that are associated with air quality meeting those standards.

With regard to studies of short-term $NO_2$ exposures, as discussed in greater detail in section II.B.1 above, the Administrator notes that epidemiologic studies provide evidence for asthma-related ED visits and hospital admissions with exposure to $NO_2$ in locations likely to have violated the current standards over at least parts of study periods. In contrast, studies have not consistently shown such $NO_2$-associated outcomes in areas that would have clearly met the current standards. In this regard, the Administrator recognizes that the $NO_2$ concentrations identified in the locations of these epidemiologic studies are based on an

[123] As discussed above, analyses in the PA estimate no occurrences of 1-hour $NO_2$ concentrations at or above 200 ppb.

$NO_2$ monitoring network that, during study periods, did not include monitors meeting the current near-road monitoring requirements. This is particularly important given that $NO_2$ concentrations near the most heavily trafficked roadways were likely to have been higher than those reflected by the $NO_2$ 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 evidence for associations with asthma-related effects in locations likely to have violated the current standards, supporting the decision to not set less stringent standards (see section II.B.3, above), they do not provide support for such associations in locations that would have clearly met those standards. As a result, these studies additionally support the decision to not set more stringent standards.

With regard to studies of long-term $NO_2$ exposures, the Administrator notes that the preponderance of evidence for respiratory health effects comes from epidemiologic studies evaluating asthma development in children. While recognizing important uncertainties related to potential copollutant confounding and exposure measurement error (*e.g.,* see U.S. EPA, 2017a, section 3.3.2.1), the Administrator considers what these studies could indicate with regard to the public health protection provided by the current standards. As discussed in section II.A.2 above, these studies report associations with long-term average $NO_2$ concentrations, while the broader body of evidence indicates the potential for repeated short-term $NO_2$ 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 $NO_2$ concentrations (U.S. EPA, 2017a, figure 2–11), when considering these studies of asthma development, the Administrator considers the protection provided by the combination of both the annual and 1-hour standards.

In doing so, he notes that key epidemiologic studies conducted in the U.S. or Canada consistently report associations between long-term $NO_2$ exposures and asthma development in children in locations likely to have violated the current standards over at least parts of study periods, but that those studies do not indicate such associations in locations that would have clearly met the current annual and 1-hour standards (U.S. EPA, 2017a, section 5.1). As discussed above for epidemiologic studies of short-term $NO_2$ exposures, this is particularly the case given that $NO_2$ concentrations near the most heavily trafficked roadways are not likely reflected by monitors in operation during study years. Thus, while the Administrator recognizes the public health significance of asthma development in children, he concludes that the available evidence supports his decision to not revise the current standards to be more stringent. In addition, while there are important uncertainties in these studies of long-term $NO_2$ exposures, the Administrator also concludes that, in light of the requirement for an adequate margin of safety, reported associations in locations likely to have violated the current standards support his decision to not revise the current standards to be less stringent.

Based on the above considerations, with their attendant uncertainties and limitations, and with consideration of advice from CASAC and public comment, the Administrator concludes that the current body of scientific evidence, in combination with the results of the quantitative analyses comparing $NO_2$ air quality with health-based benchmarks, supports his judgment that the current 1-hour and annual $NO_2$ primary standards, together, are requisite to protect public health with an adequate margin of safety, and does not call into question any of the four basic elements of those standards (*i.e.,* indicator, averaging time, level, and form). The Administrator considers these four elements collectively in evaluating the public health protection afforded by the current primary $NO_2$ standards, as discussed above (section II.B.1.a). Based on this consideration, and consistent with the CASAC advice (see, *e.g.,* Diez Roux and Sheppard, 2017, pp. 6–9), the Administrator judges that each of the elements of the current standards should be retained. In particular, taking note of the more detailed discussions elsewhere in this document and in the proposal, he judges the following:

- $NO_2$ continues to be the appropriate indicator for both the current annual and 1-hour standards, and no alternative to $NO_2$ has been advanced as a more appropriate surrogate for ambient oxides of nitrogen (section II.B.1.a.i above; 82 FR 34792, July 26, 2017, section II.F.1.a).
- The 1-hour and annual averaging times of the current standards, together, can provide protection against short- and long-term $NO_2$ exposures and should be retained (section II.B.1.a.ii above; 82 FR 34792, July 26, 2017, section II.F.1.b).
- The levels and the forms of the current short-term and long-term standards should be retained (sections II.B.1.a.iii and II.B.3 above; 82 FR 34792, July 26, 2017, section II.F.1.c).

In considering the requirement for an adequate margin of safety, the Administrator notes that the determination of what constitutes an adequate margin of safety is expressly left to the judgment of the EPA Administrator. *See Lead Industries Association* v. *EPA,* 647 F.2d at 1161–62; *Mississippi,* 744 F.3d at 1353. He further notes that in evaluating how particular standards address the requirement to provide an adequate margin of safety, it is appropriate to consider such factors as the nature and severity of the health effects, the size of sensitive population(s) at risk, and the kind and degree of the uncertainties present. Consistent with past practice and long-standing judicial precedent, and as described in this section, the Administrator takes the need for an adequate margin of safety into account as an integral part of his decision-making on a standard. *See, e.g., NRDC* v. *EPA,* 902 F. 2d 962, 973–74 (D.C. Cir. 1990).

In reaching the conclusion that the current primary $NO_2$ standards, together, are requisite to protect public health with an adequate margin of safety, the Administrator notes the following with regard to effects attributable to short-term $NO_2$ exposures:

- Meeting the current 1-hour $NO_2$ standard is expected to allow virtually no potential for exposures to $NO_2$ concentrations that have been shown most consistently to increase AR in people with asthma (*i.e.,* at or above 250 ppb), even under worst-case conditions across a variety of study areas with among the highest $NO_X$ emissions in the U.S. Based on analyses of air quality adjusted upwards to just meet the current 1-hour standard, such $NO_2$ concentrations were not estimated to occur, even at monitoring sites adjacent to some of the most heavily trafficked roadways (U.S. EPA, 2017a, section 4.2.1).
- Meeting the current 1-hour standard limits the potential for exposures to 1-hour concentrations at or above 100 ppb. Thus, the current standard protects against $NO_2$ exposures with the potential to exacerbate symptoms in some people with asthma, but for which uncertainties in the evidence take on increased importance (U.S. EPA, 2017a, section 4.2.1).

• Meeting the current 1-hour standard is expected to maintain ambient $NO_2$ concentrations below those likely to have been present in locations where key epidemiologic studies conducted in the U.S. or Canada have reported relatively precise and statistically significant associations between short-term $NO_2$ and asthma-related hospitalizations (U.S. EPA, 2017a, section 3.2.2.2).

In addition, with regard to long-term $NO_2$ 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 in section II.B.1 above, meeting the current annual and 1-hour standards is expected to maintain ambient $NO_2$ concentrations below those likely to have been present in locations where key U.S. and Canadian epidemiologic studies have reported associations between long-term $NO_2$ and asthma development (U.S. EPA, 2017a, section 3.3.2.1). 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 the annual standard, and that analyses of historical ambient $NO_2$ concentrations suggest that meeting the 1-hour standard with its level of 100 ppb would be expected to maintain annual average $NO_2$ concentrations well below the 53 ppb level of the annual standard (U.S. EPA, 2017a, section 2.3.3).[124] In this regard, the Administrator takes note of the CASAC conclusion that ''attainment of the 1-hour standard also implies that the annual DV averages 30 ppb $NO_2$'' and its advice that ''[g]iven uncertainties in the epidemiologic evidence related to lack of near road monitoring and potential confounding of traffic-related co-pollutants, there is insufficient evidence to make a scientific judgment that adverse effects occur at annual DVs less than 30 ppb $NO_2$'' (Diez Roux and Sheppard, 2017, p. 9). The Administrator observes that, as additional years of data become available from the recently deployed near-road $NO_2$ 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 $NO_2$ 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).

Based on the conclusions and considerations described above in this section, the Administrator concludes that his proposed decision, and the supporting rationale, analyses, and scientific assessments, remain valid. Accordingly, in this review, he judges that it is appropriate to retain the current 1-hour and annual primary $NO_2$ standards, without revision. As described in sections II.B.2 and II.B.3 above, the Administrator notes that his decision to retain the current primary $NO_2$ standards in this review, without revision, is consistent with the CASAC advice. In particular, the Administrator notes that in its letter on the draft PA, the CASAC stated that it ''recommends retaining, and not changing the existing suite of standards'' (Diez Roux and Sheppard, 2017, cover letter at p. 3). The Administrator further observes that in addressing the 1-hour standard the CASAC ''advise[d] that the current 1-hour standard is protective of adverse effects and that there is not a scientific basis'' for a more stringent standard (Diez Roux and Sheppard, 2017, p. 9). With respect to the annual standard, the Administrator notes that the CASAC specifically focused its conclusions on the degree of protection provided by the combination of the 1-hour and annual standards, advising that ''the suite of the 1-hour and annual standards is protective against adverse effects'' (Diez Roux and Sheppard, 2017, p. 9). In light of this advice from the CASAC, the Administrator finds it appropriate to focus on the degree of public health protection provided by the current 1-hour and annual $NO_2$ standards together in reaching his decision in this review to retain the current primary $NO_2$ NAAQS.

Inherent in the Administrator's conclusions are public health policy judgments based on his consideration of the available scientific evidence and analyses. 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 weigh their associated uncertainties. Based on these considerations and the judgments identified herein, the Administrator concludes 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, children, and older adults.

In reaching this 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 or to protect the most sensitive individual, but rather at a level that avoids unacceptable risks to public health. In this context, the Administrator's conclusion is that the current 1-hour and annual $NO_2$ standards together provide the requisite protection and that more or less stringent standards would not be requisite.

More specifically, given the increased risk of adverse effects associated with $NO_2$ 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) $NO_2$ exposures that could exacerbate respiratory effects in people with asthma, particularly those with more severe asthma; and (2) ambient $NO_2$ concentrations likely to have been present in locations where epidemiologic studies have reported associations with asthma-related hospitalizations and with asthma development in children. Consistent with these observations, the Administrator further notes the CASAC conclusion, based on its consideration of the evidence, that ''there are notable adverse effects at levels that exceed the current [1-hour] standard, but not at the level of the current [1-hour] standard'' (Diez Roux and Sheppard, 2017, p. 9) and its recommendation to retain, ''and not change, the existing suite of standards'' (*i.e.,* both 1-hour and annual) (Diez Roux and Sheppard, 2017, cover letter at p. 3). For these reasons, the Administrator concludes 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 requisite to

[124] This air quality relationship was discussed in the PA (U.S. EPA, 2017a, Figure 2–11), 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).

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 $NO_2$ exposures are amplified with consideration of progressively lower ambient $NO_2$ concentrations. In his view, based on the scientific information discussed throughout this document (*e.g.,* sections II.A.2, II.A.3, II.B.1, II.B.3), including uncertainties inherent in that information, there is appreciable uncertainty in the extent to which reductions in asthma exacerbations or asthma development would result from revising the primary $NO_2$ 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, the CASAC advised that ''there is not a scientific basis for a standard lower than the current 1-hour standard'' (Diez Roux and Sheppard, 2017, p. 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 $NO_2$ concentrations well below the level of the annual standard, and observing that there is insufficient scientific evidence to make a scientific judgment that adverse effects occur at those lower concentrations (Diez Roux and Sheppard, 2017, cover letter p. 3).

Based on all of the above considerations, and consistent with the CASAC advice, the Administrator concludes that it is appropriate to retain the current standards, without revision, in this review.

*C. Decision on the Primary Standards*

For the reasons discussed above, and taking into account information and assessments presented in the ISA and PA, the advice and recommendations from CASAC, and consideration of public comments, the Administrator concludes that the current primary 1-hour and annual $NO_2$ standards together are requisite to protect public health with an adequate margin of safety, including the health of at-risk populations, and is retaining the standards without revision.

## 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.*

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

This action is not a significant regulatory action and was, therefore, not submitted to the Office of Management and Budget (OMB) for review.

*B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Costs*

This action is not an Executive Order 13771 regulatory action because this action is not significant under Executive Order 12866.

*C. 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 revising or retaining NAAQS under section 109 of the CAA. This action retains, without any revisions, the current primary NAAQS for oxides of nitrogen.

*D. 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 retains, without revision, existing national standards for allowable concentrations of $NO_2$ in ambient air as required by section 109 of the CAA. *See also American Trucking Associations,* 175 F.3d at 1044–45 (NAAQS do not have significant impacts upon small entities because NAAQS themselves impose no regulations upon small entities).

*E. 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.

*F. 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.

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

This action does not have tribal implications, as specified in Executive Order 13175. It does not have a substantial direct effect on one or more Indian tribes. This action does not change existing regulations; it retains, without revision, the current primary NAAQS for oxides of nitrogen. The primary NAAQS protect public health, including the health of at-risk or sensitive groups, with an adequate margin of safety. Thus, Executive Order 13175 does not apply to this action.

*H. 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. We note, however, that the standards retained with this action provide protection for children and other at-risk populations against adverse health effects. The health effects evidence and risk assessment information for this action, which focuses on children and other at-risk populations, is summarized in section II.A.2 and II.A.3 above and described in the ISA and PA, copies of which are in the public docket for this action.

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

This action is not subject to Executive Order 13211, because it is not a significant regulatory action under Executive Order 12866.

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

This action does not involve technical standards.

*K. 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). This action is to retain without revision the existing primary NAAQS for oxides of nitrogen.

The NAAQS decisions are based on an explicit and comprehensive assessment of the current scientific evidence and associated exposure/risk

analyses. More specifically, the EPA expressly considers the available information regarding health effects among at-risk populations, including that available for low-income populations and minority populations, in decisions on the primary (health based) NAAQS. Where low-income populations or minority populations are among the at-risk populations, the decision on the standard is based on providing protection for these and other at-risk populations and lifestages. Where such populations are not identified as at-risk populations, NAAQS that are established to provide protection to the at-risk populations would also be expected to provide protection to all other populations, including low-income populations and minority populations.

As discussed in sections II.A.2 and II.B.1 above, and in sections II.F and II.C of the proposal, the EPA expressly considered the available information regarding health effects among at-risk populations in reaching the decision that the existing primary (health-based) standards for oxides of nitrogen are requisite. The ISA and PA for this review, which include identification of populations at risk from $NO_2$ health effects, are available in the docket, EPA–HQ–OAR–2013–0146. Based on consideration of this information and the full evidence base, quantitative exposure/risk analyses, advice from the CASAC and consideration of public comments, the Administrator concludes that the existing standards protect public health, including the health of at-risk or sensitive groups, with an adequate margin of safety (as discussed in section II.B.4 above).

*L. 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).

*M. Congressional Review Act (CRA)*

The EPA will submit a rule report to each House of the Congress and to the Comptroller General of the United States. This action is not a ''major rule'' as defined by 5 U.S.C. 804(2).

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## List of Subjects in 40 CFR Part 50

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

Dated: April 6, 2018.

**E. Scott Pruitt,**

*Administrator.*

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