United States Environmental Protection Agency

Policy Assessment for the Review of the Ozone National Ambient Air Quality Standards

First External Review Draft

DISCLAIMER

This draft document has been prepared by staff from the Ambient Standards Group, Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency (EPA). Any opinions, findings, conclusions, or recommendations are those of the authors and do not necessarily reflect the views of the Agency. This draft document is being circulated for informational purposes and to facilitate discussion with the Clean Air Scientific Advisory Committee (CASAC) to inform the EPA's consideration of the ozone National Ambient Air Quality Standards. Questions related to this draft document should be addressed to Susan Stone, U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, C504-02, Research Triangle Park, North Carolina 27711 (email: stone.susan@epa.gov).

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Policy Assessment for the Review of the Ozone National Ambient Air Quality Standards

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1. INTRODUCTION

1.1 PURPOSE

The U.S. Environmental Protection Agency (EPA) is presently conducting a review of the national ambient air quality standards (NAAQS) for ozone (O_3). An overview of the approach to reviewing the O_3 NAAQS is presented in the *Integrated Review Plan for the* O_3 *National Ambient Air Quality Standards* (IRP, US EPA, 2011a). The IRP discusses the schedule for the review; the approaches to be taken in developing key scientific, technical, and policy documents; and the key policy-relevant issues that will frame EPA's consideration of whether the current NAAQS for O_3 should be retained or revised.

As part of the review process, a Policy Assessment (PA) is prepared by staff in the EPA's Office of Air Quality Planning and Standards (OAQPS). The PA is intended to help bridge the gap between the relevant scientific information and assessments and the judgments required of the EPA Administrator in determining whether, and if so how, it is appropriate to revise the primary (health-based) and secondary (welfare-based) NAAQS for O_3. The final PA will seek to provide EPA staff conclusions related to the broadest range of policy options that could be supported by the currently available scientific evidence and technical information for consideration by the Administrator. In so doing, we recognize that the selection of a specific approach to reaching final decisions on the primary and secondary O_3 standards will reflect the judgments of the Administrator.

In this first draft of the PA, we take into account the available scientific and technical information as assessed in the third draft of the *Integrated Science Assessment for* O_3 *and Related Photochemical Oxidants* (ISA, US EPA, 2012a) and the first drafts of the exposure and risk assessment documents: *Health Risk and Exposure Assessment for Ozone: First External Review Draft* (Health REA, US EPA, 2012b) and *Welfare Risk and Exposure Assessment for Ozone: First External Review Draft* (Welfare REA, US EPA, 2012c). In so doing, we focus on information that is most pertinent to evaluating the basic elements of NAAQS: indicator[1], averaging time, form[2], and level. These elements, which together serve to define each standard, must be considered collectively in evaluating the health and welfare protection afforded by the O_3 standards. Although this first draft PA should be of use to all parties interested in this O_3 NAAQS review, it is written with an expectation that the reader has familiarity with the scientific

[1]The "indicator" of a standard defines the chemical species or mixture that is to be measured in determining whether an area attains the standard.
[2]The "form" of a standard defines the air quality statistic that is to be compared to the level of the standard in determining whether an area attains the standard.

and technical discussions contained in the third draft of the ISA and the first drafts of the Health and Welfare REAs.

Following this introductory chapter, this draft PA is organized into two main parts. Chapters 2 through 4 focus on the review of the primary O_3 NAAQS while chapters 5 through 7 focus on the review of the secondary O_3 NAAQS. The remainder of this chapter provides background information on the NAAQS program and on the O_3 NAAQS in particular (section 1.2); an overview of the O_3 ambient monitoring network, precursor emissions, and O_3 air quality (section 1.3); and an overview of the approach to reviewing the O_3 NAAQS and of the organization of the remainder of this draft PA (section 1.4).

1.2 BACKGROUND

1.2.1 Legislative Requirements

Two sections of the Clean Air Act (CAA) govern the establishment and revision of the NAAQS. Section 108 (42 U.S.C. 7408) directs the Administrator to identify and list "air pollutants" that in her "judgment, cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare" and satisfy two other criteria, including "whose presence . . . in the ambient air results from numerous or diverse mobile or stationary sources" and to issue air quality criteria for those that are listed. 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). Section 109 (42 U.S.C. 7409) directs the Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants for which air quality criteria are issued. Section 109(b)(1) defines a primary standard as one "the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health."[3] 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

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

criteria, is requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of such air pollutant in the ambient air."[4]

The requirement that primary standards include 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. *Lead Industries Association v. EPA*, 647 F.2d 1130, 1154 (D.C. Cir 1980), *cert. denied*, 449 U.S. 1042 (1980); *American Petroleum Institute v. Costle*, 665 F.2d 1176, 1186 (D.C. Cir. 1981), *cert. denied*, 455 U.S. 1034 (1982). 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 include an adequate margin of safety, the Administrator is seeking not only to prevent pollution levels that have been demonstrated to be harmful but also to prevent lower pollutant levels that may pose an unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree. The CAA does not require the Administrator to establish a primary NAAQS at a zero-risk level or at background concentration levels, *see Lead Industries Association v. EPA*, 647 F.2d at 1156 n. 51, but rather at a level that reduces risk sufficiently so as to protect public health with an adequate margin of safety.

In addressing the requirement for an adequate margin of safety, EPA considers such factors as the nature and severity of the health effects involved, the size of the population(s) at risk, 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. *Lead Industries Association v. EPA*, 647 F.2d at 1161-62; *Whitman v. American Trucking Associations*, 531 U.S. 457, 495 (2001).

In setting primary and secondary standards that are "requisite" to protect public health and welfare, respectively, as provided in section 109(b), EPA's task is to establish standards that are neither more nor less stringent than necessary for these purposes. In so doing, EPA may not consider the costs of implementing the standards. See generally, *Whitman v. America 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.

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

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 . . . ." This independent review function is performed by the Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board.[5]

1.2.2 Previous O_3 NAAQS Reviews

Table 1-1 summarizes the O_3 NAAQS that have been promulgated to date. In each review, the secondary standard has been set to be identical to the primary standard. These reviews are briefly described below.

Table 1-1. Summary of Primary and Secondary O3 NAAQS Promulgated During the Period from 1971 to 2008

Final Rule	Indicator	Averaging Time	Level (ppm)	Form
1971 (36 FR 8186)	Total photochemical oxidants	1-hr	0.08	Not to be exceeded more than one hr per year
1979 (44 FR 8202)	O_3	1-hr	0.12	Attainment is defined when the expected number of days per calendar year, with maximum hourly average concentration greater than 0.12 ppm, is equal to or less than 1
1993 (58 FR 13008)	EPA decided that revisions to the standards were not warranted at the time.			
1997 (62 FR 38856)	O_3	8-hr	0.08	Annual fourth-highest daily maximum 8-hr concentration, averaged over 3 years
2008 (73 FR 16483)	O_3	8-hr	0.075	Form of the standards remained unchanged relative to the 1997 standard

[5] Lists of CASAC members and of members of the CASAC O_3 Review Panel are available at: http://yosemite.epa.gov/sab/sabpeople.nsf/WebExternalCommitteeRosters?OpenView&committee=CASAC&secondname=Clean%20Air%20Scientific%20Advisory%20Committee and http://yosemite.epa.gov/sab/sabpeople.nsf/WebExternalSubCommitteeRosters?OpenView&committee=CASAC&subcommittee=Ozone%20Review%20Panel, respectively.

The EPA first established primary and secondary NAAQS for photochemical oxidants in 1971 (36 FR 8186, April 30, 1971). Both primary and secondary standards were set at a level of 0.08 parts per million (ppm), 1-hr average, total photochemical oxidants, not to be exceeded more than one hour per year. The standards were based on scientific information contained in the 1970 Air Quality Criteria for Photochemical Oxidants (U.S. DHEW, 1970). The first periodic review of the NAAQS for photochemical oxidants was initiated in 1977. Based on the 1978 Air Quality Criteria for Ozone and Other Photochemical Oxidants (U.S. EPA, 1978), EPA published proposed revisions to the original NAAQS in 1978 (43 FR 16962) and final revisions in 1979 (44 FR 8202). The level of the primary and secondary standards was revised from 0.08 to 0.12 ppm; the indicator was revised from photochemical oxidants to O_3; and the form of the standards was revised from a deterministic to a statistical form, which defined attainment of the standards as occurring when the expected number of days per calendar year with maximum hourly average concentration greater than 0.12 ppm is equal to or less than one.

In 1982, EPA announced plans to revise the 1978 Air Quality Criteria document (47 FR 11561), and in 1983 EPA initiated the second periodic review of the O_3 NAAQS (48 FR 38009). EPA subsequently published the 1986 Air Quality Criteria for Ozone and Other Photochemical Oxidants (U.S. EPA, 1986) and 1989 Staff Paper (U.S. EPA, 1989). Following publication of the 1986 Air Quality Criteria Document (AQCD), a number of scientific abstracts and articles were published that appeared to be of sufficient importance concerning potential health and welfare effects of O_3 to warrant preparation of a Supplement (U.S. EPA, 1992). Under the terms of a court order, on August 10, 1992 EPA published a proposed decision stating that revisions to the existing primary and secondary standards were not appropriate at the time (57 FR 35542). The notice explained that the proposed decision would complete EPA's review of information on health and welfare effects of O_3 assembled over a 7-year period and contained in the 1986 AQCD and its 1992 Supplement. The proposal also announced EPA's intention to proceed as rapidly as possible with the next review of the air quality criteria and standards for O_3 in light of emerging evidence of health effects related to 6- to 8-hour O_3 exposures. On March 9, 1993, EPA concluded the review by deciding that revisions to the standards were not warranted at that time (58 FR 13008).

In August 1992 EPA announced plans to initiate the third periodic review of the air quality criteria and O_3 NAAQS (57 FR 35542). On the basis of the scientific evidence contained in the 1996 Air Quality Criteria for Ozone and related Photochemical Oxidants (U.S. EPA, 1996a), the 1996 Staff Paper (U.S. EPA, 1996b), and related technical support documents, linking exposures to ambient O_3 to adverse health and welfare effects at levels allowed by the

then existing standards, EPA proposed to revise the primary and secondary O_3 standards on December 13, 1996 (61 FR 65716). The EPA proposed to replace the then existing 1-hour primary and secondary standards with 8-hour average O_3 standards set at a level of 0.08 ppm (equivalent to 0.084 ppm using standard rounding conventions). The EPA also proposed to establish a new distinct secondary standard using a biologically based cumulative, seasonal form. The EPA completed the review on July 18, 1997 (62 FR 38856) by setting the primary standard at a level of 0.08 ppm, based on the annual fourth-highest daily maximum 8-hr average concentration, averaged over three years, and setting the secondary standard identical to the revised primary standard.

On May 14, 1999, in response to challenges by industry and others to EPA's 1997 decision, the U.S. Court of Appeals for the District of Columbia Circuit (D.C. Circuit Court) remanded the O_3 NAAQS to EPA, finding that section 109 of the Act, as interpreted by EPA, effected an unconstitutional delegation of legislative authority. In addition, the D.C. Circuit Court directed that, in responding to the remand, EPA should consider the potential beneficial health effects of O_3 pollution in shielding the public from the effects of solar ultraviolet (UV) radiation, as well as adverse health effects. On January 27, 2000, EPA petitioned the U.S. Supreme Court for certiorari on the constitutional issue (and two other issues) but did not request review of the D.C. Circuit Court ruling regarding the potential beneficial health effects of O_3. On February 27, 2001, the U.S. Supreme Court unanimously reversed the judgment of the D.C. Circuit Court on the constitutional issue, holding that section 109 of the CAA does not delegate legislative power to the EPA in contravention of the Constitution, and remanded the case to the D.C. Circuit Court to consider challenges to the O_3 NAAQS that had not been addressed by that Court's earlier decisions. On March 26, 2002, the D.C. Circuit Court issued its final decision, finding the 1997 O_3 NAAQS to be "neither arbitrary nor capricious," and denied the remaining petitions for review. In response to the D.C. Circuit Court remand to consider the potential beneficial health effects of O_3 pollution in shielding the public from effects of solar (ultraviolet or UV) radiation, on November 14, 2001, EPA proposed to leave the 1997 8-hour NAAQS unchanged (66 FR 52768). After considering public comment on the proposed decision, EPA published its final response to this remand on January 6, 2003, reaffirming the 8-hour O_3 NAAQS set in 1997 (68 FR 614). Finally, on April 30, 2004, EPA announced the decision to make the 1-hour O_3 NAAQS no longer applicable to areas one year after the effective date of the designation of those areas for the 8-hour NAAQS (69 FR 23966). For most areas, the date that the 1-hour NAAQS no longer applied was June 15, 2005.

The EPA initiated the next periodic review of the air quality criteria and O_3 standards in September 2000 with a call for information (65 FR 57810). The schedule for completion of that

rulemaking later became governed by a consent decree resolving a lawsuit filed in March 2003 by a group of plaintiffs representing national environmental and public health organizations. Based on the Air Quality Criteria for Ozone and Other Photochemical Oxidants (US EPA, 2006) published in March 2006 and the Staff Paper (U.S EPA, 2007a) and related technical support documents published in July 2007, the proposed decision was published in the Federal Register on July 11, 2007 (72 FR 37818). The EPA proposed to revise the level of the primary standard to a level within the range of 0.075 to 0.070 ppm. Two options were proposed for the secondary standard: (1) replacing the current standard with a cumulative, seasonal standard, expressed as an index of the annual sum of weighted hourly concentrations cumulated over 12 daylight hours during the consecutive 3-month period within the O_3 season with the maximum index value, set at a level within the range of 7 to 21 ppm-hrs, and (2) setting the secondary standard identical to the revised primary standard. The EPA completed the review with publication of a final decision on March 27, 2008 (73 FR 16436), revising the level of the 8-hour primary O_3 standard from 0.08 ppm to 0.075 ppm and revising the secondary standard to be identical to the revised primary standard.

1.2.3 Litigation and Reconsideration of the 2008 O_3 NAAQS Final Rule

In May 2008, state, public health, environmental, and industry petitioners filed suit against EPA regarding that final decision. At EPA's request the consolidated cases were held in abeyance pending EPA's reconsideration of the 2008 decision. A notice of proposed rulemaking to reconsider the 2008 final decision was issued by the Administrator on January 6, 2010. Three public hearings were held. The Agency solicited CASAC review of the proposed rule on January 25, 2010 and additional CASAC advice on January 26, 2011. On September 2, 2011, the Office of Management and Budget returned the draft final rule on reconsideration to EPA for further consideration. EPA decided to coordinate further proceedings on its voluntary rulemaking on reconsideration with the ongoing periodic review, by deferring the completion of its voluntary rulemaking on reconsideration until it completes its statutorily-required periodic review. In light of that, the litigation on the 2008 final decision is no longer being held in abeyance and is proceeding. The 2008 ozone standards remain in effect.

1.2.4 Current O_3 NAAQS Review

On September 29, 2008, the EPA's NCEA-RTP announced the initiation of a new periodic review of the air quality criteria for O_3 and related photochemical oxidants and issued a call for information in the Federal Register (73 FR 56581, Sept. 29, 2008). A wide range of external experts as well as EPA staff, representing a variety of areas of expertise (e.g., epidemiology, human and animal toxicology, statistics, risk/exposure analysis, atmospheric science, ecology, biology, plant science, benefits analysis) participated in a workshop, held by

EPA on October 28-29, 2008 in Research Triangle Park, NC. The workshop provided an opportunity for a public discussion of the key policy-relevant issues around which EPA would structure this O_3 NAAQS review and the most meaningful new science that would be available to inform our understanding of these issues.

Based in part on the workshop discussions, EPA developed a draft IRP outlining the schedule, process, and key policy-relevant questions that would guide the evaluation of the air quality criteria for O_3 and the review of the primary and secondary O_3 NAAQS. A draft of the integrated review plan was released for public review and comment in September 2009 and was the subject of a consultation with the Clean Air Scientific Advisory Committee (CASAC) on November 13, 2009 (74 FR 54562; October 22, 2009).[6] Comments received from that consultation and from the public were considered in finalizing the plan and in beginning the review of the air quality criteria. The EPA's overall plan and schedule for this review is presented in the *Integrated Review Plan for the Ozone National Ambient Air Quality Standards.*[7]

As part of the process of preparing the O_3 ISA, NCEA hosted a peer review workshop in October 29-30, 2008 (73 FR 56581, September 29, 2008) on preliminary drafts of key ISA chapters. The first external review draft ISA (US EPA, 2011a; 76 FR 10893, February 28, 2011) was reviewed by CASAC and the public at a meeting held in May 19-20, 2011 (76 FR 23809; April 28, 2011). Based on CASAC and public comments, NCEA prepared a second draft ISA (US EPA, 2011b; 76 FR 60820, September 30, 2011), which was reviewed by CASAC and the public at a meeting held on January 9-10, 2012 (76 FR 236, December 8, 2011). Based on CASAC and public comments, NCEA prepared a third draft ISA (US EPA 2012a; 77 FR 36534; June 19, 2012), which will be reviewed at a CASAC meeting in September 2012.

The EPA's plans for conducting the Risk and Exposure Assessment (REA) documents that build on the scientific evidence presented in the ISA, se assessments, including the proposed scope and methods of the analyses, were presented in two planning documents titled, *Ozone National Ambient Air Quality Standards: Scope and Methods Plan for Health Risk and Exposure Assessment* and Ozone *National Ambient Air Quality Standards: Scope and Methods Plan for Welfare Risk and Exposure Assessment* (henceforth, Scope and Methods Plans).[8] These planning documents outlined the scope and approaches that staff planned to use in conducting quantitative assessments as well as key issues that would be addressed as part of the assessments.

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[6] See http://yosemite.epa.gov/sab/sabproduct.nsf/WebProjectsbyTopicCASAC!OpenView for more information on CASAC activities related to the current O_3 NAAQS review.
[7] EPA 452/R-11-006; April 2011; Available: http://www.epa.gov/ttn/naaqs/standards/ozone/data/2011_04_OzoneIRP.pdf
[8] EPA-452/P-11-001 and -002; April 2011; Available: http://www.epa.gov/ttn/naaqs/standards/ozone/s_o3_2008_pd.html

The documents were released for public comment in April 2011, and were the subject of a consultation with the CASAC on May 19-20, 2011 (76 FR 23809; April 28, 2011). In designing and conducting the initial health risk and visibility impact assessments, we considered CASAC comments (Samet 2011) on the Scope and Methods Plans as well as public comments. In May 2012, a memo titled, *Updates to information presented in the Scope and Methods Plans for the Ozone NAAQS Health and Welfare Risk and Exposure Assessments*, was made available that described changes to elements of the scope and methods plans and provided a brief explanation of each change and the reason for it.

On July 16, 2012, the EPA made available for CASAC review and public comment two draft assessment documents titled, *Health Risk and Exposure Assessment for Ozone, First External Review Draft* and *Welfare Risk and Exposure Assessment for Ozone, First External Review Draft* (77 FR 42495, July 19, 3023). These two draft assessment documents describe the quantitative analyses the EPA is conducting as part of the review of O_3 NAAQS. Along with the third draft ISA and this PA, these documents will be reviewed at a CASAC meeting in September 2012.

1.3 OVERVIEW OF O3 MONITORING AND AIR QUALITY

This section provides overviews of the ambient monitoring network for O_3 (section 1.3.1); O_3 precursor emissions and atmospheric chemistry (section 1.3.2); of ambient concentrations (section 1.3.3); and the available evidence and information related to background O_3 (section 1.3.4). These issues are also discussed in detail in the chapter 3 of the ISA (US EPA, 2012a).

1.3.1 O_3 Monitoring Network

To monitor compliance with the NAAQS, state and local monitoring agencies operate O_3 monitoring sites at various locations, depending on the size of the area and typical peak O_3 concentrations (US EPA, 2012a, sections 3.5.6.1, 3.7.4). In 2010, there were 1,250 State and Local O_3 monitors reporting concentrations to EPA (US EPA, Figures 3-21 and 3-22). The minimum number of O_3 monitors required in a Metropolitan Statistical Area (MSA) ranges from zero, for areas with a population under 350,000 and with no recent history of an O_3 design value greater than 85% of the level of the NAAQS, to four, for areas with a population greater than 10 million and an O_3 design value greater than 85% of the NAAQS.[9] For areas with required O_3 monitors, at least one site must be designed to record the maximum concentration for that particular metropolitan area. The spatial scales for O_3 sites are neighborhood, urban, and

[9]The current monitor and probe siting requirements have an urban focus and do not address siting in non-urban, rural areas. States may operate O_3 monitors in non-urban or rural areas to meet other objectives (e.g., support for research studies of atmospheric chemistry or ecosystem impacts).

regional.[10] Since O_3 concentrations decrease significantly in the colder parts of the year in many areas, O_3 is required to be monitored only during the "ozone season," which varies by state (US EPA, 2012a, section 3.5.6 and Figure 3-20).[11]

1.3.2. Emissions and Atmospheric Chemistry

O_3 is formed by photochemical reactions of precursor gases and is not directly emitted from specific sources. In the stratosphere, ozone occurs naturally and provides protection against harmful solar ultraviolet radiation. In the troposphere, near ground level, O_3 forms through atmospheric reactions involving two main classes of precursor pollutants: volatile organic compounds (VOCs) and nitrogen oxides (NO_X). Carbon monoxide (CO) and methane (CH_4) are also important for O_3 formation in some areas (US EPA, 2012a, section 3.2.2).

Emissions of O_3 precursor compounds can be divided into anthropogenic and natural source categories, with natural sources further divided into biogenic emissions (from vegetation, microbes, and animals) and abiotic emissions (from biomass burning, lightning, and geogenic sources). Anthropogenic sources, including mobile sources and power plants, account for the majority of NOx and CO emissions. Anthropogenic sources are also important for VOC emissions, though in some locations and at certain times of the year (e.g., southern states during summer) the majority of VOC emissions come from vegetation (US EPA, 2012a, section 3.2.1). In practice, the distinction between natural and anthropogenic sources is often unclear, as human activities directly or indirectly affect emissions from what would have been considered natural sources during the preindustrial era. Thus, emissions from plants, animals, and wildfires could be considered either natural or anthropogenic, depending on whether emissions result from agricultural practices, forest management practices, lightning strikes, or other types of events. (US EPA, 2012a, sections 3.2 and 3.7.1).

Rather than varying directly with emissions of its precursors, O_3 changes in a nonlinear fashion with the concentrations of its precursors. NO_x emissions lead to both the formation and destruction of O_3, depending on the local quantities of NO_x, VOC, and radicals. In areas dominated by fresh emissions of NO_x, these radicals are removed, which lowers the O_3 formation rate. In addition, the scavenging of O_3 by reaction with NO is called "titration," and is often found in downtown metropolitan areas, especially near busy streets and roads, and in power plant plumes. This short-lived titration results in local valleys in which O_3 concentrations are low

[10]Neighborhood scale represents concentrations within some extended area of the city that has relatively uniform land use with dimensions in the 0.5-4.0 km range. Urban scale represents concentrations within an area of city-like dimensions, on the order of 4-50 km. Regional scale usually defines a rural area of reasonably homogeneous geography without large sources, and extends from tens to hundreds of kilometers.

[11]Some States and Territories operate O_3 monitors year-round, including Arizona, California, Hawaii, Louisiana, Nevada, New Mexico, Puerto Rico, Texas, American Samoa, Guam and the Virgin Islands.

compared to surrounding areas, but produces NO_2 that contributes to O_3 formation later and further downwind. Consequently, O_3 response to reductions in NO_x emissions is complex and may include ozone decreases at some times and locations and, in others, increases of ozone to fill in the local valleys of low ozone. In areas with low NO_x concentrations, such as those found in remote continental areas to rural and suburban areas downwind of urban centers, O_3 production typically varies directly with NO_x concentrations (e.g. increases with increasing NO_x emissions).

The formation of O_3 from precursor emissions is also affected by the intensity and spectral distribution of sunlight and atmospheric mixing. Major episodes of high ground level O_3 concentrations in the eastern United States are associated with slow moving high pressure systems. High pressure systems during the warmer seasons are associated with the sinking of air, resulting in warm, generally cloudless skies, with light winds. The sinking of air results in the development of stable conditions near the surface which inhibit or reduce the vertical mixing of O_3 precursors. The combination of inhibited vertical mixing and light winds minimizes the dispersal of emitted pollutants emitted in urban areas, allowing their concentrations to build up. In addition, in some parts of the United States (e.g., in Los Angeles), mountain barriers limit mixing and result in a higher frequency and duration of days with high O_3 concentrations. Photochemical activity involving precursors is enhanced during warmer seasons because of higher temperatures and the availability of sunlight (US EPA, 2012a, section 3.2).

Ozone concentrations in a region are affected both by local formation and by transport of O_3 and its precursors from surrounding areas. Ozone transport occurs on many spatial scales including local transport between cities, regional transport over large regions of the U.S. and international/long-range transport. In addition, O_3 is transfered into the troposphere from the stratosphere, which is rich in O_3, through stratosphere-troposphere exchange (STE). These inversions or “foldings” usually occur behind cold fronts, bringing stratospheric air with them (U.S. EPA, 2012, section 3.4.1.1).

1.3.3 Air Quality Concentrations

Because O_3 is a secondary pollutant formed in the atmosphere from precursor emissions, concentrations are generally more regionally homogeneous than concentrations of primary pollutants emitted directly from stationary and mobile sources (US EPA, 2012a, section 3.6.2.1). However, variation in local emissions characteristics, meteorological conditions, and topography can result in daily and seasonal temporal variability in ambient O_3 concentrations, as well as local and national-scale spatial variability.

Temporal variation in ambient O_3 concentrations results largely from daily and seasonal patterns in temperature, sunlight, precursor emissions, and meteorological conditions (US EPA,

2012a, section 3.7.5). On average, ambient O_3 concentrations follow well-recognized daily and seasonal patterns, particularly in urban areas. Specifically, daily maximum O_3 concentrations in urban areas tend to occur in mid-afternoon, with more pronounced peaks in the warm months of the O_3 season than in the colder months (US EPA, 2012a, Figures 3-54, 3-156 to 3-157). Rural sites also followed this general pattern, though it is less pronounced in colder months (US EPA, 2012a, Figure 3-55). With regard to seasonal variability, median maximum daily average 8-hour (MDA8) O_3 concentrations in U.S. cities in 2007-2009 were approximately 47 ppb, with typical ranges between 35 to 60 ppb and the highest MDA8 concentrations above 100 ppb in several U.S. cities.

In addition to temporal variability, there is also considerable spatial variability in ambient O_3 concentrations within cities and across different cities in the United States. With regard to spatial variability within a city, local emissions characteristics, geography, and topography can have important impacts. For example, fresh NO emissions from motor vehicles titrate O_3 present in the urban background air, resulting in an O_3 gradient around roadways with O_3 concentrations increasing as distance from the road increases (US EPA, 2012a, section 3.6.2.1). In comparing urban areas, the ISA notes that measured O_3 concentrations are relatively uniform and well-correlated across some cities (e.g., Atlanta) while they are more variable in others (e.g., Los Angeles) (US EPA, 2012a, section 3.6.2.1 and Figures 3-28 to 3-36). In addition to differences in local emissions characteristics, such differences in the uniformity of ambient O_3 concentrations across urban areas can also result from differences in local geography and topography (US EPA, 2012a, section 3.6.2.1).

With regard to spatial variability across cities, when the ISA evaluated the distributions of 8-hour O_3 concentrations for the years 2007 to 2009 in 20 cities, the highest concentrations were reported in Los Angeles, with high concentrations also reported in several eastern and southern cities. The maximum recorded MDA8 was 137 ppb in Los Angeles, and was near or above 120 ppb in Atlanta, Baltimore, Dallas, New York City, Philadelphia, and St. Louis (US EPA, 2012a, Table 3-10). The pattern was similar for the 98th percentile of the distribution of MDA8 concentrations[12], with Los Angeles recording the highest 98th percentile concentration (91 ppb) and many eastern and southern cities reporting 98th percentile concentrations near or above 75 ppb. In contrast, somewhat lower 98th percentile O_3 concentrations were recorded in cities in the western United States outside of California (US EPA, 2012a, Table 3-10).

Although rural monitoring sites tend to be less directly affected by anthropogenic pollution sources than urban sites, rural sites can be affected by transport of O_3 or O_3 precursors

[12] Table 3-10 in the ISA analyzes the warm season. Therefore, the 98th percentile values would be an approximation of the 4th highest value.

from upwind urban areas and by local anthropogenic sources such as motor vehicles, power generation, biomass combustion, or oil and gas operations (US EPA, 2012a, section 3.6.2.2). In addition, O_3 tends to persist longer in rural than in urban areas due to lower rates of chemical scavenging in non-urban environments. At higher elevations, increased O_3 concentrations can also result from stratospheric intrusions (US EPA, 2012a, sections 3.4, 3.6.2.2). As a result, O_3 concentrations measured in some rural sites can be higher than those measured in nearby urban areas (US EPA, 2012a, section 3.6.2.2) and the ISA concludes that cumulative exposures for humans and vegetation in rural areas can be substantial, and often higher than cumulative exposures in urban areas (US EPA, 2012a, section 3.7.5).

1.3.4 Background O_3

As discussed above, and in more detail in the ISA (US EPA, 2012a, Chapter 3), ambient concentrations of O_3 in a given location can be influenced by emissions from both anthropogenic and natural sources, by long-range transport from within and outside the United States, and by intermixing of stratospheric and tropospheric air masses. In the last review of the O_3 NAAQS, EPA distinguished between ambient O_3 that could be controlled through U.S. regulations or through international agreements with neighboring countries and ambient O_3 not generally controllable in this manner (US EPA, 2007, section 2.7). This distinction was judged appropriate because it had the effect of focusing policy considerations on health risks that would be controllable through U.S. regulations and/or policies. To facilitate such a distinction, EPA defined policy relevant background (PRB), referred to as North American Background (NAB) in the current draft ISA (US EPA, 2012a, section 3.4) and in this draft PA, as the distribution of O_3 concentrations that would be observed in the U.S. in the absence of North American (i.e., U.S., Canada, and Mexico) anthropogenic emissions. The primary implication of this distinction was that O_3-related health risks were characterized for ambient O_3 concentrations above PRB (NAB in current review).[13] In this section, we discuss sources and contributions of background O_3, as well as estimated concentrations of background O_3 across the U.S., with a focus on how background O_3 varies spatially and temporally across the U.S. and with respect to measured or simulated total O_3 concentrations (US EPA, 2012a, section 3.4).

In this first draft PA, we discuss three definitions of background O_3 concentrations: (1) NAB, which is simulated O_3 concentrations that would exist in the absence of anthropogenic

[13]In this review, the first draft REA (US EPA, 2012b) focuses on estimation of risks down to zero concentrations of O_3 and down to lowest measured levels (LML) of O_3, as reflected in the epidemiology studies used in the REA. This is in agreement with CASAC members' recommendation that EPA move away from using PRB in calculating risks (Henderson, 2007). In simulating air quality that just meets the current O_3 NAAQS, the first draft REA uses modeled U.S. background concentrations as lowest values for the rollback (i.e., O_3 concentrations are not rolled back below U.S. background concentrations) (chapter 3, below).

emissions from the U.S., Canada and Mexico; (2) U.S. background (USB), which is simulated O_3 concentrations that would exist in the absence of anthropogenic emissions from the U.S.; and (3) natural background (NB), which is simulated O_3 concentrations in the absence of all anthropogenic emissions globally. All of these definitions include contributions from natural sources including the STE of O_3, O_3 resulting from photochemical reactions of emissions from natural sources (e.g., wildfires, lightning, soil, biogenic), and global methane emissions, although approximately 60% of global methane emissions are anthropogenic (Olivier et al, 2005). In addition, both NAB and USB include international transport of O_3 and O_3 precursor emissions from outside of North America into the U.S.[14]

While some of these sources contribute to background O_3 in a more consistent manner, with limited day-to-day variability (e.g. biogenic and soil emissions), other sources contribute to background O_3 more episodically (e.g. stratospheric intrusions, international transport events, wildfires). These episodic events usually occur in relation to a specific event, such as a strong cold front or a wildfire, and occur more often in specific geographical locations, such as at high elevations and in wildfire prone areas during the local dry season. In addition, these episodic sources of background have been found to be the primary drivers of high background concentrations (US EPA, 2012a, section 3.7.3). It should also be noted that EPA has policies for treatment of air quality monitoring data affected by these types of events. For example, EPA's 2007 Treatment of Data Influenced by Exceptional Events Rule allows exclusion of air quality monitoring data from regulatory determinations related to exceedances or violations of the NAAQS and to avoid designating an area as nonattainment if a State adequately demonstrates that an exceptional event have caused an exceedance or violation of a NAAQS.[15] In addition, Section 179B of the CAA also provides for treatment of air quality data from international transport when emissions emanating from outside of the United States have caused an exceedance or violation of a NAAQS.[16]

Historically, two approaches have been used to estimate background O_3 concentrations. In the 1996 O_3 AQCD, and in earlier reviews, measurements from remote monitoring sites were used to estimate background concentrations. However, this approach has the disadvantage of not

[14] USB also includes the transport of O_3 and O_3 precursor emissions from Canada and Mexico into the U.S.

[15] EPA's 2007 Treatment of Data Influenced by Exceptional Events Rule section 319(b)(3)(B) and section 107(d)(3) of the CAA: Exceptional events are unusual or naturally occurring events that can affect air quality but are not reasonably controllable using techniques that tribal, state, or local air agencies may implement (http://www.epa.gov/ttn/analysis/exevents.htm). Additional guidance related to this rule is currently under development.

[16] Section 179B states: "Notwithstanding any other provision of law, any State that establishes to the satisfaction of the Administrator that, with respect to an ozone nonattainment area in such State, such State would have attained the national ambient air quality standard for ozone by the applicable attainment date, but for emissions emanating from outside of the United States, shall not be subject to the provisions of section 181(a)(2) or (5) or section 185."

allowing unambiguous attribution of ambient O_3 concentrations to background sources. As noted in the 2006 O_3 AQCD (U.S. EPA, 2006, section 3.9), given long-range transport of O_3 and O_3 precursors from anthropogenic source regions, estimates of background concentrations in the U.S. cannot be obtained directly from measurements of ambient O_3, even measurements obtained at relatively remote monitoring sites. In support of this conclusion, recent analyses by Parrish et al. (2009) indicated that measured O_3 concentrations at Trinidad Head, CA, a site that has historically been characterized as reflecting NAB, only reflected background concentrations about 30% of the time during spring, with local anthropogenic source influences present on most days (US EPA, 2012a, section 3.4.2).

Since background O_3 concentrations as defined above are a construct that cannot be directly measured, the 2006 AQCD adopted the use of chemical transport models (CTMs) to estimate NAB (referred to as PRB in the 2006 AQCD). An advantage of using CTMs is that they are able to provide a broad range of O_3 concentrations, spatially and temporally, from various different environments. Another advantage of using these models to estimate background O_3 concentrations is that specific emissions sources can be turned on or off in the model, providing insight into contributions to ambient O_3 concentrations in the U.S. from natural sources and international transport, when compared to measured or simulated base case concentrations of O_3 concentrations photochemically produced from all emissions sources. However, it should be noted that modeled concentrations of O_3 background are an estimate of O_3 concentrations in the absence of specific anthropogenic emissions, and because of the nonlinear nature of O_3 chemistry, are only an approximation of how much of the O_3 measured or simulated in a given area is due to background contributions. In this way, there are important limitations to consider when interpreting the modeling results.

Recent modeling efforts from Zhang et al. (2011) and Emery et al. (2012) have sought to improve the spatial and temporal resolution of background estimates and to better characterize important sources of background O_3 such as fires and international transport. These applications have produced the latest estimates for background O_3 concentrations documented in the recent literature, and the results of these modeling efforts are discussed in more detail in the ISA (US EPA, 2012a, section 3.4) and below. The analyses provided by Zhang et al. (2011) (hereafter referred to as GEOS-Chem) utilized the GEOS-Chem model at a grid spacing of 0.5º x 0.667º (~50 km) over North America for modeling NAB, USB, NA, and base case O_3. The analyses provided in Emery et al. (2012) (hereafter referred to as CAMx) employed the CAMx model at an even finer grid spacing of 12km x 12km to model NAB and base case O_3, with boundary conditions being provided by a GEOS-Chem model run at a grid spacing of 2º x 2.5º. The most readily discernible differences in the two modeling applications are in the model grid spacing

and the treatment of wildfires. The ISA discusses in detail the model performance of the GEOS-Chem and CAMx base case model runs, as well as the estimates of background O_3 (US EPA, 2012a, section 3.4). In addition, the information from the 2006 GEOS-Chem and CAMx model runs are analyzed in Henderson et al. (2012) to provide additional information about variations in the O_3 background concentrations spatially, temporally, and with respect to the distribution of simulated base case O_3.

In the remainder of this section, we discuss the estimated average background O_3 values across the U.S. (section 1.3.4.1), compare how the estimated MDA8 background O_3 contribution varies with simulated O_3 concentrations (section 1.3.4.2) based on the GEOS-Chem and CAMx results for 2006, and provide a summary of this information (section 1.3.4.3).

1.3.4.1 Average Background O_3 in the U.S.

The ISA finds that both GEOS-Chem and CAMx were capable of simulating measured seasonal or monthly mean MDA8 O_3 within a few parts per billion throughout the U.S., with less acceptable model performance in California (US EPA, 2012a, section 3.4.3.2). Both modeling applications showed that background concentrations vary spatially and temporally, and that simulated mean background concentrations are highest in the Intermountain West (i.e. at high altitudes) in spring and lowest in the Northeast during the summer. Table 3-1 in the ISA (US EPA, 2012a) provides the seasonal mean modeled MDA8 NAB O_3 concentrations for five regions of the U.S. for 39 CASTNET site locations. Spring mean MDA8 O_3 concentrations were simulated by GEOS-Chem and CAMx to be 38-42 ppb in the West (including California) and 30-33 ppb in the rest of the country (i.e. North Central, Northeast, and Southeast). Summer mean MDA8 O_3 concentrations were simulated by the two modeling approaches to be 37-42 ppb in the West and 27-33 ppb in the rest of the country (US EPA, 2012a, Table 3-1).

GEOS-Chem estimated March-August 2006 mean MDA8 NAB and NB concentrations at CASTNET site locations to be approximately 29 ppb and 18 ppb, respectively, at low elevations (<1,500 m) and approximately 40 ppb and 27 ppb, at high elevations (>1,500 m). These data suggest that intercontinental pollution contributes approximately 9 ppb at low-elevation sites and 13 ppb at sites in the Intercontinental West to seasonal average MDA8 O_3 concentrations. These results reflect the increased importance of background sources such as stratospheric intrusions and intercontinental transport with altitude.

GEOS-Chem results for seasonal mean MDA8 USB and NAB concentrations suggest that USB concentrations are on average 1-3 ppb higher than NAB background, reflecting the influence of anthropogenic sources in Canada and Mexico. Very little variability was found in these concentrations, except in areas in the U.S. that bordered Canada and Mexico, where

international transport from these two countries plays a greater role in contributing to O_3 background concentrations (US EPA, 2012a, Figure 3-9). These results were similar to those reported by Wang et al. (2009).

Biomass burning has been found to be a significant contributor to background O_3, particularly in the West. For a small number of western locations, generally not near major urban centers, NAB concentrations were estimated by Emery et al. (2012) to be considerably higher than the NAB concentrations estimated for the majority of the region. When Emery et al. (2012) removed biomass burning from the model runs, these high concentrations were dramatically reduced, suggesting that the highest estimates of NAB concentrations in the West are driven largely by wildfires. This result is consistent with other research indicating that biomass burning, including wildfires and the intentional burning of vegetation, can make important contributions to background O_3 concentrations. Biomass burning exhibits strong seasonality, with most fires occurring during the local dry season (US EPA, 2012a, section 3.4.1.2). Several studies have reported effects of U.S. or international wildfires on O_3 concentrations in the U.S. (Wang et al., 2006; Generoso et al., 2007; Jaffe et al., 2008; Mathur et al., 2008). Specifically, Jaffe et al. (2008) reported a strong correlation between the area burned in the western U.S. and the summer mean O_3 concentrations measured at various national park and CASTNET sites in the surrounding regions. The authors estimated that, on average, O_3 concentrations increased by 3.5 ppb during mean fire years and 8.8 ppb during maximum fire years (US EPA, 2012a, section 3.4.1.2).

1.3.4.2 Distributions of Background O_3 in the U.S.

In addition to discussing average background concentrations, it is also important to understand how estimated background concentrations vary with measured or simulated O_3 concentrations, as well as to understand the contributing sources. The remainder of this section focuses on the results detailed by Henderson et al. (2012), which compares distributions of background O_3 concentrations with simulated total O_3, as adapted from the GEOS-Chem and CAMx model simulations performed by Zhang et al. (2011) and Emery et al. (2012). In this way, we provide a more robust analysis by focusing on better understanding the variability of concentrations across a region for many days rather than just one day of predicted 4th highest MDA8 O_3 concentrations in a grid cell.

The analysis presented by Henderson et al. (2012) divides the country into 5 regions: Northeast, Southeast, North Central, West (except for California), and California. It presents NAB contributions at AQS, CASTNET, and other special study monitoring sites by season to concentrations simulated by both GEOS-Chem and CAMx. The analysis also uses Combined Statistical Areas (CSA) to distinguish between “urban” and “non-urban” sites, and presents

results for CSA versus non-CSA areas in each region. In addition, results are presented for the location of high elevation versus low elevation monitoring sites in the West. The following discussion focuses on these regional results. Overall, NAB concentrations are found to be lowest in the Northeast, and highest in the West, particularly at high elevation sites.

Little or no differences were found in estimated NAB concentrations for the location of "urban" and "non-urban" monitoring sites, and so the results discussed below are for the location all monitoring sites within each region. In addition, because O_3 concentrations are usually highest in the spring and summer, we focus our discussion on these two seasons. The analysis presented by Henderson et al. (2012) compares the contribution of modeled NAB to modeled base case O_3 and the results are broken into 5 ppb increment bins from >= 20 ppb to >=135 ppb, based on MDA8 concentration values.

The median, 75th , and 95th percentile MDA8 values for the five regions of the U.S., discussed below and shown in Table 1-2, are 2006 MDA8 NAB concentrations estimated by GEOS-Chem and CAMx (as presented in Henderson et al. (2012)) when simulated base case O_3 MDA8 values were greater than 55 ppb. Median values provide a more robust indicator than extreme values of the distribution for the purpose of examining and comparing the regional and seasonal variability in NAB. The NAB predictions toward the higher end of the distribution (e.g. 75th and 95th percentiles) are more reflective of infrequent or atypical events. Due to the overall uncertainties and assumptions in the inputs to the two modeling systems, the higher percentile NAB predictions are likely to have a greater degree of uncertainty than the median values.

As shown in Table 1-2, similar concentration values for NAB were also found in North Central and Southeast. On days when simulated base case spring-time O_3 concentrations were above 55 ppb, median MDA8 NAB concentrations for GEOS-Chem and CAMx were 28 ppb and 33 ppb for North Central and 30 ppb and 34 ppb for the Southeast. The 75th percentile MDA8 NAB concentrations were 33 ppb and 37 ppb for North Central and 34 ppb and 38 ppb for the Southeast, as estimated by GEOS-Chem and CAMx. The 95th percentile MDA8 NAB concentrations were estimated to be 40 ppb and 42 ppb for North Central, and 41 ppb and 45 ppb for the Southeast. The NAB concentrations were lower in the summer. Summertime median MDA8 NAB concentrations for the two models were 24 ppb and 33 ppb for North Central, and 29 ppb and 31 ppb for the Southeast. The 75th percentile NAB concentrations were 28 ppb and 36 ppb for North Central and 36 ppb and 34 ppb for the Southeast, as predicted by GEOS-Chem and CAMx. The 95th percentile NAB concentrations were estimated to be 39 ppb and 41 ppb for North Central and 44 ppb and 41 ppb for the Southeast.

Estimated NAB background concentrations were lowest in the Northeast region. On days when predicted spring-time O_3 concentrations were above 55 ppb, median MDA8 NAB

concentrations in the spring in the Northeast were 23 ppb and 31 ppb for the two models, with estimated 75th percentile NAB concentrations of 26 ppb and 34 ppb. In the spring, 95th percentile NAB concentrations were estimated to be 33 ppb and 38 ppb. O_3 background concentrations were lower in the summer. Summertime median MDA8 values estimated by GEOS-Chem and CAMx were 18 ppb and 29 ppb, and 75th percentile NAB concentrations were 23 ppb and 32 ppb, when simulated base case O_3 concentrations were above 55 ppb. Ninety-fifth percentile NAB concentrations were estimated to be 34 ppb and 36 ppb

Compared to the eastern U.S., NAB O_3 concentrations in the West are more variable across locations. As compared to the rest of the western U.S., relatively lower background O_3 concentrations have been estimated for California, where total ambient O_3 concentrations are among the highest in the nation. In addition, higher background concentrations have also been found at higher elevation sites, compared to lower elevation sites (US EPA, 2012a, Figure 3-12). In light of this spatial variability, we discuss separately background O_3 in California. Since most of the high elevation sites are in the West, we also discuss NAB background concentrations at monitoring sites in the West at high (>1500 m) versus low (<1500 m) elevation sites.

Spring and summer median MDA8 NAB concentrations in California were similar, when simulated base case O_3 concentrations were above 55 ppb. Median MDA8 NAB concentrations for the two models were 34 ppb and 35 ppb in the spring, and 30 ppb and 36 ppb in the summer. Seventy-fifth percentile MDA8 NAB concentrations estimated to be 40 ppb in the spring, and 36 ppb and 40 ppb in the summer, while 95th percentile MDA8 NAB concentrations were estimated to be 48 ppb in the spring, and 45 ppb and 47 ppb in the summer.

Table 1-2. Modeled median and 75th percentile 2006 MDA8 NAB concentrations at monitoring site locations (as presented in Henderson et al. (2012) and adapted from GEOS-Chem and CAMx modeling applications) when simulated base case O_3 MDA8 values were greater than 55 ppb.

Region		Spring (GEOS-Chem/CAMx)			Summer (GEOS-Chem/CAMx)		
		Median (ppb)	**75th percentile (ppb)**	**95th percentile (ppb)**	**Median (ppb)**	**75th percentile (ppb)**	**95th percentile (ppb)**
California		34/35	40/40	48/48	30/36	36/40	45/47
North Central		28/33	33/37	40/42	24/33	28/36	39/41
Northeast		23/31	26/34	33/38	18/29	23/32	34/36
Southeast		30/34	34/38	41/45	29/31	36/34	44/41
West	*All sites*	44/43	47/48	52/55	41/41	46/46	54/52
	Low-elevation sites	43/41	46/44	51/51	40/39	45/44	52/52
	High-elevation sites	45/48	48/52	53/57	42/43	47/48	54/53

For the rest of the West, on days when spring-time O_3 concentrations were estimated to be above 55 ppb, median MDA8 NAB O_3 concentrations for the two models were 44 ppb and 43 ppb, with 75th percentile MDA8 NAB concentrations of 47 ppb and 48 ppb and 95th percentile MDA8 NAB concentrations of 52 ppb and 55 ppb. Lower values of background were estimated in the summer, with median MDA8 NAB concentrations of 41 ppb. Seventy-fifth percentile NAB concentrations were estimated to be 46 ppb for both models, and 95th percentile NAB concentrations were estimated to be 54 ppb and 52 ppb.

Higher NAB concentrations were estimated at high-elevation site locations, compared to low-elevation site locations, in the West. On days when spring-time O_3 concentrations were estimated to be above 55 ppb, median MDA8 NAB O_3 concentrations estimated by the two models at high-elevation site locations were 45 ppb and 48 ppb, compared to low-elevation site locations with median MDA8 NAB concentrations of 43 ppb and 41 ppb. The 75th percentile MDA8 NAB concentrations at high-elevation site locations were estimated by the two models to

be 48 ppb and 52 ppb, compared to low elevation sites with 75th percentile MDA8 NAB concentrations of 46 ppb and 44 ppb, when simulated base case O_3 concentrations were above 55 ppb. The 95th percentile MDA8 NAB concentrations at high-elevation site locations were estimated to be 53 ppb and 57 ppb, compared to low elevation sites with 95th percentile MDA8 NAB concentrations of 51 ppb. A similar pattern, with somewhat lower concentrations, was also estimated in the summertime.

In general, for all areas of the country, background concentrations increase with increasing total O_3 up to MDA8 values of approximately 55-60 ppb. Above MDA8 concentrations of 55-60 ppb, the NAB O_3 concentrations do not vary significantly across the 5 ppb bins between 55-135 ppb (Henderson et al, 2012). This result was also illustrated in decreasing percent contribution of NAB to O_3 concentrations with increasing O_3 concentrations above MDA8 concentrations of approximately 55-60 ppb (Henderson et al, 2012). In addition, the median values of NAB are not dramatically higher than the typical seasonal average background concentrations for the region. These results suggest that anthropogenic sources within the U.S. are largely responsible for the highest MDA8 O_3 concentrations.

It is important to understand source contributions to the background concentrations discussed above and how they relate to U.S. EPA polices for data treatment. The GEOS-Chem and CAMx results from the applications used for this analysis demonstrate that NAB O_3 concentrations are quite variable across U.S., with lower background concentrations in the East and higher concentrations in the West. As discussed above, and in the ISA (US EPA, 2012a, section 3.4.3,2), high values of background O_3 are believed to be mainly due to some combination of wildfires, stratospheric intrusions, and Eurasian emissions, with stronger influences of Canadian and Mexico emissions also affecting areas bordering those countries. For example, in the western U.S., fire emissions have been found to be a significant contributor to background O_3, particularly in the West. Emery et al. (2012) found that removing fire emissions in the West resulted in reductions of MDA8 NAB O_3 concentrations of 10-50 ppb, with smaller reductions elsewhere. Emery et al. (2012) found the highest values of background in Idaho, Oregon, Washington, and in the upper northwestern corner of California from wildfires. This result is consistent with other research indicating that biomass burning, including wildfires and the intentional burning of vegetation, can make important contributions to background O_3 concentrations (Wang et al., 2006; Generoso et al., 2007; Jaffe et al., 2008; Mathur et al., 2008).

In addition to wildfires and as discussed above, STE of O_3 can contribute to surface level O_3 concentrations, especially at the high elevations found in the mountainous regions of the western U.S. These events usually contribute episodically to high background O_3. Lin et al. (2012) estimated that contributions from strong stratospheric intrusions to surface O_3 could range

up to approximately 55 ppb in the western U.S. While it is challenging to accurately estimate the exact contribution to surface-level O_3 from relatively small direct or indirect (i.e., resulting from shallow intrusions into the mid and upper troposphere that are then mixed downward into the planetary boundary layer) stratospheric intrusion events, some strong events have been identified and their contributions to surface level O_3 concentrations have been characterized (Langford et al., 2009, Hocking et al., 2007, US EPA, 2006).

1.3.4.3 Summary

While numerous large urban areas in the U.S. experience high ambient O_3 concentrations during the warm season, recent modeling efforts indicate that anthropogenic emission sources are the dominant contributor to these ambient concentrations (US EPA, 2012a, section 3.4.3 and Henderson et al., 2012). In the Southeast, Northeast, and North Central, background concentrations were lower in the summer (than in the spring) when measured O_3 concentrations are usually the highest and the 4th highest MDA8 values usually occur. In addition, the GEOS-Chem and CAMx model results suggest that background concentrations on the days with the highest total O_3 concentrations are not dramatically higher than typical seasonal average background concentrations and, therefore, that anthropogenic sources within the U.S. are largely responsible for 4th highest 8-hour daily maximum O_3 concentrations. In areas where background O_3 is highest, such as the western U.S. and at higher elevation sites, the sources contributing to high background concentrations have been identified as wildfires, stratospheric intrusions, and intercontinental transport (US EPA, 2012a, section 3.4.3). As noted above, EPA has policies that allow exclusion of air quality monitoring data affected by these types of events.

1.4. GENERAL APPROACH AND ORGANIZATION OF THIS DOCUMENT

The final PA will identify as broad an array of options for consideration as is supportable by the available scientific evidence and exposure and risk information, recognizing that the final decisions on the O_3 NAAQS will reflect the judgments of the Administrator. In developing that range options for consideration, staff's approach is framed by the series of policy-relevant issues identified in the IRP (US EPA, 2011a, Chapter 3), and as discussed in subsequent chapters of this document. Consistent with the approaches used in previous reviews, the current approach to reviewing the O_3 NAAQS is based most fundamentally on considering the scientific evidence and the results of exposure and risk analyses to inform staff conclusions on the range of policy options that could be supported. The approaches used in previous reviews of the O_3 NAAQS, and the preliminary approaches used in the current review, are discussed in more detail in chapters 4 (primary standard) and 7 (secondary standard), below.

Following this introductory chapter, this first draft PA is organized into two main parts. Chapters 2 through 4 focus on the review of the O_3 primary NAAQS while chapters 5 through 7 focus on the review of the O_3 secondary NAAQS. Staff's preliminary consideration of the scientific evidence and exposure/risk information related to the primary standard are discussed in chapters 2 and 3, respectively. Staff's preliminary conclusions on the adequacy of the current primary O_3 standard are discussed in chapter 4. Staff's preliminary consideration of the scientific evidence and exposure/risk information related to the secondary standard are discussed in chapters 5 and 6, respectively. Staff's preliminary conclusions on the adequacy of the current secondary O_3 standard are discussed in chapter 7.

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2. CONSIDERATION OF THE HEALTH EVIDENCE

In this chapter, we pose the following overarching question:

- **To what extent has scientific information become available that alters or substantiates our understanding of the health effects that occur following short-term or long-term exposures to O_3, and our understanding of the O_3 concentrations at which such effects occur?**

To inform our consideration of this issue, we consider the weight-of-evidence conclusions from the ISA (section 2.1); the scientific evidence linking short-term O_3 exposures to morbidity and mortality (section 2.2); and the scientific evidence linking long-term O_3 exposures to morbidity and mortality (section 2.3). The public health implications of O_3 exposures are discussed in section 2.4 and an integrated discussion of the evidence is provided in section 2.5.

2.1 WEIGHT-OF-EVIDENCE CHARACTERIZATION IN THE ISA

Since the conclusion of the last review, the Agency has developed a more formal framework for reaching causal inferences from the body of scientific evidence. This framework provides the basis for a robust, consistent, and transparent process for evaluating the scientific evidence, including uncertainties in the evidence, and drawing conclusions and causal judgments regarding air pollution-related health effects. The causality framework and the approach to characterizing the weight-of-evidence is discussed briefly below (section 2.1.1) and is described in more detail in the third draft ISA (US EPA, 2012a, Preamble). The ISA weight-of-evidence conclusions for O_3 are summarized in section 2.1.2.

2.1.1 Approach to Characterizing the Weight-of-Evidence

Characterization of the weight-of-evidence in the third draft ISA is based on the evaluation and synthesis of evidence from across scientific disciplines. Three general types of studies inform consideration of weight-of-evidence conclusions for human health effects: controlled human exposure, epidemiologic, and toxicological studies (US EPA 2012a, Preamble). Each of these types of studies has strengths and limitations, as discussed briefly below and in more detail in the third draft ISA (US EPA, 2012a, Preamble).

The most direct evidence in support of a causal relationship between pollutant exposures and human health effects comes from controlled human exposure studies. These experimental studies evaluate the health effects of administered exposures in human volunteers under highly controlled laboratory conditions. Limitations of controlled human exposure studies include generally small sample sizes and short exposure periods; the potential for responses to be

influenced by uncharacterized pollutant exposures in the hours and days preceding the study;[1] and the use of relatively healthy individuals, not representing the most sensitive individuals in the population. Given these limitations, the ISA notes that not observing an effect in controlled human exposure studies does not necessarily mean that a causal relationship does not exist and further concludes that the effects reported in controlled human exposure studies may underestimate the response in certain at-risk populations (US EPA, 2012a, Preamble).

Epidemiologic studies also provide important information on the links between adverse health effects and exposures of human populations to ambient air pollution. These studies have the advantages of allowing the evaluation of more severe health effects than can be studied in controlled human exposure studies (e.g., hospital admissions, premature mortality); the assessment of pollutant-associated effects across a broad population, including particularly at-risk groups within that population; and providing information on real world impacts of pollution exposures, which occur within the context of a complex multi-pollutant atmosphere. Key uncertainties that affect interpretation of epidemiologic studies include the extent to which a particular health outcome is due to the pollutant of interest, as opposed to one or more co-occurring pollutants, and the extent to which exposure measurement error influences associations (US EPA, 2012a, Preamble). Confounding by co-pollutants can result in overestimates in the contribution of a given pollutant to a health effect while exposure error can make it more difficult to detect pollutant-associated effects, even when such effects are present.

The third main type of health effects evidence, animal toxicological studies, provides information on the pollutant's biological action under controlled and monitored exposure circumstances. Understanding the biological mechanisms underlying various health outcomes can prove crucial in establishing or negating causality, particularly in the absence of data from controlled human exposure studies. However, given species differences, there are important uncertainties associated with quantitative extrapolations of reported pollutant-induced pathophysiological alterations between laboratory animals and humans (US EPA, 2012a, Preamble).

In considering available evidence from each of these types of studies, the O_3 ISA draws conclusions within the context of a causality framework with a five-level hierarchy. This framework is used to classify the overall weight-of-evidence into one of the following categories: causal relationship, likely to be a causal relationship, suggestive of a causal relationship, inadequate to infer a causal relationship, and not likely to be a causal relationship

[1]Though in a number of the available O_3 controlled human exposure studies, researchers have addressed this issue by using a randomized, crossover design with each subject serving as their own control (US EPA, 2012a, section 6.2.1.1).

(US EPA 2012a, Preamble Table II). In making such judgments regarding causality, the ISA evaluates several aspects of the evidence including the consistency of effects across studies, the coherence of the evidence across different types of studies, the strength of reported associations,[2] and the biological plausibility of a causal relationship (US EPA, 2012a, Preamble, Table I). Confidence increases that O_3 exposures cause a given health effect as the number of consistently supportive studies increases, as the coherence of the evidence across different types of studies increases, as the strength of the relationship with O_3 increases, and as the support for biological plausibility increases. The ISA also evaluates evidence related to concentration-response and exposure-response relationships in order to inform conclusions on the concentrations at which effects are present. Considerations related to weight-of-evidence conclusions and concentration- and exposure-response relationships are discussed in more detail in the Preamble to the third draft of the O_3 ISA (US EPA, 2012a).

2.1.2 Weight-of-Evidence Conclusions for O_3

In the last review of the O_3 NAAQS, the strongest evidence was for respiratory effects following short-term exposures. The 2006 AQCD concluded that there was clear, consistent evidence of a causal relationship between short-term exposures to O_3 and respiratory health effects (US EPA, 2006). In the current review, in applying the updated causality framework, the ISA draws the following weight-of-evidence conclusions (US EPA 2012a, section 2.5.2):

1. "there is a **causal** relationship between short-term O_3 exposure and respiratory health effects" which include a spectrum of respiratory-related morbidity endpoints and respiratory-related mortality;

2. "there is **likely to be a causal** relationship between short-term O_3 exposures and total mortality";

3. "there is **likely to be a causal** relationship between long-term exposure to O_3 and respiratory health effects" which include respiratory-related morbidity endpoints, including new-onset asthma, and respiratory-related mortality;

4. "the evidence is **suggestive of a causal** relationship between long-term O_3 exposures and total mortality";

5. "the overall body of evidence across disciplines is **suggestive of a causal** relationship for both relevant short- and long-term exposures to O_3 and cardiovascular effects";

6. "the evidence from studies of short- and long-term exposure to O_3 is **suggestive of a causal** relationship between O_3 exposure and central nervous system effects";

[2]The strength of the association refers to the magnitude of the association (i.e., the size of the effect estimate in epidemiologic studies) and its statistical precision.

7. "the evidence is **suggestive of a causal** relationship between long-term exposures to O_3 and reproductive and developmental effects"; and

8. "the evidence is **inadequate** to determine if a causal relationship exists between ambient O_3 exposures and cancer."

The following sections provide an overview of the scientific evidence for the health endpoints linked to short-term (section 2.2) and long-term (section 2.3) O_3 exposures, with a particular focus on studies that evaluate health endpoints judged in the third draft ISA to be caused by, or likely to be caused by, exposures to O_3.

2.2 HEALTH EFFECTS FOLLOWING SHORT-TERM EXPOSURES TO O_3

Given the weight-of-evidence conclusions in the ISA, staff's consideration of health effects linked to short-term O_3 exposures focuses on respiratory effects (section 2.2.1) and all-cause mortality (section 2.2.2). Other effects linked to short-term exposures are also considered, including cardiovascular effects (section 2.2.3) and central nervous system (CNS) and developmental effects (section 2.2.4). In discussing the evidence in this draft PA, although we consider the total body of available evidence of effects following short-term exposures to O_3, we focus the majority of our discussion on the studies that are most likely to inform policy decisions regarding the adequacy of the current standard and potential alternative standards, as discussed in chapter 4.

2.2.1 Respiratory Effects

The ISA concludes that "the clearest evidence for health effects associated with exposure to O_3 is provided by studies of respiratory effects" (US EPA, 2012a, chapter 1, p. 1-5). Collectively, there is a vast amount of evidence spanning several decades that supports a causal association between exposures to O_3 and a continuum of respiratory effects (US EPA, 2012a, section 2.5). The majority of this evidence is derived from studies investigating short-term exposures (i.e., hours to weeks). In this section, we revisit the overarching question of this chapter, as it relates to respiratory effects following short-term O_3 exposures.

In the last review, the 2006 O_3 Air Quality Criteria Document (AQCD) concluded that there was clear, consistent evidence of a causal relationship between short-term exposure to O_3 and respiratory health effects (US EPA, 2006). This causal association was substantiated by the coherence of effects observed across controlled human exposure, epidemiologic, and toxicological studies indicating associations of short-term O_3 exposures with a range of

respiratory health endpoints from respiratory tract inflammation to respiratory emergency department (ED) visits and hospital admissions. Across disciplines, short-term O_3 exposures induced or were associated with statistically significant declines in lung function. An equally strong body of evidence from controlled human exposure and toxicological studies demonstrated O_3-induced inflammatory responses, increased epithelial permeability, and airway hyperresponsiveness. Toxicological studies provided additional evidence for O_3-induced impairment of host defenses. Combined, these findings from experimental studies suggested a mechanism whereby O_3 reacts with lipids and antioxidants in airway epithelial lining fluid and epithelial cell membranes, activating a cascade of events that can lead to oxidative stress, inflammation, and epithelial cell damage in the airways. These experimental and mechanistic results provided support for epidemiologic evidence, in which short-term O_3 exposure was consistently associated with increases in respiratory symptoms and asthma medication use in asthmatic children, respiratory-related hospital admissions, and asthma-related emergency department visits. The combined evidence across disciplines supported a causal relationship between short-term O_3 exposure and respiratory effects (US EPA, 2006).

Consistent with the strong body of evidence presented in the 2006 O_3 AQCD, recent studies continue to support the conclusion that short-term O_3 exposures cause a variety of respiratory effects (US EPA, 2012, sections 2.5, 6.2). As discussed in more detail below, recent controlled human exposure studies report decrements in pulmonary function, increased respiratory symptoms, and increased airway inflammation following exposures of young, healthy adults to O_3 concentrations as low as 60-70 ppb. In addition, a number of recent epidemiologic studies report associations with respiratory hospital admissions and emergency department visits, as well as respiratory-related mortality, across the U.S., Europe, and Canada. This recent evidence is supported by a large body of epidemiologic panel studies reporting associations with respiratory symptoms in children with asthma; by some recent studies reporting O_3-associated increases in indicators of airway inflammation and oxidative stress in children with asthma; by controlled human exposure and animal toxicological studies reporting O_3-induced airway hyperresponsiveness, decreased pulmonary function, allergic responses, lung injury, impaired host defense, and airway inflammation; and by recent evidence indicating that antioxidant capacity may modify the risk of respiratory morbidity associated with O_3 exposures. Together, the ISA judges that the total body of evidence integrated across controlled human exposure, epidemiologic, and toxicological studies, and across the spectrum of respiratory health endpoints, continues to demonstrate that there is a causal relationship between short-term O_3 exposure and respiratory health effects.

The extensive body of evidence supporting a causal relationship between short-term O_3 exposures and adverse respiratory health effects is discussed in detail in the ISA (US EPA, 2012, Chapter 6) and is summarized below for lung function (section 2.2.1.1); pulmonary inflammation and injury (section 2.2.1.2); airway hyperresponsiveness (section 2.2.1.3); respiratory symptoms and medication use (section 2.2.1.4); lung host defense (section 2.2.1.5); hospital admissions and emergency department visits (section 2.2.1.6); and respiratory mortality (section 2.2.1.7).

2.2.1.1 Lung function

In the last review, a large number of controlled human exposure studies had reported O_3-induced lung function decrements in healthy adults engaged in intermittent, moderate exertion following 6.6 hour exposures to O_3 concentrations at or above 80 ppb, while a relatively smaller number of studies had reported effects following exposures to lower concentrations. In addition, epidemiologic panel studies had reported O_3-associated lung function decrements in a variety of different populations likely to experience increased exposures. In the current review, additional controlled human exposure studies are available that have evaluated exposures to O_3 concentrations of 60 or 70 ppb.

In considering the overall body of evidence, the ISA notes that the link between O_3 exposures and changes in lung function has been evaluated in a large number of controlled human exposure studies and epidemiologic studies, as well as in some animal toxicological studies. The majority of controlled human exposure studies of lung function have investigated effects, such as the forced expiratory volume in one second (FEV_1), in young healthy nonsmoking adults (18-35 years of age) (US EPA, 2012, section 6.2.1.1) and during exposures to fixed concentrations of O_3 under carefully regulated environmental conditions and subject activity levels. Epidemiologic studies have evaluated associations between ambient O_3 and lung function in children and adults, including in outdoor working and exercising populations. Controlled human exposure and epidemiologic studies are discussed in detail in section 6.2.1 of the ISA (US EPA, 2012) and are summarized briefly in this section.

<u>Controlled human exposure studies</u>

In assessing controlled human exposure studies of lung function, the ISA considers both group mean changes in lung function and inter-individual variability in such changes (US EPA, 2012, section 6.2.1.1). Consideration of group mean changes is important for discerning whether observed effects are due to O_3 exposures themselves, as opposed to chance alone. Consideration of inter-individual variability in responses is important when assessing the fraction of the population that might experience clinically relevant effects following O_3 exposure (US EPA, 2012, section 6.2.1.1).

In healthy adults, increasing the duration of O_3 exposures and increasing ventilation rates decreases the O_3 exposure concentrations required to impair lung function. Ozone exposure concentrations well above those typically found in ambient air are required to impair lung function in healthy resting individuals, while exposure to O_3 concentrations at or below those in the ambient air have been reported to impair lung function in healthy individuals exposed for longer durations while undergoing intermittent, moderate exertion (US EPA, 2012a, section 6.2.1.1). Figure 6-1 in the ISA summarizes the available evidence from multiple studies evaluating group mean changes in FEV_1 following prolonged O_3 exposures (i.e., 6.6 hours) at moderate levels of physical activity (US EPA, 2012, section 6.2.1.1). With regard to the group mean changes reported in these studies, the ISA specifically notes the following (US EPA, 2012a, section 6.2.1.1, Figure 6-1):

1. Prolonged exposure to 40 ppb O_3 results in a small decrease in group mean FEV_1 that is not statistically different from responses following exposure to filtered air (Adams, 2002; Adams, 2006).
2. Prolonged exposure to an average O_3 concentration of 60 ppb results in group mean FEV_1 decrements ranging from 1.8% to 3.6% (Adams 2002; Adams, 2006;[3] Schelegle et al., 2009; Kim et al., 2011). Based on data from multiple studies, the weighted average group mean decrement was 2.7%. In some analyses, these group mean decrements in lung function were statistically significant (Brown et al., 2008; Kim et al., 2011) while in other analyses, they were not (Adams, 2006; Schelegle et al., 2009).[4]
3. Prolonged exposure to an average O_3 concentration of 70 ppb results in a statistically significant group mean decrement in FEV_1 of about 6% (Schelegle et al., 2009).
4. Prolonged square-wave exposure to average O_3 concentrations of 80 ppb, 100 ppb, or 120 ppb O_3 results in statistically significant group mean decrements in FEV_1 ranging from 6 to 8%, 8 to 14%, and 13 to 16%, respectively (Folinsbee et al., 1988; Horstman et al., 1990; McDonnell et al., 1991; Adams, 2002; Adams, 2003; Adams, 2006).

[3] Adams (2006a); (2002) both provide data for an additional group of 30 healthy subjects that were exposed via facemask to 60 ppb (square-wave) O_3 for 6.6 hours with moderate exercise (V_E = 23 L/min per m^2 BSA). These subjects are described on page 133 of Adams (2006) and pages 747 and 761 of Adams (2002). The FEV_1 decrement may be somewhat increased due to a target V_E of 23 L/min per m^2 BSA relative to other studies with which it is listed having the target V_E of 20 L/min per m^2 BSA. The facemask exposure is not expected to affect the FEV_1 responses relative to a chamber exposure.

[4] Adams (2006) did not find effects on FEV_1 at 60 ppb to be statistically significant. In an analysis of the Adams (2006) data, Brown et al. (2008) addressed the more fundamental question of whether there were statistically significant differences in responses before and after the 6.6 hour exposure period and found the average effect on FEV_1 at 60 ppb to be small, but highly statistically significant using several common statistical tests, even after removal of potential outliers.

As illustrated in Figure 6-1 of the ISA, there is a smooth dose-response curve without evidence of a threshold for exposures between 40 and 120 ppb O_3 (US EPA, 2012a, Figure 6-1). When these data are taken together, the ISA concludes that "mean FEV_1 is clearly decreased by 6.6-h exposures to 60 ppb O_3 and higher concentrations in subjects performing moderate exercise" (US EPA, 2012a, p. 6-9).

Given the considerable inter-individual variability in the FEV_1 response in controlled human exposure studies of O_3 (US EPA, 2012a, section 6.2.1.1), the ISA notes that the interpretation of biologically small group mean decrements requires careful consideration. Specifically, the ISA notes that, even when the group mean FEV_1 decrement is small, some individuals within the group could experience clinically meaningful decrements in lung function. When considering what constitutes a clinically meaningful decrement in lung function, the ISA notes that a 10% FEV_1 decrement is generally accepted as a clinically relevant abnormal response (Dryden et al., 2010) (US EPA, 2012, section 6.2.1.1). In addition, CASAC has previously stated that "[a] 10% decrement in FEV_1 can lead to respiratory symptoms, especially in individuals with pre-existing pulmonary or cardiac disease. For example, people with chronic obstructive pulmonary disease have decreased ventilatory reserve (i.e., decreased baseline FEV_1) such that a ≥10% decrement could lead to moderate to severe respiratory symptoms" (Samet, 2011).

The ISA notes that following prolonged exposures to an average concentration of 60 ppb O_3, the proportion of study subjects with 10% or greater FEV_1 decrements was 20% in Adams (2002), 3% in Adams (2006), 16% in Schelegle et al. (2009), and 5% in Kim et al. (2011). When the results from these studies were combined, the ISA notes that 10% of subjects exposed to an average O_3 concentration of 60 ppb had FEV_1 decrements at or above 10%.[5] In addition, the ISA notes that responses within an individual tend to be reproducible over a period of several months, indicating that inter-individual differences reflect differences in the intrinsic responsiveness. Given this, the ISA concludes that "a considerable fraction" of healthy individuals experience clinically meaningful decrements in lung function when exposed for 6.6 hours to 60 ppb O_3 during intermittent, moderate exertion (US EPA, 2012a, section 6.2.1.1, p. 6-18).

Controlled human exposure studies of O_3-induced lung function decrements suggest that an initial phase of recovery proceeds relatively rapidly following the cessation of O_3 exposure in healthy individuals, with acute decrements resolving within about 2 to 4 hours (Folinsbee and Hazucha, 1989). Residual lung function effects are almost completely resolved within 24 hours.

[5]The ISA also notes that by considering uncorrected responses, 10% is an underestimate of the proportion of healthy individuals that are likely to experience clinically meaningful changes in lung function following exposure for 6.6 hours to 60 ppb O_3 during intermittent moderate exertion (US EPA, 2012, section 6.2.1.1).

In addition, with repeated O_3 exposures over several days, O_3-induced lung function decrements are attenuated (US EPA, 2012a, section 6.2.1.1). Although this attenuation in O_3-induced lung function decrements is correlated with an attenuation of respiratory symptoms, ongoing cellular damage persists as indicated by markers of inflammation and injury (section 2.2.1.2 below and US EPA, 2012a, section 6.2.3).

Epidemiologic studies

Epidemiologic studies have consistently reported that short-term ambient O_3 concentrations are associated with lung function decrements in diverse populations (US EPA, 2012a, section 6.2.1.2), including in groups expected to experience elevated O_3 exposure concentrations and/or with higher exertion levels, such as children attending summer camps and adults exercising or working outdoors, and in groups with pre-existing respiratory diseases such as asthmatic children (US EPA, 2012a, section 6.2.1.2). The ISA notes that, among epidemiologic studies, those that evaluate individuals engaged in outdoor recreation, exercise, or work are more comparable to controlled exposure studies because of improved estimates of O_3 exposures, measurement of lung function before and after discrete periods of outdoor activity, and examination of O_3 effects during exertion when the dose of O_3 reaching the lungs may be higher because of higher ventilation and inhalation of larger volumes of air (US EPA, 2012a, section 6.2.1.2).

Studies of children attending summer camps have provided important insights into the impact of ambient O_3 exposure on respiratory effects in young, healthy children. These studies have been noted for their on-site measurement of ambient O_3 and daily assessment of lung function by trained staff (US EPA, 2012a, section 6.2.1.2). In groups mostly comprising healthy children (ages 7-17 years), lung function decrements, as measured by within subject changes in FEV_1 and peak expiratory flow (PEF), have been consistently reported to be associated with ambient O_3 concentrations averaged over the 1-8 hours preceding lung function measurement (US EPA, 2012a, Figure 6-3 and Table 6-3). For FEV_1, group mean decrements ranged from approximately 0.3% to 2.2% per 40 ppb increase in 1-hour O_3 concentrations (US EPA, 2012a, Table 6-3). In most cases, associations between O_3 and lung function were statistically significant (US EPA, 2012a, Figure 6-3, Table 6-3). Maximum 1-hour O_3 concentrations in these studies ranged from 95 ppb to 245 ppb (US EPA, 2012a, Table 6-2). In the one study that specifically evaluated different ranges of ambient O_3 concentrations (Spektor et al., 1988a), associations with lung function decrements remained statistically significant when the analysis was restricted to 1-hour O_3 concentrations below 60 ppb (US EPA, 2012a, Table 6-6).

Similar to the camp studies discussed above, studies of individuals exercising outdoors have evaluated subjects over days with a wide range in ambient O_3 concentrations and have used

onsite assessment of O_3 exposures during discrete periods of outdoor exercise. Collectively, these studies report that ambient O_3 concentrations are associated with small (< 1% to 4% per standardized increment in O_3[6]) group mean decrements in lung function in adults and children during exercise of variable duration and intensity (US EPA, 2012a, Figure 6-4 and Table 6-4). Most of these associations were statistically significant and, in studies that presented analyses restricted to O_3 concentrations below 61 ppb (Brunekreef et al., 1994) or below 80 ppb (Spektor et al., 1988b) , associations with lung function decrements remained (though associations in the restricted analysis of Brunekreef were no longer statistically significant) (US EPA, 2012a, Table 6-6). In addition, when Korrick et al. (1998) restricted their analyses to 2-12 hour O_3 concentrations greater than 40 ppb (maximum concentration was 74 ppb), O_3 was associated with larger lung function decrements than in their analysis encompassing the full distribution of O_3 concentrations (US EPA, 2012a, Table 6-6).[7]

In addition to the camp studies and the outdoor exercise studies, studies of outdoor workers have also consistently reported that ambient O_3 concentrations are associated with decrements in lung function (US EPA, 2012a, section 6.2.1.2, Figure 6-5, Table 6-5). Although most of these studies assessed O_3 exposures using central site measurements, they were noteworthy for the long periods of time spent outdoors (6-14 hours) and because associations with lung function decrements were reported for time periods with relatively low ambient O_3 concentrations (Chan and Wu, 2005; Brauer et al., 1996; Hoppe et al., 1995) (US EPA, 2012a, section 6.2.1.2, Figure 6-5, Table 6-1).[8] In the study by Brauer et al. (1996), associations between ambient O_3 and lung function decrements remained statistically significant in analyses restricted to maximum hourly concentrations below 40 ppb. Similar to other outdoor exposure studies, group mean O_3-associated lung function decrements in outdoor workers were relatively small (>1% to 3.6% per standardized increment in O_3 concentration) (US EPA, 2012a, section 6.2.1.2).

The majority of the epidemiologic studies discussed above were not specifically focused on populations with respiratory diseases such as asthma. Epidemiologic studies of children and adults with respiratory disease provide additional support for the link between exposure to ambient O_3 and lung function decrements. Although these studies typically rely on central site monitoring and self-administered lung function tests, they provide important information on

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[6] Effect estimates are standardized to a 40 ppb increase in O_3 concentrations averaged over 1-hour or less and to a 30 ppb increase in O_3 concentrations averaged over 12 hours (US EPA, 2012a, Table 6-3).

[7] Ozone averaging times ranged from 10 minutes to 2.4 hours in Brunekreef et al. (1994), were 30-minutes in Spektor et al. (1988b), and ranged from 2 to 12 hours in Korrick et al. (1988) (US EPA, 2012a, Table 6-4).

[8] The maximum reported 8-hour concentration in the study by Chan and Wu (2005) was 65 ppb. In the other studies, maximum 1-hour (Brauer et al., 1996) and 30-minute (Hoppe et al., 1995) concentrations were 84 ppb and 77 ppb, respectively (US EPA, 2012a, Table 6-2). Maximum 8-hour concentrations in these studies would have been lower.

factors that may confer increased susceptibility to the respiratory effects of O_3 exposures (US EPA, 2012a, section 6.2.1.2).

Collectively, the large body of evidence for O_3-associated lung function decrements in asthmatic children, which includes two U.S. multi-city studies (Mortimer et al., 2000; Mortimer et al., 2002; O'Connor et al., 2008), demonstrates that increases in ambient O_3 exposure are associated with decrements in lung function in asthmatic children and with increases in the percent of asthmatic children who experience clinically significant lung function decrements (US EPA, 2012a, section 6.2.1.2, Figures 6-6 and 6-7, Tables 6-7 and 6-8). Such associations have been reported to persist even when analyses are restricted to days with relatively low ambient O_3 concentrations (i.e., to 8-hour concentrations below 80 ppb in Mortimer et al., 2002[9]). With regard to inter-individual variability, Mortimer et al. (2002) reported that for a 30 ppb increase in 8-hour O_3 concentrations, there was a 30% increase in the incidence of PEF decrements greater than 10%. In addition, Hoppe et al. (2003) reported that 47% of asthmatic children experienced lung function decrements greater than 10% on days with 30-minute maximum O_3 concentrations greater than 50 ppb, relative to days with 30-minute maximum concentrations less than 40 ppb.

Epidemiologic studies have reported that O_3-associated lung function decrements may be clinically significant in asthmatic children, based on concurrent increases in respiratory symptoms (section 2.2.1.4, below). Similar lung function decrements have been reported in studies evaluating children without respiratory disease but without concurrent increases in respiratory symptoms. Because of the higher overall lung function, the decrements may not be large enough to be clinically significant in healthy children (section 2.2.1.4 below; US EPA, 2012a, section 6.2.1.2).

A number of epidemiologic studies of O_3-associated decrements in lung function have evaluated the impacts of potential confounders, including temperature, pollen, and co-occurring pollutants. Available studies have consistently reported that associations between O_3 and decrements in lung function are not driven by the effects of either temperature or pollen (US EPA, 2012a, section 6.2.1.2). With regard to co-pollutants, several studies have reported low co-pollutant concentrations or the lack of associations between co-pollutants and lung function decrements, suggesting that co-pollutants were not responsible for reported associations with O_3. Other studies have evaluated statistical models that include co-pollutants such as $PM_{2.5}$, PM_{10}, sulfate, NO_2 and/or SO_2.

[9]The 80 ppb cutoff in the restricted analysis is by Mortimer et al. (2002) reflects O_3 concentrations averaged across multiple monitors.

Among studies that have evaluated co-pollutant models, associations between O_3 and lung function decrements generally remained robust, though results have been somewhat variable for co-pollutant models that include sulfate (US EPA, 2012a, section 6.2.1.2, Figure 6-9, Table 6-14). In one study (Neas et al., 1999), the association with O_3 was attenuated in a co-pollutant model that included sulfate, while another study (Thurston et al., 1997) reported a larger O_3-associated decrement in lung function when sulfate was included in the model. In the study by Thurston (1997), when a single influential day was removed (a day when both sulfate and O_3 were at their peaks), the sulfate effect was attenuated while the O_3 effect remained robust. Several studies did not provide quantitative results from co-pollutant models but reported that O_3 effects on lung function remained statistically significant in models that included PM_{10}, sulfate, NO_2, nitrate, or ammonium (US EPA, 2012a, section 6.2.1.2).

2.2.1.2 Pulmonary inflammation and injury

As discussed in detail in the ISA (US EPA, 2012a, section 6.2.3), O_3 exposure can increase respiratory tract inflammation. In the last review, controlled human exposure studies reported O_3-induced airway inflammation following exposures at or above 80 ppb. In the current review, additional epidemiologic studies, as well as a controlled human exposure study conducted following exposures to 60 ppb O_3, are also available.

Inflammation is a host response to injury and the induction of inflammation is evidence that injury has occurred. The link between O_3 exposures and inflammation and injury has been evaluated in controlled human exposure studies, epidemiologic studies, and animal toxicological studies. Controlled human exposure studies have generally been conducted in healthy individuals or asthmatics and have evaluated one or more indicators of inflammation, including neutrophil (PMN) influx, increased permeability of the respiratory epithelium, and/or prevalence of proinflammatory cytokines (US EPA, 2012a, section 6.2.3.1). Epidemiologic studies have generally evaluated associations between ambient O_3 and markers of inflammation and/or oxidative stress, which has been reported to play a key role in initiating and sustaining inflammation (US EPA, 2012a, section 6.2.3.2). These two types of studies are discussed in detail in the ISA (US EPA, 2012a, section 6.2.3) and are summarized briefly below.

<u>Controlled human exposure studies</u>

Short-term exposures to O_3 concentrations at or above typical ambient concentrations (i.e., 60 ppb to 400 ppb) result in inflammation and tissue damage in the respiratory tract, as indicated by a variety of endpoints including PMN influx, increased epithelial permeability, and elevated levels of proinflammatory markers (US EPA, 2012a, section 6.2.3.1). As with lung function, inflammatory responses to O_3 are generally reproducible within an individual and some

individuals (e.g., asthmatics) appear to be intrinsically more at-risk than others. Unlike O_3-induced decrements in lung function, which are attenuated following repeated exposures over several days (US EPA, 2012a, section 6.2.1.1), some markers of O_3-induced inflammation and tissue damage remain elevated during repeated exposures, indicating ongoing damage to the respiratory system (US EPA, 2012a, section 6.2.3.1).

Many of the controlled human exposure studies evaluating O_3-induced inflammation have used O_3 concentrations above those typically found in the ambient air in the United States (e.g., 200 to 400 ppb). However, a few studies have reported increases in markers of respiratory inflammation following exposures to relatively low O_3 concentrations. In a recent study, Kim et al. (2011) reported a statistically significant increase in sputum neutrophil levels following a 6.6-hour exposure to 60 ppb O_3 in young healthy adults engaged in intermittent, moderate exertion. Other studies (Devlin et al., 1991; Alexis et al., 2010) have reported increases in inflammatory markers following 6.6-hour exposures to 80 ppb O_3 in healthy adults (US EPA, 2012a, 6.2.3.1), though one of these studies (Alexis et al., 2010) did not use a filtered air control.

Epidemiologic studies

In the 2006 O_3 AQCD (US EPA, 2006), epidemiologic evidence for O_3-associated changes in pulmonary inflammation was limited. Since 2006, as a result of the development of less invasive methods, the number of studies assessing ambient O_3-associated changes in airway inflammation and oxidative stress has increased. Most of these recent studies have evaluated biomarkers of inflammation or oxidative stress[10] in exhaled breath, nasal lavage fluid, or induced sputum. As noted in the ISA, these recent studies form a larger body of evidence to help establish coherence with findings from controlled human exposure and animal toxicological studies that have measured similar or related endpoints and provide further biological plausibility for associations of ambient O_3 exposure with other effects such as respiratory symptoms. However, important uncertainties limit the interpretation of recent biomarker studies, including uncertainty regarding the clinical relevance of observed changes in biomarker levels. In addition, the limited available information on the time course of changes in biomarker levels, on the subject factors that contribute to inter-individual variability, and on standardized sample collection approaches contributes to differences among study results (US EPA, 2012a, section 6.2.3.2).

While epidemiologic studies have reported mixed results when evaluating associations between ambient O_3 concentrations and different markers of oxidative stress or inflammation

[10]As discussed in the ISA (US EPA, 20112a, section 6.2.3.2), oxidative stress has been used as an indicator of pulmonary inflammation in epidemiologic studies.

(US EPA, 2012a, section 6.2.3.2, Figure 6-10, Tables 6-15, 6-16, and 6-17), these studies do provide some insight into the mechanism of O_3-induced inflammation. With regard to mechanism, in a study in Mexico City, O_3-associated increases in pulmonary inflammation were attenuated with higher antioxidant intake (Sienra-Monge et al., 2004). This result suggests that inhaled O_3 may be an important source of reactive oxygen species in airways and may increase airway inflammation via oxidative stress mediated mechanisms. In addition, though results of epidemiologic studies have been mixed, a study conducted in Mexico reported associations between O_3 and markers of airway inflammation with 8-hour O_3 concentrations at or below about 61 ppb (Romieu et al., 2008) (US EPA, 2012a, Table 6-17).

The clinical significance of O_3-induced increases in oxidative stress and inflammation is supported by the small number of studies that have correlated O_3-associated inflammation with other endpoints, including respiratory symptoms. In subjects with asthma, ambient O_3 exposure was associated with increases in markers of oxidative stress and inflammation that were accompanied by a concomitant increase in cough (Barraza-Villarreal et al., 2008) and by a decrease in a quality of life score (Khatri et al., 2009). These findings, though limited, support the clinical relevance of O_3-associated airway inflammation in asthmatics.

2.2.1.3 Airways hyperresponsiveness

Airway hyperresponsiveness refers to a condition in which the conducting airways undergo enhanced bronchoconstriction in response to a variety of stimuli (US EPA, 2012a, section 6.2.2). Increased airway responsiveness is an important consequence of exposure to ambient O_3 because the airways are then predisposed to narrowing upon inhalation of a variety of ambient stimuli including specific allergens, SO_2, and cold air. Asthmatics often exhibit increased airway responsiveness at baseline relative to healthy controls, and they can experience further increases in responsiveness following exposures to O_3 (US EPA, 2012a, section 6.2.2.1).

Airway responsiveness is often quantified by measuring changes in pulmonary function following the inhalation of an aerosolized allergen or a nonspecific bronchoconstricting agent (e.g., methacholine) or following exposure to a bronchoconstricting stimulus such as cold air. In the last review, controlled human exposure studies reported that exposures to O_3 concentrations at or above 80 ppb increased airway responsiveness in human subjects, as indicated by a reduction in the concentration of specific (e.g., ragweed) and non-specific (e.g., methacholine) agents required to produce a given reduction in lung function (e.g., as measured by FEV_1 or specific airway resistance) (US EPA, 2012a, section 6.2.2.1). Horstman et al. (1990) reported increased airway responsiveness in healthy volunteers following 6.6 hour exposures to O_3 concentrations at or above 80 ppb (subjects engaged in intermittent, moderate exertion).

A number of animal toxicology studies, including some recent studies conducted since the last review, provide support for the O_3-induced airway hyperresponsiveness reported in humans (US EPA, 2011, section 6.2.2.2). Although most of these studies evaluated O_3 concentrations above those typically found in ambient air in cities in the United States (i.e., most studies evaluated O_3 concentrations of 100 ppb or greater), one study reported that a very low exposure concentration (50 ppb for 4 hours) induced airway hyperresponsiveness in some rat strains, suggesting a genetic component (Depuydt et al., 1999). Additional rodent studies have reported O_3-induced airway hyperresponsiveness following exposures to O_3 concentrations from 100 to 500 ppb (Johnston et al., 2005; Chhabra et al., 2010; Larsen et al., 2010). In characterizing the relevance of these exposure concentrations, the ISA noted that a study using radiolabeled O_3 suggests that even very high O_3 exposure concentrations in rodents could be equivalent to much lower exposure concentrations in humans. Specifically, a 2000 ppb (2 ppm) O_3 exposure concentration in resting rats was reported to be roughly equivalent to a 400 ppb exposure concentration in exercising humans (Hatch et al., 1994). Given this relationship, the ISA noted that animal data obtained in resting conditions could underestimate the risk of effects for humans, though the ISA also cautioned that there are important limitations in the approach used in this study, leading to uncertainty in such interspecies comparisons (US EPA, 2012a, section 5.5.1).

Changes in airway responsiveness after O_3 exposure appear to resolve more slowly than changes in FEV_1 or respiratory symptoms (e.g., 18 to 24 hours, though longer in some individuals, as reported in Folinsbee and Hazucha (1989, 2000)) and tend to be somewhat less likely to attenuate with consecutive exposures (Gong et al., 1997; Folinsbee et al., 1994; Kulle et al., 1982; Dimeo et al., 1981) (US EPA, 2012a, section 6.2.2.1). In animal studies a 3-day continuous exposure resulted in attenuation of O_3-induced airway hyperresponsiveness (Johnston et al., 2005) while repeated exposures for 2 hours per day over 10 days did not (Chhabra et al., 2010), suggesting that attenuation could be lost when repeated exposures are interspersed with periods of rest (US EPA, 2012a, section 6.2.2.2). Studies reporting increased airway responsiveness after O_3 exposure contribute to a plausible link between ambient O_3 exposure and increased respiratory symptoms in asthmatics, and increased hospital admissions and emergency department visits for asthma (see below and US EPA, 2012a, section 6.2.2).

2.2.1.4 Respiratory symptoms and medication use

Because respiratory symptoms are associated with limitations in activity and are the primary reason for using asthma medication and seeking medical care, studies evaluating the link between O_3 exposures and such symptoms allow a characterization of the clinical and public health significance of ambient O_3 exposure (US EPA, 2012a, section 6.2.4). The link between

subjective respiratory symptoms and O_3 exposures has been evaluated in both controlled human exposure and epidemiologic studies. In the last review, controlled human exposure studies reported statistically significant increases in respiratory symptoms following exposures to O_3 concentrations at or above 80 ppb, with non-significant increases reported following exposures to lower concentrations. In addition, epidemiologic studies reported associations between ambient O_3 and respiratory symptoms in a variety of locations and populations, including asthmatic children living in U.S. cities. In the current review, additional controlled human exposure studies have evaluated respiratory symptoms following exposures to O_3 concentrations below 80 ppb and recent epidemiologic studies have evaluated associations with respiratory symptoms. These studies are discussed in detail in the ISA (US EPA, 2012a, sections 6.2.1 and 6.2.4) and summarized briefly below.

Controlled human exposure studies

In controlled human exposures studies, statistically significant increases in respiratory symptoms have been consistently reported in healthy volunteers engaged in intermittent, moderate exertion following 6.6 hour exposures to average O_3 concentrations at or above 80 ppb (Adams, 2003; Adams, 2006; Schelegle et al., 2009). In addition, Schelegle et al. (2009) reported a statistically significant increase in respiratory symptoms following 6.6 hour exposures to an average O_3 concentration of 70 ppb. In contrast, increased respiratory symptoms following exposures to O_3 concentrations below 70 ppb have not been consistently reported. Adams (2006) reported an increase in respiratory symptoms in healthy volunteers during a 6.6 hour exposure protocol with an average O_3 exposure concentration of 60 ppb. With one of the exposure protocols tested in this study (i.e., the triangular exposure protocol), the increase in symptoms was significantly different from initial respiratory symptoms but not from filtered air controls. Neither Schelegle et al. (2009) nor Kim et al. (2011) reported a statistically significant increase in respiratory symptoms following exposures to 60 ppb O_3, though Schelegle reported a non-significant trend toward increased symptoms.

Epidemiologic studies

In epidemiologic studies, respiratory symptom data are typically self-reported by subjects or their parents. Such symptom diaries are a convenient and useful tool for collecting individual-level data from a large number of subjects. However, several limitations of this approach are well-recognized, including recall error, differences among subjects in the interpretation of symptoms, and biased reporting between participants with and without asthma. Most of these limitations are sources of random error that can bias effect estimates to the null or increase the uncertainty around effect estimates. Most epidemiologic studies of O_3 and respiratory symptoms

have been conducted in children and/or adults with asthma, with fewer studies, and less consistent results, in non-asthmatic populations.

Single-city and multi-city epidemiologic studies have generally reported positive associations between ambient O_3 concentrations and respiratory symptoms and medication use in children with asthma (US EPA, 2012a, Figures 6-11, 6-12; Tables 6-19, 6-20). The ISA concludes that the epidemiologic evidence clearly demonstrates that short-term ambient O_3 exposure is associated with increases in respiratory symptoms and asthma medication use in asthmatic children, with a smaller body of literature also supporting such associations in asthmatic adults (US EPA, 2012a, section 6.2.4.2). In studies that evaluated the potential for confounding by meteorological factors, pollen counts, or co-pollutants, associations with O_3 remained robust (US EPA, 2012a, Table 6-25), though disentangling the independent effects of O_3 exposure in these studies is complicated due to the high correlations observed between pollutants and the different averaging times and lags of exposure examined for co-pollutants (US EPA, 2012a, section 6.2.4.4). The consistency of associations among individuals with asthma, with and without adjustment for co-pollutants, combined with evidence from controlled human exposure studies for the direct effects of O_3 exposure (see above), provide substantial evidence for the independent effects of ambient O_3 exposure on increases in respiratory symptoms (US EPA, 2012a, section 6.2.4.5). Multi-city and single-city epidemiologic studies are discussed in detail in the ISA (US EPA, 2012a, section 6.2.4) and summarized briefly below.

A multi-city study by Mortimer et al. (2002) reported a positive and statistically significant association between O_3 and morning asthma symptoms in children across eight U.S. communities. This association remained positive and statistically significant when the analysis was restricted to 8-hour O_3 concentrations below 80 ppb.[11] In co-pollutant models that included SO_2, NO_2, or PM_{10}, the association between O_3 and respiratory symptoms remained positive, though not statistically significant. The ISA notes that the interpretation of these co-pollutant models is complicated because of the different averaging times and lags of exposure examined for O_3 and co-pollutants (US EPA, 2012a, section 6.2.4.4).

Other multi-city studies conducted in the United States and North America have reported mixed results in asthmatic children. Specifically, Schildcrout et al. (2006) reported positive associations with respiratory symptoms across nine North American cities, though these associations were not statistically significant. Schildcrout did not report an association with medication use. In addition, O'Connor et al. (2008) reported both positive and negative associations with wheeze and nighttime asthma, respectively, in seven U.S. communities. These

[11]The 80 ppb cutoff in the restricted analysis is by Mortimer et al. (2002) reflected O_3 concentrations that were averaged across multiple monitors.

associations were not statistically significant (US EPA, 2012a, section 6.2.4; Figures 6-11, 6-12; Tables 6-19, 6-20).

Single-city studies conducted in the United States generally reported associations with symptoms and/or medication use that were positive, but not statistically significant, in asthmatic children (US EPA, 2012a, Figures 6-11, 6-12; Tables 6-19, 6-20). For associations in locations with relatively low ambient O_3 concentrations, positive associations with respiratory symptoms were statistically significant in a cool-season study by Rabinovitch et al. (2004) (maximum 1-hour concentration was 70 ppb) and not statistically significant in a study by Delfino et al. (2003) (maximum 1-hour concentration was 52 ppb). In addition to these studies conducted in the United States, a study conducted in Amsterdam, with a maximum 8-hour O_3 concentration of 57 ppb during the study period, reported a positive and statistically significant association between O_3 concentrations and upper respiratory symptoms and a positive, but not statistically significant, association with medication use (Gielen, et al., 1997) (US EPA, 2012a, Figures 6-11, 6-12; Tables 6-19, 6-20).

A relatively small number of epidemiologic studies have evaluated associations with respiratory symptoms and/or activity levels in adults with respiratory disease (US EPA, 2012a, section 6.2.4.2). In Los Angeles, Eiswerth et al. (2005) reported that increased O_3 concentrations were associated with lower probabilities of participating in both indoor and outdoor activities, though only the association with indoor activities was statistically significant. Khatri et al. (2009) reported that an increase in ambient O_3 concentrations was associated with lower scores on a quality of life assessment that characterizes symptoms, mood, and activity limitations. In a panel study of asthmatic adults and children, conducted in an area with relatively low concentrations of O_3 and aeroallergens (i.e., in East Moline, Illinois, with a maximum 8-hour O_3 concentration of 78 ppb), O_3 was associated with increased morning and evening respiratory symptoms (Ross et al., 2002). These associations remained statistically significant with adjustment for weather and aeroallergens.

2.2.1.5 Lung host defense

The mammalian respiratory tract has a number of closely integrated defense mechanisms that, when functioning normally, provide protection from the potential health effects attributed to exposure to a wide variety of inhaled particles and microbes. The previous O_3 AQCD (US EPA, 2006) concluded that animal toxicological studies provided evidence that acute O_3 exposures as low as 80 to 500 ppb can increase susceptibility to infectious diseases due to modulation of lung host defenses. A few recent studies have added to this body of evidence, which includes controlled human exposure and/or animal toxicological evidence for O_3 effects on mucociliary clearance, alveolar macrophage functioning, and effects on infection and adaptive immunity (US

EPA, 2012a, section 6.2.5). Of the immune-related effects with clear functional implications, only impaired alveolar macrophage functioning and increased susceptibility to bacterial infections have been reported following exposures to O_3 concentrations near the level of the current O_3 standard.

With regard to macrophage function, a controlled human exposure study reported decrements in the ability of alveolar macrophages to phagocytize yeast following 6.6 hour exposures of healthy adult volunteers undergoing intermittent, moderate exertion to O_3 concentrations from 80 to 100 ppb (Devlin et al., 1991). In addition, 2-hour exposures of rabbits to 100 ppb O_3 was reported to inhibit phagocytosis while a 3-hour exposure to 250 ppb decreased lysosomal enzyme activities (Driscoll et al., 1987; Hurst et al., 1970). Alveolar macrophages from rats exposed to 100 ppb O_3 for 1 or 3 weeks exhibited reduced hydrogen peroxide production (Cohen et al., 2002).

With regard to susceptibility to bacterial infections, the ISA notes (US EPA, 2012a, section 6.2.5.4) that in animal models of bacterial infection, exposure to 80 ppb O_3 has been reported to increase streptococcus-induced mortality, regardless of whether O_3 exposure precedes or follows infection (Miller et al., 1978; Coffin and Gardner, 1972; Coffin et al., 1967). Although increases in mortality were due to the infectious agent, thereby reflecting an O_3-induced functional impairment of host defenses, results have been inconsistent across species. For example, although both mice and rats exhibit impaired bactericidal macrophage activity after O_3 exposure, mortality due to infection is only observed in mice. In addition, although mice and humans share many host defense mechanisms, there is little compelling evidence from epidemiologic studies to suggest an association between O_3 exposures and decreased resistance to bacterial infection (US EPA, section 6.2.7).

2.2.1.6 Hospital admissions and emergency department visits

The 2006 O_3 AQCD (US EPA, 2006) identified a number of epidemiologic studies reporting positive associations between ambient O_3-exposures and increased respiratory hospital admissions and emergency department visits. Overall, the AQCD concluded that these studies provided evidence of a causal relationship between short-term ambient ozone exposures and increased respiratory morbidity during the warm season (US EPA, 2012a, section 6.2.7.1). A number of recent studies conducted in the United States, Canada, Europe, and Asia provide additional support for O_3-associated increases in both hospital admissions and emergency department visits for respiratory outcomes (US EPA 2012a, section 6.2.7, Figures 6-18 and 6-19). Consistent with studies available in the last review, recent studies have reported stronger associations during the warm season than the cold season (US EPA, 2012a, Figure 6-18, Table 6-28) and that O_3 effect estimates remained relatively robust upon the inclusion of PM and gaseous

co-pollutants in two-pollutant models (US EPA, 2012a, Figure 6-19; Table 6-29 and section 6.2.7.5).

This section discusses multi-city and single-city studies that have evaluated the relationship between O_3 and respiratory-related hospital admissions and emergency department visits (US EPA, 2012a, section 6.2.7). In the majority of these studies, all respiratory-related admissions or emergency department visits have been evaluated, though several recent studies have evaluated cause-specific endpoints, including admissions or emergency department visits for COPD, asthma, and pneumonia. This section is divided by endpoint into discussions of hospital admissions for all respiratory causes, cause-specific hospital admissions, emergency department visits for all respiratory causes, and cause-specific emergency department visits.

Hospital admissions for all respiratory causes

The APHENA study (APHENA is for Air Pollution and Health: A European and North American Approach) analyzed air pollution and health outcome data from existing Canadian, European, and U.S. multi-city studies and examined the influence of varying model specification to control for season and weather (Katsouyanni et al., 2009). The U.S.-based portion of the APHENA study utilized the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) cohort which, for the Katsouyanni et al. (2009) analysis, comprised respiratory hospital admissions among individuals 65 years of age and older from 14 US cities with O_3 data from 1985-1994 (7 cities had summer only O_3 data). For the year round analysis, Katsouyanni et al. (2009) reported consistently positive, and statistically significant in models with 8 degrees of freedom per year (US EPA, 2012a, section 6.2.7.2), associations between 1-hour O_3 concentrations and respiratory hospital admissions across the datasets from the U.S., Canada, and Europe (US EPA 2012a, Figure 6-14).[12] In co-pollutant models adjusting for PM_{10}, O_3 effect estimates remained positive, though effect estimates were somewhat attenuated in the U.S. and European datasets, possibly due to the PM sampling schedule (US EPA 2012a, Figure 6-14). Effect estimates for the warm season were larger than for the year-round analysis in the Canadian dataset, but generally similar in magnitude to the year-round analysis in the U.S. and European datasets.

Several additional multicity studies examined respiratory disease hospital admissions in Canada and Europe. Cakmak et al. (2006) reported a statistically significant increase in respiratory hospital admissions in 10 Canadian cities (4.4% increase per 20 ppb increase in 24-

[12]The study by Katsouyanni et al. (2009) evaluated different statistical models. Although the investigators did not identify the model they deemed to be the most appropriate for comparing the results across study locations, they did specify that "overall effect estimates (i.e., estimates pooled over several cities) tended to stabilize at high degrees of freedom" (Katsouyanni et al., 2009). In discussing of the results of this study, the ISA focused on models with 8 degrees of freedom per year (US EPA, 2012a, section 6.2.7.2).

hour average O_3, 95% CI: 2.2, 6.5%). In analyses of potential effect modifiers of the O_3-respiratory hospital admission relationship, individuals with an education level less than the 9th grade were found to be at greater risk. Dales et al. (2006) reported a 5.4% (95% CI: 2.9, 8.0%) increase in neonatal respiratory hospital admissions for a 20 ppb increase in 24-h avg O_3 concentrations in 11 Canadian cities from 1986 to 2000. In contrast, Biggeri et al. (2005) did not detect an association between short-term O_3 exposure and respiratory hospital admissions in four Italian cities from 1990 to 1999.

In addition to the large multi-city studies discussed above, several smaller-scale studies have also reported associations with total respiratory hospital admissions. Specifically, Lin et al. (2008) reported a positive association between O_3 and pediatric (i.e., <18 years) respiratory admissions, though results were not presented quantitatively, in an analysis of 11 geographic regions in New York state from 1991 to 2001. In co-pollutant models with PM_{10}, the authors reported that region-specific O_3 associations with respiratory hospital admissions remained relatively robust. A recent study (Neidell, 2009; Neidell and Kinney, 2010) conducted in Southern California reported positive and statistically significant O_3 effect estimates for children, working age adults, and older adults. This study reported that controlling for avoidance behavior on days with O_3 alerts increases O_3 effect estimates for respiratory hospital admissions in children and older adults, providing preliminary evidence that epidemiologic studies may underestimate associations between O_3 exposure and health effects by not accounting for behavioral modification when public health alerts are issued.

<u>Cause-specific hospital admissions</u>

With regard to cause-specific respiratory outcomes, the limited evidence available in the last review indicated that the strongest findings were for ambient O_3 associated asthma and chronic obstructive pulmonary disease (COPD) respiratory hospital admissions (US EPA 2012a, 6.2.7.2). Since the last review, a few additional studies have investigated cause-specific respiratory admissions (i.e., COPD, asthma, pneumonia) in relation to O_3 exposure (Medina-Ramon et al, 2006; Yang et al., 2005; Zanobetti and Schwartz, 2006; Silverman and Ito, 2010).

With regard to COPD, Medina-Ramon et al. (2006) examined the association between short-term ambient O_3 concentrations and Medicare hospital admissions among individuals ≥ 65 years of age for COPD in 35 cities in the U.S. for the years 1986-1999. The authors reported a 1.6% increase (95% CI: 0.48, 2.9%) in COPD admissions for lag 0-1 in the warm season for a 30 ppb increase in 8-h max O_3 concentrations. The authors found no evidence for such associations in cool season or in year round analyses. In a co-pollutant model with PM_{10}, the association between O_3 and COPD hospital admissions remained robust. In a single-city study conducted in Vancouver from 1994-1998, a location with low ambient O_3 concentrations (US

EPA, 2012a, Table 6-26), Yang et al. (2005) reported a statistically non-significant 8.8% (95% CI: -12.5, 32.6%) increase in COPD admissions per 20 ppb increase in 24-hour average O_3 concentrations. In two-pollutant models with every-day data for NO_2, SO_2, CO, and PM_{10}, O_3 risk estimates remained robust, though not statistically significant (US EPA, 2012a, Figure 6-19; Table 6-29). In addition, Wong et al. (2009) reported increased O_3-associated COPD admissions during periods of increased influenza activity in Hong Kong.

The ISA assessed a study that evaluated asthma-related hospital admissions in New York City (US EPA, 2012a, section 6.2.7.2) (Silverman and Ito, 2010). This study examined the association of 8-hour maximum O_3 concentrations with severe acute asthma admissions (i.e., those admitted to the Intensive Care Unit [ICU]) during the warm season in the years 1999 through 2006 (Silverman and Ito, 2010)). The investigators reported positive associations between O_3 and ICU asthma admissions for the 6- to 18-year age group (26.8% [95% CI: 1.4, 58.2%] for a 30 ppb increase in maximum 8-hour average O_3 concentrations, but little evidence of associations for the other age groups examined (<6 years, 19-49, 50+, and all ages). However, positive associations were observed for each age-stratified group and all ages for non-ICU asthma admissions, but again the strongest association was reported for the 6- to 18-years age group (28.2% [95% CI: 15.3, 41.5%]; lag 0-1). In two-pollutant models, O_3 effect estimates for both non-ICU and ICU hospital admissions remained robust to adjustment for $PM_{2.5}$. In an additional analysis, using a smooth function, the authors examined whether the shape of the concentration-response curve for O_3 and asthma hospital admissions (i.e., both general and ICU for all ages) is linear. When comparing the curve to a linear fit line, the authors found that the linear fit was a reasonable approximation of the concentration-response relationship between O_3 and asthma hospital admissions, but the limited data density at relatively low O_3 concentrations contributes to uncertainty in the shape of the concentration-response relationship at the low end of the distribution of O_3 concentrations (US EPA, 2012a, Figure 6-15).

In contrast to COPD and asthma, the evidence for pneumonia-related admissions was less consistent. Medina-Ramon et al. (2006) examined the association between short-term ambient O_3 concentrations and Medicare hospital admissions among individuals ≥ 65 years of age for pneumonia. The authors reported an increase in pneumonia hospital admissions in the warm season (2.5% [95% CI: 1.6, 3.5%] for a 30 ppb increase in 8-h max O_3 concentrations, with no evidence of an association in the cool season or year round. In two-pollutant models restricted to days for which PM_{10} data was available, the association between O_3 exposure and pneumonia hospital admissions remained robust. In contrast, Zanobetti and Schwartz (2006) reported a 6.0% (95% CI: -11.1, -1.4%) decrease in pneumonia admissions for a 20 ppb increase in 24-h average O_3 concentrations in Boston for the average of lags 0 and 1.

Emergency department visits for all respiratory causes

A large single-city study conducted in Atlanta by Tolbert et al. (2007), and subsequently reanalyzed by Darrow et al. (2011) using different air quality data and evaluating associations with different metrics, provides evidence for associations between short-term exposures to ambient O_3 concentrations and respiratory emergency department visits. Tolbert et al. (2007) reported a 3.9% (95% CI: 2.7, 5.2%) increase in respiratory emergency department visits for a 30 ppb increase in 8-h max O_3 concentrations during the warm season. In copollutant models with CO, NO_2, and PM_{10}, limited to days in which data for all pollutants were available, associations between O_3 and respiratory emergency department visits remained positive, but were attenuated. Darrow et al. (2011) reported the strongest associations with respiratory emergency department visits for 8-hour daily maximum, 1-hour daily maximum, and day-time O_3 exposure metrics (all associations positive and statistically significant), while positive, but statistically non-significant, associations were reported with 24-hour average and commuting period exposure metrics. In addition, a negative association was observed when using the night-time exposure metric (US EPA, 2012a, Figure 6-16). The results of Darrow et al. (2011) suggest that averaging over nighttime hours may lead to smaller O_3 effect estimates for respiratory emergency department visits due to dilution of relevant O_3 concentrations (i.e., the higher concentrations that occur during the daytime); and potential negative confounding by other pollutants (e.g., CO, NO_2) during the nighttime hours (US EPA, 2012a, section 6.2.7.3).

Cause-specific emergency department visits

In evaluating cause-specific emergency department visits in an all-year analysis, a Canadian multi-city study (Stieb et al., 2009) reported that 24-hour O_3 concentrations were positively associated with emergency department visits for asthma (4.7% [95% CI: -1.4, 11.1%] at lag 1 and 3.5% [95% CI: 0.33, 6.8%] at lag 2). Though the authors did not present seasonal analyses, they stated that no associations were observed with emergency department visits in the winter season, suggesting that the positive associations reported in the all-year analysis were due to the warm season (Stieb et al., 2009). In addition to asthma, the authors reported that O_3 was positively associated with COPD emergency department visits in all-year analyses, but that associations with COPD visits were statistically significant only for the warm season (i.e., April-September) 6.8% [95% CI: 0.11, 13.9%].

Several single-city studies have also provided evidence for positive associations between asthma emergency department visits and ambient O_3 concentrations. Ito et al. (2007) reported positive and statistically significant associations with asthma emergency department visits in New York City during the warm season (percent increased risk ranged from 8.6 to 16.9% across models that controlled for the potential confounding effects of weather using different

approaches), and an inverse association in the cool season (ranging from -23.4 to -25.1%), for a 30 ppb increase in 8-hour maximum O_3 concentrations. In two-pollutant models with $PM_{2.5}$, NO_2, SO_2, and CO, the authors found that O_3 risk estimates were not substantially changed during the warm season (US EPA, 2012a, Figure 6-19; Table 6-29).

Strickland et al. (2010) examined the association between O_3 exposure and pediatric asthma emergency department visits (ages 5-17 years) in Atlanta using air quality data over the same years as Darrow et al. (2011b) and Tolbert et al. (2007), but using population-weighting to combine daily pollutant concentrations across monitors. Strickland et al. (2010) reported a 6.4% (95% CI: 3.2, 9.6%) increase in emergency department visits for a 30 ppb increase in 8-h max O_3 concentrations in an all-year analysis. In seasonal analyses, stronger associations were observed during the warm season (i.e., May-October) (8.4% [95% CI: 4.4, 12.7%]; lag 0-2) than the cold season (4.5% [95% CI: -0.82, 10.0%]; lag 0-2). In co-pollutant analyses that included CO, NO_2, $PM_{2.5}$ elemental carbon, or $PM_{2.5}$ sulfate, Strickland et al. (2010) reported that O_3 risk estimates were not substantially changed. The authors also examined the concentration-response relationship between O_3 exposure and pediatric asthma emergency department visits and reported that positive associations with O_3 persist at 8-hour ambient O_3 concentrations (3-day average of 8-hour daily maximum concentrations) at least as low as 30 ppb.

In a single-city study conducted in Seattle, WA, Mar and Koenig (2009) examined the association between O_3 exposure and asthma emergency department visits for children (< 18) and adults (≥ 18). For children, positive and statistically significant associations were reported across multiple lags, ranging from a 19.1-36.8% increase in asthma emergency department visits for a 30 ppb increase in 8-hour maximum O_3 concentrations, with the strongest associations observed at lag 0 (33.1% [95% CI: 3.0, 68.5]) and lag 3 (36.8% [95% CI: 6.1, 77.2]). Ozone was also found to be positively associated with asthma emergency department visits for adults at all lags, ranging from 9.3-26.0%, except at lag 0. The slightly different lag times for children and adults suggest that children may be more immediately responsive to O_3 exposures than adults (Mar and Koenig, 2009).

In addition to the U.S. single-city studies discussed above, a single-city study conducted in Alberta, Canada (Villeneuve et al., 2007) provides support for the findings from Stieb et al. (2009), but also attempts to identify those lifestages at greatest risk for O_3-associated asthma emergency department visits. Villeneuve et al. reported an increase in asthma emergency department visits in an all-year analysis across all ages (12.0% [95% CI: 6.8, 17.2] for a 30 ppb increase in max 8-h average O_3 concentrations at lag 0-2) with associations being stronger during the warmer months (19.0% [95% CI: 11.9, 28.1]). When stratified by age, the strongest associations were observed in the warm season for individuals 5-14 (28.1% [95% CI: 11.9, 45.1];

lag 0-2) and 15-44 (19.0% [95% CI: 8.5, 31.8]; lag 0-2). These associations were not found to be confounded by the inclusion of aeroallergens in age-specific models.

2.2.1.7 Respiratory mortality

The 2006 O_3 AQCD found inconsistent evidence for an association between short-term O_3 exposure and respiratory mortality (US EPA, 2006). In contrast, recent multicity studies have consistently reported positive associations, particularly during the summer months (US EPA, 2012a, Figure 6-37). Specifically, Zanobetti and Schwartz (2008) reported a positive and statistically significant association with respiratory mortality across 48 U.S. cities in the summer [2.51% (95% CI 1.1.4 to 3.89) increase in respiratory mortality per 30 ppb increase in 8-hour daily maximum O_3]. Consistent with this study, the APHENA study reported positive associations with respiratory mortality across cities in the U.S., Canada, and Europe, with larger effect estimates in the warm season than in all-year analyses and with some effect estimates statistically significant (US EPA, 2012a, Figure 6-36).[13] In analyses of potential co-pollutant confounding, Katsouyanni et al. (2009) reported O_3 respiratory mortality risk estimates were robust to the inclusion of PM_{10} in co-pollutant models in all year analyses of the Canadian and US datasets. In summer-only analyses, O_3 respiratory mortality risk estimates remained robust to the inclusion of PM_{10} in co-pollutant models using the US dataset, but were attenuated in analyses of the European dataset. In addition to these U.S. studies, associations with respiratory mortality have been reported to be positive, and in some cases statistically significant, in multi-city studies conducted in Europe and Asia (Samoli et al., 2009; Stafoggia et al., 2010; Wong et al., 2010).

2.2.1.8 Summary of respiratory effects

As discussed in detail in the ISA (US EPA, 2012a, section 2.5.2 and chapter 6), recent studies build upon the strong body of evidence presented in the 1996 and 2006 O_3 AQCDs, supporting the conclusion that there is a causal relationship between short-term O_3 exposure and respiratory health effects. Recent controlled human exposure studies demonstrate statistically significant group mean decreases in pulmonary function following exposures as low as 60 and 70 ppb O_3 in young, healthy adults. These studies are supported by the strong, cumulative evidence from epidemiologic studies. Equally strong evidence demonstrated associations of ambient O_3 with respiratory hospital admissions and emergency department visits across the U.S., Europe, and Canada. Several multicity studies and a multi-continent study reported associations between

[13]As noted above (section 2.2.1.6), the study by Katsouyanni et al. (2009) evaluated different statistical models. Although the investigators did not identify the model they deemed to be the most appropriate for comparing the results across study locations, they did specify that "overall effect estimates (i.e., estimates pooled over several cities) tended to stabilize at high degrees of freedom" (Katsouyanni et al., 2009). In discussing of the results of this study, the ISA focused on models with 8 degrees of freedom per year (US EPA, 2012a, section 6.2.7.2).

short-term increases in ambient O_3 concentrations and increases in respiratory mortality. This evidence is supported by a large body of individual-level epidemiologic panel studies that demonstrate associations of ambient O_3 with respiratory symptoms in children with asthma. Further support is provided by recent studies that found O_3-associated increases in indicators of airway inflammation and oxidative stress in children with asthma. Across respiratory endpoints, evidence indicates antioxidant capacity may modify the risk of respiratory morbidity associated with O_3 exposure. The potentially elevated risk of populations with diminished antioxidant capacity and the reduced risk of populations with enhanced antioxidant capacity identified in epidemiologic studies is strongly supported by similar findings from controlled human exposure studies and by evidence that characterizes O_3-induced decreases in intracellular antioxidant levels as a mode of action for downstream effects. By demonstrating O_3-induced airway hyperresponsiveness, decreased pulmonary function, allergic responses, lung injury, impaired host defense, and airway inflammation, toxicological studies have characterized O_3 modes of action and provided biological plausibility for epidemiologic associations of ambient O_3 concentrations with lung function and respiratory symptoms, hospital admissions, emergency department visits, and mortality. Together, the ISA concludes that the evidence integrated across controlled human exposure, epidemiologic, and toxicological studies and across the spectrum of respiratory health endpoints continues to demonstrate that there is a causal relationship between short-term O_3 exposure and respiratory health effects (US EPA, 2012a, section 2.5.2).

2.2.2 Total Mortality

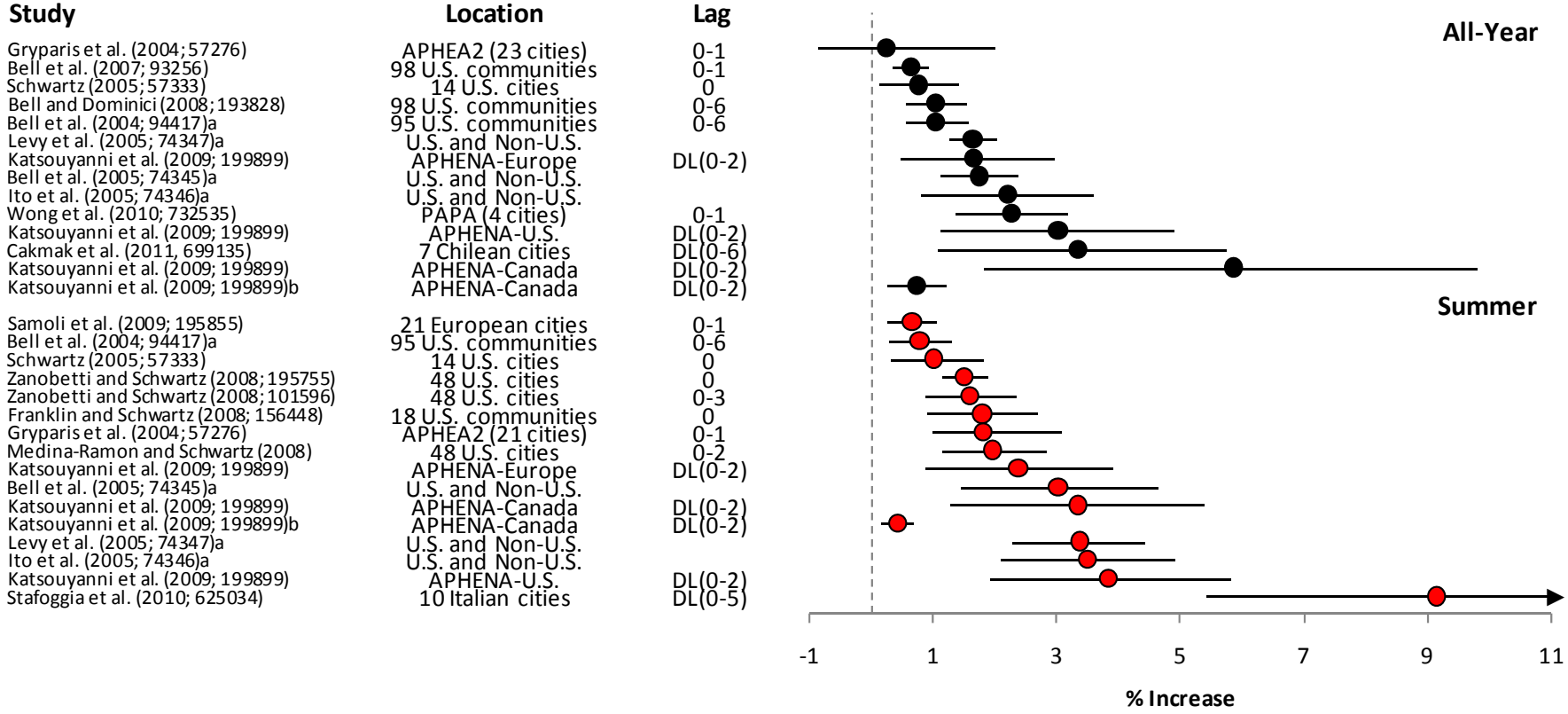
The 2006 O_3 AQCD reviewed a large number of time-series studies of associations between short-term O_3 exposures and total mortality including single- and multicity studies, and meta-analyses. In the large U.S. multicity studies that examined all-year data, effect estimates corresponding to single-day lags ranged from a 0.5-1% increase in all-cause (nonaccidental) total mortality per a 20 ppb (24-hour), 30 ppb (8-hour maximum), or 40 ppb (1-hour maximum) increase in ambient O_3 (US EPA, 2012a, section 6.6.1). Available studies reported some evidence for heterogeneity in O_3 mortality risk estimates across cities and across studies. Studies that conducted seasonal analyses reported larger O_3 mortality risk estimates during the warm season. Overall, the 2006 O_3 AQCD identified robust associations between various measures of daily ambient O_3 concentrations and all-cause mortality, which could not be readily explained by confounding due to time, weather, or copollutants. With regard to cause-specific mortality, consistent positive associations were reported between short-term O_3 exposure and cardiovascular mortality, with less consistent evidence for associations with respiratory mortality. The majority of the evidence for associations between O_3 and cause-specific mortality were from single-city studies, which had small daily mortality counts and subsequently limited

statistical power to detect associations. The 2006 O_3 AQCD concluded that "the overall body of evidence is highly suggestive that O_3 directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality" (US EPA, 2012a, section 6.6.1).

Recent studies have further confirmed the association between short-term O_3 concentrations and mortality, including a number of studies reporting associations with non-accidental as well as cause-specific mortality. Multi-continent and multicity studies have consistently reported positive and statistically significant associations between short-term O_3 concentrations and all-cause mortality, with evidence for larger mortality risk estimates during the warm or summer months (Figure 2-1 below, reprinted from the ISA) (US EPA, 2012a, Figure 6-26; Table 6-42). Similarly, evaluations of cause-specific mortality have reported consistently positive associations with O_3, particularly in analyses restricted to the warm season (US EPA, 2012a, Figure 6-36; Table 6-53).[14]

[14]Respiratory mortality is discussed in more detail in section 2.2.1.6, above.

Figure 2-1. Summary of mortality risk estimates for short-term O_3 and all-cause (nonaccidental) mortality[15]



[15]Figure 2-1 is reprinted from the ISA (US EPA, 2012a, Figure 6-26).

In assessing the evidence for O_3-related mortality, the 2006 AQCD also noted that multiple uncertainties remained regarding the relationship between O_3 and mortality, including the extent of residual confounding by co-pollutants; characterization of the factors that modify the O_3-mortality association; the appropriate lag structure for identifying O_3-mortality effects; and the shape of the O_3-mortality concentration-response function and whether a threshold exists. Many of the studies published since the last review have attempted to address one or more of these uncertainties. The following sections discuss the extent to which recent studies have evaluated these uncertainties in the relationship between O_3 and mortality.

Confounding by co-pollutants

Recent epidemiologic studies have examined potential confounders of the O_3-mortality relationship, with a focus on PM and its constituents. However, because of the temporal correlation among these PM components and O_3, and their possible interactions, the interpretation of results from co-pollutant models that attempt to disentangle the health effects associated with each pollutant is challenging. Further complicating the interpretation of copollutant results, in some cases, is the every-3rd or -6th day PM sampling schedule employed in most locations, which limits the number of days where both PM and O_3 data are available.

Katsouyanni et al. (2009) investigated the influence of PM_{10} on O_3-mortality estimates among the three APHENA datasets (i.e., US, Canada, Europe). The sensitivity of O_3 effect estimates varied across the datasets and age groups. In the U.S. dataset, O_3 risk estimates for all-cause mortality remained positive, but were reduced, in both the year-round and summer-only analyses (Figure 6-29; Table 6-45). Risk estimates for cause-specific mortality were more variable in co-pollutant models in the U.S. dataset, with risk estimates for respiratory mortality larger in co-pollutant models than in single pollutant models and risk estimates for cardiovascular mortality both larger and smaller than in single pollutant models, depending on the age groups being evaluated (Figure 6-29; Table 6-45). In the Canadian dataset, O_3 risk estimates for all-cause mortality remained positive, though they were modestly reduced, when adjusted for PM_{10}. Variable results were reported for cause-specific mortality, with O_3 risk estimates reduced for cardiovascular mortality and increased for respiratory mortality in co-pollutant models with PM_{10} (US EPA, 2012a, Figure 6-29; Table 6-45). In the European dataset, O_3 risk estimates for total mortality and cause-specific mortality generally remained robust in co-pollutant models that included PM_{10} in the year-round analyses. When analyses were restricted to the summer months, moderate reductions were observed in O_3 risk estimates.

Bell et al. (2007) used data on 98 U.S. urban communities from the NMMAPS study to evaluate the potential for confounding effects of PM_{10} and $PM_{2.5}$ on the O_3-mortality relationship. An examination of the correlation between PM (PM_{10} and $PM_{2.5}$) and O_3 across

various strata of daily PM_{10} and $PM_{2.5}$ concentrations found that neither PM size fraction was highly correlated with daily, 8-hour maximum, or 1-hour maximum O_3 concentrations. National and community-specific effect estimates of the association between short-term O_3 exposure and mortality were robust to inclusion of PM_{10} or $PM_{2.5}$ in time-series models, though O_3 risk estimates were not statistically significant in co-pollutant models, likely due to the limited number of days with both O_3 and PM data available (i.e., Bell et al. (2007) reported that only 9.2% of days had both O_3 and $PM_{2.5}$ data). Smith et al. (2009) re-analyzed the publicly available NMMAPS database used in Bell et al. (2007). In analyses conducted to examine the potential confounding effects of PM_{10}, the authors reported that, in most cases, O_3 mortality risk estimates were reduced by between 22% and 33% in co-pollutant models.

Franklin and Schwartz (2008) examined the sensitivity of O_3 mortality risk estimates to the inclusion of $PM_{2.5}$ or PM chemical components associated with secondary aerosols. The association between O_3 and non-accidental mortality was examined in single-pollutant models and after adjustment for $PM_{2.5}$, sulfate, organic carbon, or nitrate concentrations. In the single-pollutant model, the authors found a 0.89% (95% CI: 0.45, 1.33%) increase in nonaccidental mortality with a 10 ppb increase in same-day 24-h summertime O_3 concentrations across the 18 U.S. communities. Adjustment for $PM_{2.5}$ mass, which was available for 84% of the days, decreased the O_3-mortality risk estimate only slightly (e.g., from 0.88% to 0.79% for $PM_{2.5}$ mass). Similar results were reported for nitrate. In contrast, the inclusion of sulfate in the model reduced the O_3 risk estimate by 31%. However, this could be attributed to only 18% of days having both O_3 and sulfate data.

Effect modification

Several multicity studies have reported that O_3-related mortality risk estimates vary regionally across the United States. For example, Bell and Dominici (2008) reported that O_3-mortality risk estimates were larger in the Northeast (1.44% [95% CI: 0.78, 2.10%]) and Industrial Midwest (0.73% [95% CI: 0.11, 1.35%]) than in other regions of the country, where null associations were found (US EPA, 2012a, Table 6-49; Figure 6-31). Similar regional variability was reported by Smith et al. (2009) (US EPA, 2012a, Figure 6-32). In addition, Franklin and Schwartz (2008) indicated that between-city heterogeneity in the effect of O_3 exposure on mortality may contribute to greater uncertainty in assessing this association than co-pollutant confounding. In light of this regional heterogeneity, multicity studies have evaluated a number of factors that may modify the O_3-mortality relationship and explain the observed regional heterogeneity. These potential effect modifiers can be categorized as either individual-level or community-level characteristics.

Of the individual-level characteristics that have been evaluated, the most consistent evidence for effect modification has been for older adults. Medina-Ramón and Schwartz (2008) evaluated the warm season in 48 U.S. cities to identify populations potentially at greatest risk for O_3-related mortality. Across cities, the authors reported a 1.96% (95% CI: 1.14-2.82%) increase in mortality (lag 0-2) for a 30 ppb increase in 8-hour maximum O_3 concentrations. Older adults (i.e., ≥ 65 years of age) were at increased risk for O_3-related mortality compared to younger individuals [i.e., older adults had an additional 1.10% (95% CI: 0.44, 1.77) increase in O_3-related mortality] (US EPA, 2012a, Table 6-47). Other multicity studies conducted outside the U.S. have reported similar results for individuals 85 years or older (Stafoggia et al., 2010) and for individuals older than 75 years (Cakmak et al., 2011).

Other individual-level characteristics have also been reported to modify the O_3-mortality relationship, though these factors have typically either not been examined across multiple studies or different studies have reported inconsistent results. For example, Medina-Ramon et al. (2008) reported larger O_3-associated mortality risks in women > 60 years of age compared to men, in black individuals compared to non-black individuals, and in individuals with atrial fibrillation compared to individuals without atrial fibrillation (US EPA, 2012a, Table 6-47). Cakmak et al. (2011) reported the largest O_3-related mortality risks in males and in individuals at the low end of the socioeconomic spectrum. In addition, studies have not consistently demonstrated that individuals with diabetes are potentially at increased risk for O_3 associated mortality (Schwartz, 2005; Medina-Ramon et al., 2008, Stafoggia et al., 2010).

Several studies have also examined community-level variables in an attempt to explain the observed city-to-city variation in estimated O_3-mortality risk estimates. Bell and Dominici (2008) analyzed 98 U.S. urban communities from NMMAPS for the period 1987-2000. In the all-year regression model that included no community-level variables, a 20 ppb increase in 24-h average O_3 concentrations during the previous week was associated with a 1.04% (95% CI: 0.56, 1.55) increase in mortality. The authors reported that larger O_3-mortality effect estimates were associated with higher percent unemployment, fraction of the population Black/African-American, and percent of the population that take public transportation to work. In addition, the authors reported larger O_3 mortality effect estimates in locations with lower temperatures and with lower prevalence of central air conditioning (US EPA, 2012a, Figure 6-30). In the APHENA study, Katsouyanni et al. (2009) reported generally inconsistent results across the U.S., Canadian, and European datasets for potential effect modifiers, though larger O_3 mortality risks were reported for cities with higher unemployment and lower temperatures (a surrogate for lower prevalence of air conditioning) in the U.S. dataset (US EPA, 2012a, Table 6-48).

Ren et al. (2008) examined the possible interaction between O_3 and temperature during the warm months in the 60 largest eastern U.S. communities from the NMMAPS dataset. In the northeast region, a 20 ppb increase in 24-h avg O_3 concentrations at lag 0-2 was associated with an increase in mortality of 4.49% (95% posterior interval [PI]: 2.39, 6.36%), 6.21% (95% PI: 4.47, 7.66%) and 12.8% (95% PI: 9.77, 15.7%) for low, moderate, and high temperature levels, respectively. The corresponding percent increases in mortality in the southeast region were 2.27% (95% PI: -2.23, 6.46%) for low temperature, 3.02% (95% PI: 0.44, 5.70%) for moderate temperature, and 2.60% (95% PI: -0.66, 6.01%) for high temperature. This observed difference may in part reflect the higher air conditioning prevalence in communities with higher long-term average temperatures. Therefore, the findings from Ren et al. (2008) indicating generally lower O_3 risk estimates in the southeast region, where the average temperature is higher, than in the northeast region is consistent with the regional results reported by Bell and Dominici (2008).

Lag structure

Several studies have evaluated different lag structures in order to assess the possibility that O_3 mortality risks reported for short lags could result from small shifts in the day of death for individuals who are already frail, such that those frail individuals die slightly earlier than would otherwise have been the case (mortality displacement). Zanobetti and Schwartz (2008a) examined this issue in 48 U.S. cities during the warm season (i.e., June-August) for the years 1989-2000. The authors reported a 0.96% (95% CI: 0.60, 1.30%) increase in all-cause mortality across all 48 cities for a 30 ppb increase in 8-hour maximum O_3 concentrations at lag 0, whereas a combined estimate using an unconstrained distributed lag model (lag 0-20) was 1.54% (95% CI: 0.15, 2.91%). Similarly, when examining the cause-specific mortality results, larger risk estimates were observed for the distributed lag model compared to estimates based on a 0 day lag (US EPA, 2012a, Table 6-50). Samoli et al. (2009) conducted a similar analysis in 21 European cities. The authors reported that the 21 day distributed lag model resulted in O_3-related mortality estimates that were approximately 10-fold larger than estimates from the 0 lag model, suggesting that using single-day exposures may underestimate O_3-related respiratory mortality. In contrast, the 21-day distributed lag models yielded non-significant negative estimates of O_3-related total mortality and cardiovascular mortality (US EPA, 2012a, Table 6-51).

Overall, the evidence for mortality displacement remains mixed, with inconsistent results across studies and for total mortality and cardiovascular mortality versus respiratory mortality. Interpretation of these studies is also complicated by the finding that O_3-related mortality effect estimates are reduced late in the summer (i.e., 0.84% in August) compared to earlier in the summer (1.96% in July), potentially supporting the existence of an adaptive response for O_3-related mortality (Zanobetti and Schwartz, 2008b). Such an adaptive response may complicate

the interpretation of the distributed lag coefficients with long lag periods because the decreased coefficients may reflect diminished effects of the late summer, rather than mortality displacement. Although interpretation of these studies is complicated, both Samoli et al. (2009) and Zanobetti and Schwartz (2008a), as well as other studies that evaluated multiple lags (e.g., Katsouyanni et al., 2009), suggest that the positive associations between O_3 and mortality are observed mainly in the first few days after exposure.

Concentration-response relationship

Recent studies have evaluated different statistical approaches to examine the shape of the O_3-mortality concentration-response relationship and to evaluate whether a threshold exists for O_3-related mortality. In an analysis of the NMMAPS data, Bell et al. (2006) evaluated the potential for a threshold in the O_3-mortality relationship. The authors reported positive and statistically significant associations with mortality in a variety of restricted analyses, including analyses restricted to days with 24-hour average O_3 concentrations below 60, 55, 50, 45, 40, 35, and 30 ppb. In these restricted analyses O_3 effect estimates were of similar magnitude, were statistically significant, and had similar statistical precision. In analyses restricted to days with 24-hour average O_3 concentrations below 25 ppb, the O_3 effect estimate was similar in magnitude to the effect estimates resulting from analyses with the higher cutoffs, but had somewhat lower statistical precision, with the estimate approaching statistical significance (i.e., based on observation of Figure 2 in Bell et al., 2006). In analyses restricted to days with lower 24-hour average O_3 concentrations (i.e., below 20 and 15 ppb), effect estimates were similar in magnitude to analyses with higher cutoffs, but with notably less statistical precision, and were not statistically significant (i.e., confidence intervals included no O_3-associated mortality based on observation of Figure 2 in Bell et al., 2006). Ozone was no longer positively associated with mortality when the analysis was restricted to days with 24-hour O_3 concentrations below 10 ppb. Given the relatively small number of days included in these restricted analyses, especially for cut points of 20 ppb and below,[16] statistical uncertainty is increased.

Bell et al. (2006) also evaluated the shape of the concentration-response relationship between O_3 and mortality. Although the results of this analysis suggested the lack of threshold in the O_3-mortality relationship, the ISA noted that it is difficult to interpret such a curve because: (1) there is uncertainty around the shape of the concentration-response curve at 24-h average O_3 concentrations generally below 20 ppb and (2) the concentration-response curve does not take into consideration the heterogeneity in O_3-mortality risk estimates across cities (US EPA, 2012a, section 6.6.2.4).

[16]For example, Bell et al. (2006) reported that for analyses restricted to 24-hour O_3 concentrations at or below 20 ppb, 73% of days were excluded on average across the 98 communities.

Several additional studies have used the NMMAPS dataset to evaluate the O_3-mortality concentration-response relationship. For example, using the same data as Bell et al. (2006), Smith et al. (2009) conducted a subset analysis, but instead of restricting the analysis to days with O_3 concentrations below a cutoff the authors only included days above a defined cutoff. The results of this analysis were consistent with those reported by Bell et al. (2006). Specifically, the authors reported consistent positive associations for all cutoff concentrations up to concentrations where the total number of days available were so limited that the variability around the central estimate was increased (US EPA, 2012a, section 6.6.2.4). In addition, using NMMAPS data for 1987-1994 for Chicago, Pittsburgh, and El Paso, Xia and Tong (2006) reported evidence for a threshold around a 24-hour average O_3 concentration of 25 ppb, though the threshold values estimated in the analysis were sometimes in the range of where data density was low (US EPA, 2012a, section 6.6.2.4). Stylianou and Nicolich (2009) examined the existence of thresholds following an approach similar to Xia and Tong (2006) using data from NMMAPS for nine major U.S. cities (i.e., Baltimore, Chicago, Dallas/Fort Worth, Los Angeles, Miami, New York, Philadelphia, Pittsburgh, and Seattle) for the years 1987-2000. The authors reported that the estimated O_3-mortality risks varied across the nine cities, with the models exhibiting apparent thresholds in the 10-45 ppb range for O_3. However, given the city-to-city variation in risk estimates, combining the city-specific estimates into an overall estimate complicated the interpretation of the results. Additional studies in Europe, Canada, and Asia did not report the existence of a threshold (Katsouyanni et al., 2009), with inconsistent and/or inconclusive results across cities, or a non-linear relationship in the O_3-mortality concentration-response curve (Wong et al., 2010).

In light of the above evidence, the ISA concluded that O_3 mortality studies do not provide evidence for the existence of a threshold within the range of 24-hour O_3 concentrations most commonly observed in the U.S. during the O_3 season (US EPA, 2012a, section 2.5.4.4). Although recent evidence suggests that the shape of the O_3-mortality relationship remains linear across the this range of O_3 concentrations, evidence indicates less certainty in the shape of the concentration-response curve at the lower end of the distribution of O_3 concentrations, and city-to-city heterogeneity complicates the interpretation of a combined concentration-response curves (US EPA, 2012a, section 2.5.4.4). Overall, recent evidence continues to support the conclusion from the 2006 O_3 AQCD, which stated that "if a population threshold level exists in O_3 health effects, it is likely near the lower limit of ambient O_3 concentrations in the United States" (US EPA, 2012a, p. 6-266).

2.2.3 Other Effects

In contrast to the extensive bodies of evidence linking short-term O_3 exposures to respiratory effects and to total mortality (discussed above), more limited evidence links short-term O_3 exposures to other health endpoints. Specifically, in recognition of the limitations and uncertainties in the health evidence, the ISA concluded that the evidence is suggestive of a causal relationship with cardiovascular effects and CNS effects. In addition, the evidence was judged inadequate to determine if a causal relationship exists between ambient O_3 exposures and cancer (US EPA, 2012a, section 2.5.2). The health evidence supporting these conclusions is discussed in detail in the ISA (US EPA, 2012a) and is summarized briefly below for cardiovascular effects (2.2.3.1) and CNS effects (2.2.3.2).

2.2.3.1 Cardiovascular effects

In past O_3 AQCDs the effects of short-term exposure to O_3 on the cardiovascular system could not be thoroughly evaluated due to limitations in the evidence available. However, some recent experimental and epidemiologic studies have investigated O_3-related cardiovascular events (US EPA, 2012a, summarized in section 2.5.2).

Animal toxicological studies provide evidence that short-term O_3 exposure can lead to cardiovascular morbidity. These studies have reported O_3-induced atherosclerosis and ischemia/reperfusion injury, in some cases in conjunction with a systemic oxidative, pro-inflammatory environment; disruption of NO-induced vascular reactivity; decrease in cardiac function; and increase in heart rate variability (HRV). The observed increase in HRV is supported by a recent controlled human exposure study that reported increased high frequency HRV, but not altered blood pressure, following O_3 exposure. The mechanism by which O_3 inhalation may cause systemic toxicity remains unclear, though the cardiovascular effects of O_3 found in animals are consistent with the development of an extra-pulmonary oxidative, proinflammatory environment that may result from pulmonary inflammation.

There is only limited and inconsistent evidence for O_3-related cardiovascular morbidity in epidemiologic studies examining short-term exposures to O_3. This is highlighted by the multiple studies that examined the association between short-term increases in ambient O_3 concentrations and cardiovascular-related hospital admissions and emergency department visits and other various cardiovascular effects and found no evidence of a consistent relationship with O_3 exposure. Positive associations between short-term increases in O_3 concentration and cardiovascular mortality have been consistently reported in multiple epidemiologic studies. However, the lack of coherence between the results from studies that examined associations between short-term increases in O_3 concentration and cardiovascular morbidity and subsequently

cardiovascular mortality, complicate the interpretation of the evidence for O_3-induced cardiovascular mortality.

Overall, animal toxicological studies provide some evidence for O_3-induced cardiovascular effects, but the effects observed were not consistently supported by controlled human exposure studies or epidemiologic studies. Although the toxicological evidence provides initial support to the relatively strong body of evidence indicating O_3-induced cardiovascular mortality, there is a lack of coherence with controlled human exposure and epidemiologic studies of cardiovascular morbidity which together do not support O_3-induced cardiovascular effects. Thus, the ISA concludes that the overall body of evidence across disciplines is suggestive of a causal relationship for both relevant short- and long-term exposures to O_3 and cardiovascular effects (US EPA, 2012a, section 2.5.2).

2.2.3.2 CNS effects

Recent evidence suggests that O_3 may impart health effects through biological mechanisms not previously considered. For example, recent toxicological studies add to earlier evidence that short-term exposures to O_3 can produce a range of effects on the central nervous system and behavior. Additionally, an epidemiologic study demonstrated that long-term exposure to O_3 affects memory in humans as well (US EPA, 2012a, section 2.5.2).

2.3 HEALTH EFFECTS FOLLOWING LONG-TERM EXPOSURES TO O_3

Given the weight-of-evidence conclusions in the ISA, staff's consideration of health effects linked to long-term O_3 exposures focuses on respiratory effects (section 2.3.1). Other effects linked to long-term O_3 exposures, including cardiovascular, reproductive, and CNS effects are also considered (section 2.3.2). In discussing the evidence in this draft PA, although we consider the total body of available evidence of effects of long-term exposures to O_3, we focus the majority of our discussion on the studies that are most likely to inform policy decisions regarding the adequacy of the current standard and potential alternative standards with respect to long-term exposures to O_3, as discussed in chapter 4.

Long-term exposure has been defined in the ISA (EPA, 2012a) to include durations of approximately 30 days (1 month) or longer. Epidemiologic studies generally present O_3-related effect estimates for mortality and morbidity health outcomes based on an incremental change in an exposure period. For example, studies traditionally present the relative risk per an incremental change equal to the interquartile range in O_3 concentrations or some other arbitrary value (e.g., 10 ppb). Additionally, various short-term exposure metrics are used in O_3 epidemiologic studies, with the three most common being the maximum 1-hour average within a

24-hour period (1-hour maximum), the maximum 8-hour average within a 24-hour period (8-hour maximum), and 24-hour average (24-hour average). For the purpose of presenting results from short-term studies that use different exposure metrics, the ISA (EPA, 2012a) consistently applies the same O_3 increments to facilitate comparisons between the results of various studies that may present results for different incremental changes. Differences due to the use of varying exposure metrics (e.g., 1-hour maximum, 24-hour average) become less apparent when averaged across longer exposure periods, because levels are typically lower and less variable. As such, throughout the ISA and hence in this chapter, an increment of 10 ppb was consistently applied across long-term exposure studies, regardless of exposure metric, to facilitate comparisons between the results from these studies.

2.3.1 Respiratory Effects

The ISA concludes that "the clearest evidence for health effects associated with exposure to O_3 is provided by studies of respiratory effects" (US EPA, 2012a, section 1, p. 1-5). Collectively, there is a vast amount of evidence spanning several decades that supports a causal association between exposure to O_3 and a continuum of respiratory effects (US EPA, 2012a, section 2.5). While the majority of this evidence is derived from studies investigating short-term exposures, evidence from animal toxicological studies and recent epidemiologic evidence demonstrate that long-term exposures (i.e., months to years) may also be detrimental to the respiratory system. In this section, we revisit the overarching question of this chapter, as it relates to respiratory effects following long-term O_3 exposures.

In the 2006 O_3 AQCD, evidence was examined for relationships between long-term O_3 exposure (several months to yearly) and effects on respiratory health outcomes including declines in lung function, increases in inflammation, and development of asthma in children and adults. Animal toxicology data provided a clearer picture indicating that long-term O_3 exposure may have lasting effects. Chronic[17] exposure studies in animals have reported biochemical and morphological changes suggestive of irreversible long-term O_3 impacts on the lung. In contrast to supportive evidence from chronic animal studies, the epidemiologic studies on longer-term (annual) lung function declines, inflammation, and new asthma development remained inconclusive.

Several epidemiologic studies collectively indicated that O_3 exposure averaged over several summer months was associated with smaller increases in lung function growth in children. For longer averaging periods (annual), the analysis in the Children's Health Study

[17] Unless otherwise specified, the term "chronic" generally refers to an annual exposure duration for epidemiology studies and a duration of greater than 10% of the lifespan of the animal in toxicological studies.

(CHS) reported by Gauderman et al. (2004) provided little evidence that such long-term exposure to ambient O_3 was associated with significant deficits in the growth rate of lung function in children. Limited epidemiologic research examined the relationship between long-term O_3 exposures and inflammation. Cross-sectional studies detected no associations between long-term O_3 exposures and asthma prevalence, asthma-related symptoms or allergy to common aeroallergens in children. However, longitudinal studies provided evidence that long-term O_3 exposure influences the risk of asthma development in children and adults.

The currently available body of evidence supporting a likely causal relationship between long-term O_3 exposures and adverse respiratory health effects is discussed in detail in the ISA (EPA 2012a, section 7.2). New evidence reports interactions between genetic variants and long-term O_3 exposure in effects on new-onset asthma in U.S. cohorts in multi-community studies where protection by specific oxidant gene variants was restricted to children living in low O_3 communities. A new line of evidence reports a positive concentration-response relationship between first asthma hospitalization and long-term O_3 exposure. Related studies report coherent relationships between asthma severity and control, and respiratory symptoms among asthmatics and long-term O_3 exposure. These studies are summarized briefly below for new-onset asthma (section 2.3.1.1), asthma hospital admissions and other morbidity effects (section 2.3.1.2), pulmonary structure and function (section 2.3.1.3), and respiratory mortality (section 2.3.1.4).

2.3.1.1 New-onset asthma

Asthma is a heterogeneous disease with a high degree of temporal variability. The progression and symptoms can vary within an individual's lifetime, and the course of asthma may vary markedly in young children, older children, adolescents and adults. In the previous review, longitudinal cohort studies that examined associations between long-term O_3 exposures and the onset of asthma in adults and children indicated a direct effect of long-term O_3 exposures on asthma risk in adults and effect modification by O_3 in children. Since that review, important new evidence has become available about the association between long-term exposures to O_3 and new-onset asthma that has increased our understanding of the gene-environment interaction and the mechanisms and biological pathways most relevant to assessing O_3-related effects.

Associations between annual mean O_3 exposure and new cases of asthma were reported in a cohort of non-smoking adults in California (McDonnell et al., 1999a, 15-year follow-up; Greer et al., 1993, 10-year follow-up). Both the 10- and 15-year follow-up studies reported a positive association between new-onset asthma and O_3, but only in males. No other pollutants were associated with the development of asthma in either males or females, and adjusting for copollutants did not diminish the association between O_3 and asthma incidence in males. The consistency of the results of the two studies with different follow-up times, as well as the

independent and robust association between annual mean O_3 concentrations and asthma incidence provide supportive evidence that long-term O_3 exposure may be associated with the development of asthma in adult males.

In children, the relationship between long-term O_3 exposure and new-onset asthma has been extensively studied in the CHS; a long-term study that was initiated in the early1990's and has evaluated effects in several cohorts of children. The CHS was initially designed to examine whether long-term exposure to ambient pollution was related to chronic respiratory outcomes in children in 12 communities in southern California. In the CHS, new-onset asthma was classified as having no prior history of asthma at study entry with subsequent report of physician-diagnosed asthma at follow-up, with the date of onset assigned to be the midpoint of the interval between the interview date when asthma diagnosis was first reported and the previous interview date.

The results of one study (McConnell et al., 2002) available in the previous review indicated that within high O_3 communities, asthma risk was 3.3 times greater for children who played three or more sports as compared with children who played no sports. There was no evidence of an association in low-O_3 communities. Communities were stratified by 4-year average 1-hour maximum O_3 levels, with six high-O_3 communities (mean 75.4 ppb) and six low-O_3 communities (mean 50.1 ppb). Analyses aimed at distinguishing the effects of O_3 from effects of other pollutants indicated that in communities with high O_3 and low levels of other pollutants there was a 4.2-fold increased risk of asthma in children playing three or more sports, compared to children who played no sports. These results provide additional support that the effects of physical activity on asthma are modified by long-term O_3 exposure. Overall, the results from McConnell et al. (2002) suggest that playing sports may indicate greater outdoor activity when O_3 levels are higher and an increased ventilation rate, which may lead to increased O_3 exposure.

For this review, as discussed in section 7.2.2.1 of the ISA (US EPA 2012a), recent studies from the CHS provide evidence for gene-environment interactions in effects on new-onset asthma by indicating that the lower risks associated with specific genetic variants are found in children who live in lower O_3 communities. Risk for new-onset asthma is related in part to genetic susceptibility, as well as behavioral factors and environmental exposure. The onset of a chronic disease, such as asthma, is partially the result of a sequence of biochemical reactions involving exposures to various environmental agents metabolized by enzymes related to a number of different genes. Oxidative stress has been proposed to underlie these mechanistic hypotheses. Understanding the relation between genetic polymorphisms and environmental

exposure can help identify high-risk subgroups in the population and provide better insight into pathway mechanisms for these complex diseases.

The CHS analyses have found that asthma risk is related to interactions between O_3 and variants in genes for enzymes such as heme-oxygenase (HO-1), arginases (ARG1 and 2), and glutathione S transferase P1 (GSTP1). Biological plausibility for these findings is provided by evidence that these enzymes have antioxidant and/or anti-inflammatory activity and participate in well-recognized modes of action in asthma pathogenesis. Further, several lines of evidence demonstrate that secondary oxidation products of O_3 initiate the key modes of action that mediate downstream health effects (ISA, Section 5.3.2, US EPA, 2012a).

One study (Islam et al., 2008) found that functional polymorphisms of the heme oxygenase-1 gene (HMOX-1) influenced the risk of new-onset asthma, depending on ethnicity and long-term community O_3 concentrations. Analyses were restricted to children of Hispanic[18] or non-Hispanic white ethnicity and were conducted with long-term pollutant levels averaged from 1994 to 2003. For HMOX-1, the interaction indicated a greater protective effect of one allele among non-Hispanic white children who lived in the low-O_3 community (shown in Figure 7-1, p. 7-8, ISA, EPA, 2012a). Among children residing in low-O_3 communities (community mean O_3 level 38.4 ppb), the hazard ratio (HR) of new-onset asthma associated with this allele was significantly reduced compared to non-Hispanic white children who lived in low-O_3 communities without it. Biological plausibility for these results is provided by evidence that the expression of the protective allele is more readily induced than the other. However, this allele was found to have a less protective effect in non-Hispanic white children who resided in high-O_3 communities (community mean O_3 level 55.2 ppb) compared to non-Hispanic white children in low O_3 communities without the allele, indicating that in environments of low ambient O_3, enzymes with greater antioxidative activity may have the capacity to counter any temporary imbalance in an oxidant-antioxidant relationship. In the presence of high background O_3, the protective effect may be attenuated because with higher exposure to oxidants, the antioxidant genes may be at their maximal level of expression, and variation in promoters no longer affects levels of expression. No significant interactions were observed between PM_{10} or other pollutants and the HMOX-1 gene, and average O_3 levels showed low correlation with the other monitored pollutants.

Expanding on the results of McConnell et al. (2002), Islam et al. (2009) provided evidence that variants in GSTM1 and GSTP1 may influence associations between outdoor exercise and new-onset asthma. A primary conclusion that the authors (Islam et al., 2009)

[18] HMOX-1 variants were not associated with asthma risk in Hispanic children.

reported was that variants of the GSTP1 genotype and the GSTM1 null genotype increased risk of new-onset asthma during adolescence. The highest risk was found for participation in three or more team sports (compared to no sports) among children with variants of the GSTP1 genotype living in high-O_3 communities (community mean O_3 level 55.2 ppb). No three-way interaction was found for GSTM1. These results demonstrate the potential importance of a combination of genetic variability, O_3 exposure, and outdoor activity on asthma risk.

The CHS also provided evidence of interactions between O_3 exposure and variants in genes for arginase (Salam et al., 2009). Higher arginase activity can limit production of NO and subsequent nitrosative stress. While epidemiologic evidence of associations of arginase variants with asthma is limited, asthmatic subjects have been found to have higher arginase activity than non-asthmatic subjects. The modifying effect of O_3 and atopy on the association between variants in genes for arginase and asthma were evaluated. Different haplotypes were associated with different odds of childhood-onset asthma, modified by community O_3 levels. High O_3 communities were defined as having an annual mean O_3 level greater than 50 ppb, and low O_3 communities were defined as having an annual mean O_3 level less than 50 ppb. The implications of these findings are somewhat limited because the functional relevance of the variants is not clear.

Two cross-sectional analyses provide further evidence relating O_3 exposure and the risk of asthma. In a nationwide study of more than 32,000 Taiwanese school children, Hwang et al. (2005) assessed the effects of air pollutants on the risk of asthma. The study population was recruited from elementary and middle schools within 1 km of air monitoring stations. The risk of asthma was related to O_3 in the one-pollutant model. The addition of other pollutants (NO_X, CO, SO_2, and PM_{10}), in two-pollutant and three-pollutant models, increased the O_3 risk estimates. In another cross-sectional analysis, Akinbami et al. (2010) examined the association between chronic exposure to outdoor pollutants (12-month average levels by county) and asthma outcomes in a national sample of children ages 3-17 years living in U.S. metropolitan areas (National Health Interview Survey). A 5-ppb increase in estimated 8-hour max O_3 concentration (annual average) yielded a positive association for both currently having asthma and for having at least 1 asthma attack in the previous year, while the adjusted odds ratios for other pollutants were not statistically significant. Models in which pollutant value ranges were divided into quartiles produced comparable results, as did multi-pollutant models (SO_2 and PM). The median value for 12-month average O_3 levels was 39.5 ppb and the IQR was 35.9-43.7 ppb, with a positive concentration-response relationship apparent from the lowest quartile to the highest.

2.3.1.2 Asthma hospital admissions and other morbidity effects

The studies on O_3-related hospital discharges and emergency department (ED) visits for asthma and respiratory disease that were available in the 2006 O_3 AQCD mainly looked at the daily time metric. Collectively, the short-term O_3 studies presented in section 6.2.7.5 of the ISA EPA 2012a) and discussed above in section 2.2.1.6 indicate that there is evidence for increases in both hospital admissions and ED visits related to both all respiratory outcomes and asthma with stronger associations in the warm months. New studies also evaluated long-term O_3 exposure metrics, providing a new line of evidence that suggests a positive exposure-response relationship between first asthma hospital admission and long-term O_3 exposure.

An ecologic study (Moore et al., 2008) evaluated time trends in associations between declining warm-season O_3 concentrations and hospitalization for asthma in children in California's South Coast Air Basin. Quarterly 1-hour average daily maximum O_3 concentrations were used (median 87.8 ppb). Ozone was the only pollutant associated with increased hospital admissions over the study period. A linear relationship was observed for asthma hospital discharges.

In a cross-sectional study, Meng et al. (2010) examined associations between air pollution and asthma morbidity in the San Joaquin Valley in California by using the 2001 California Health Interview Survey data from subjects ages 1 to 65+ who reported physician-diagnosed asthma. Subjects were assigned annual average concentrations for O_3 based on residential ZIP code and the closest air monitoring station within 8 km, but did not have data on duration of residence. Co-pollutant models for O_3 and PM did not differ substantially from single-pollutant estimates, indicating that pollutant multi-collinearity was not a problem. The authors reported increased asthma-related ED visits or hospitalizations for O_3 for all ages. Positive and statistically significant associations for symptoms in adults (ages 18 +) were observed; positive associations were obtained for symptoms for all ages.

Evidence associating long-term O_3 exposure to first asthma hospital admission in a concentration-response relationship is provided in a retrospective cohort study (Lin et al., 2008b). This study investigated the association between chronic exposure to O_3 and childhood asthma admissions by following a birth cohort of more than 1.2 million babies born in New York State (1995-1999) to first asthma admission or until 31 December 2000. Three annual indicators (all 8-hour maximum from 10:00 a.m. to 6:00 p.m.) were used to define chronic O_3 exposure: (1) mean concentration during the follow-up period (41.06 ppb); (2) mean concentration during the O_3 season (50.62 ppb); and (3) proportion of follow-up days with O_3 levels >70 ppb. The effects of co-pollutants were controlled, and interaction terms were used to assess potential effect modifications. A positive association between chronic exposure to O_3 and childhood asthma

hospital admissions was observed, indicating that children exposed to high O_3 levels over time are more likely to develop asthma severe enough to be admitted to the hospital. The various factors were examined and differences were found for younger children (1-2 years), poor neighborhoods, Medicaid/self-paid births, geographic region and others. As shown in the ISA, Figure 7-3 (EPA 2012a, p. 7-18), positive concentration-response relationships were observed. Asthma admissions were significantly associated with increased O_3 levels for all chronic exposure indicators. Thus, this study provides evidence associating long-term O_3 exposure to first asthma hospital admission in a concentration-response relationship.

Asthma severity and control, bronchitic symptoms and school absences

In a cross-sectional study (Rage et al., 2005) involving an adult cohort in five French cities, asthma severity over the previous 12 months was assessed using both clinical events and treatment, as well as reported symptoms. Two measures of exposure were also assessed, using the monitoring data closest to the participant's residence, and a validated spatial model assigning air pollutants to the geocoded residential addresses of all participants. Higher asthma severity scores were significantly related to both the 8-hour average O_3 levels during April-September, and the number of days with 8-hour O_3 averages above 55 ppb. Both exposure assessment methods and severity score methods resulted in very similar findings. Effect estimates of O_3 were similar in three-pollutant models, which included NO_2. Although no PM data were available, since there are usually substantial correlations between PM and NO_2, the authors expressed the view that the findings are not likely explained by ambient PM.

A follow-up study (Jacquemin et al., In Press) examines the relationship between asthma, O_3, NO_2 and PM_{10}. New aspects considered include examination of three domains of asthma control (symptoms, exacerbations, and lung function), levels of asthma control (controlled, partially controlled, and uncontrolled asthma), and a multi-pollutant analysis including PM_{10}. The results of a separate analysis suggest that the effects of O_3 and PM_{10} on asthma control are independent. Both annual and summer (April-September) O_3 levels were used as variables. Both O_3-sum and PM_{10} were positively associated with partly controlled and uncontrolled asthma, with a clear gradient from controlled, partly controlled and uncontrolled asthma. The analysis of the associations between air pollution for all asthma subjects and each one of the three asthma control domains showed positive associations between O_3-sum and lung function, symptoms, and exacerbations. Since the estimates for both pollutants were more stable and significant when using the integrated measure of asthma control, this indicates that the results are not driven by one domain. These results support an effect of long-term exposure to O_3 on asthma control in adults with pre-existing asthma.

The CHS also examined interactions between TNF-α 308 genotype and long-term O_3 exposure in the occurrence of bronchitic symptoms among children with asthma (Lee et al., 2009b). Increased airway levels of the cytokine TNF-α have been related to inflammation, and the GG genotype has been linked to lower expression of TNF-α. Asthmatic children with the GG genotype had a lower prevalence of bronchitic symptoms compared with children carrying at least one A-allele (e.g., GA or AA genotype). Low- versus high-O_3 communities was defined as an average of less than or greater than 50 ppb O_3. Asthmatic children with TNF-308 GG genotype had a significantly reduced risk of bronchitic symptoms in low-O3 communities, whereas the risk was not reduced in children living in high-O_3 communities. The difference in genotypic effects between low- and high-O_3 communities was statistically significant among asthmatics, but not significant among non-asthmatic children. Figure 7-2 (ISA, EPA 2012a, p.7-12) presents adjusted O_3 community-specific regression coefficients plotted against ambient O_3 concentrations. Investigators further reported no substantial differences in the effect of the GG genotype on bronchitic symptoms by long-term exposure to PM_{10}, $PM_{2.5}$, NO_2, acid vapor, or second-hand smoke.

Another CHS analyses reported interrelationships between variants in CAT and 1 myeloperoxidase (MPO) genes, ambient pollutants, and respiratory-related school absences for Hispanic and non-Hispanic white cohort children (Wenten et al., 2009). A related study evaluated in the 2006 O_3 AQCD, Gilliland et al. (2001), found increased O_3 exposure to be related to greater school absenteeism due to respiratory illness but did not consider genetic variants. Wenten et al. (2009) hypothesized that variation in the level or function of antioxidant enzymes would modulate respiratory illness risk, especially under high levels of oxidative stress expected from high ambient O_3 exposure. The joint effect of variants in these two genes (genetic epistasis) on respiratory illness was examined because the enzyme products operate on the same substrate within the same biological pathway. Risk of respiratory-related school absences was elevated for children with one set of variants in the two genes and reduced for children with a different set of variants. In analyses that stratified communities into high and low O_3 exposure groups by median levels (46.9 ppb O_3), the protective effect of variants in the two genes was largely limited to children living in communities with high ambient O_3 levels. The association of respiratory-illness absences with functional variants in CAT and MPO that differ by air pollution levels illustrates the need to consider genetic epistasis in assessing gene-environment interactions. Collective evidence from CHS provides an important demonstration of gene-environment interactions, which helps to dissect disease mechanisms in humans by using information on susceptibility genes to focus on the biological pathways that are most relevant to that disease.

2.3.1.3 Pulmonary structure and function

Evidence from epidemiology studies

In the 2006 O_3 AQCD, few studies had investigated the effect of chronic O_3 exposure on pulmonary function. The strongest evidence was for medium-term effects of extended O_3 exposures over several summer months on lung function (FEV_1) in children, i.e., reduced lung function growth being associated with higher ambient O_3 levels. Longer-term studies (annual), investigating the association of chronic O_3 exposure on lung function (FEV_1) such as the 8-year follow-up analysis of the first cohort (Gauderman et al., 2004) provided little evidence that long-term exposure to ambient O_3 at current levels is associated with significant deficits in the growth rate of lung function in children. Analyses indicated that there was no evidence that either 8-hour average O_3 (10 a.m. to 6 p.m.) or 24-hour average O_3 was associated with any measure of lung function growth over a 4-year (age 10 to 14 years; Gauderman et al., 2000) or 8-year (age 10 to 18 years; Gauderman et al., 2004) period. However, most of the other pollutants examined (including $PM_{2.5}$, NO_2, acid vapor, and elemental carbon) were found to be significantly associated with reduced growth in lung function. In addition, there was only about a 2- to 2.5-fold difference in O_3 concentrations from the least to most polluted communities (mean annual average of 8-hour average O_3 ranged from 30 to 65 ppb), versus the ranges observed for the other pollutants (which had 4- to 8-fold differences in concentrations).

A later CHS study (Islam et al., 2007) examined relationships between air pollution, lung function, and new-onset asthma and reported no substantial differences in the effect of O_3 on lung function. In a more recent CHS study, Breton et al. (2011) hypothesized that genetic variation in genes on the glutathione metabolic pathway may influence the association between ambient air pollutant exposures and lung function growth in children. They investigated whether genetic variation in glutathione genes was associated with lung function growth in healthy children using data collected on more than 2,100 children over an 8-year time-period. Breton et al. (2011) found that variation in these genes was associated with altered risk of children for lung function growth deficits associated with NO_2, PM_{10}, $PM_{2.5}$, elemental carbon, organic carbon, and O_3. When compared to the other pollutants, O_3 was associated with larger decreases in lung function in children with a different genetic variation than the other pollutants, and only the association with maximal midexpiratory flow (MMEF) was statistically significant.

Short-term O_3 exposure studies presented in ISA (EPA, 2012a, Section 6.2.1.2) provide a cumulative body of epidemiologic evidence that strongly supports associations between ambient O_3 exposure and decrements in lung function among children. A recent study of long-term exposure to O_3, not described above, observed a relationship with pulmonary function declines in school-aged children where O_3 and other pollutant levels were higher (90 ppb at high end of the

range) than those in the CHS. Two studies of adult cohorts provide mixed results where long-term exposures were at the high end of the range with levels of 49.5 ppb in one study and 27 ppb IQR in the other. Toxicological studies examining monkeys have provided data for airway resistance in an asthma model but this is difficult to compare to FEV_1 results. Thus there is little new evidence to build upon the very limited studies of pulmonary function (FEV_1) from the 2006 O_3 AQCD.

Evidence from toxicological studies and non-human primate models

Long-term studies in animals allow for greater insight into the potential effects of prolonged exposure to O_3 that may not be easily measured in humans, such as structural changes in the respiratory tract. As reviewed in the 1996 and 2006 O_3 AQCDs and Chapter 5 of the ISA (US EPA 2012a), there are both qualitative and quantitative uncertainties in the extrapolation of data generated by rodent toxicology studies to the understanding of health effects in humans. Despite these uncertainties, epidemiologic studies observing functional changes in humans can attain biological plausibility in conjunction with long-term toxicological studies, particularly O_3-inhalation studies performed in non-human primates whose respiratory system most closely resembles that of the human. An important series of studies have used nonhuman primates to examine the effect of O_3 alone or in combination with an inhaled allergen, house dust mite antigen (HDMA), on morphology and lung function. These animals exhibit the hallmarks of allergic asthma defined for humans. Hyde et al. (2006) compared asthma models of rodents (mice) and the nonhuman primate model to responses in humans and concluded that the unique responses to inhaled allergen shown in the rhesus monkeys make it the most appropriate animal model of human asthma. These studies and others have demonstrated changes in pulmonary function and airway morphology in adult and infant nonhuman primates repeatedly exposed to environmentally relevant concentrations of O_3. Many of the observations found in adult monkeys have also been noted in infant rhesus monkeys, although a direct comparison of the degree of effects between adult and infant monkeys has not been reported. The findings of these nonhuman primate studies have also been observed in rodent studies discussed in section 7.2.3.2 and included in Table 7-1of the ISA (US EPA, 2012a, p. 7-28).

Collectively, evidence from animal studies strongly suggests that chronic O_3 exposure is capable of damaging the distal airways and proximal alveoli, resulting in lung tissue remodeling and leading to apparent irreversible changes. Potentially, persistent inflammation and interstitial remodeling play an important role in the progression and development of chronic lung disease. Further discussion of the modes of action that lead to O_3-induced morphological changes can be found in Section 5.3.7 of the ISA (US EPA, 2012a). The findings reported in chronic animal studies offer insight into potential biological mechanisms for the suggested association between

seasonal O_3 exposure and reduced lung function development in children as observed in epidemiologic studies (see Section 7.2.3). Discussion of mechanisms involved in lifestage susceptibility and developmental effects 10 can be found in Section 5.4.2.4. 11

2.3.1.4 Respiratory mortality

A limited number of epidemiologic studies have assessed the relationship between long-term exposure to O_3 and mortality. The 2006 O_3 AQCD concluded that an insufficient amount of evidence existed "to suggest a causal relationship between chronic O_3 exposure and increased risk for mortality in humans" (U.S. EPA, 2006b). Though total and cardio-pulmonary mortality were considered in these studies, respiratory mortality was not specifically considered. In the most recent follow-up analysis of the ACS cohort (Jerrett et al., 2009), cardiopulmonary deaths were separately subdivided into respiratory and cardiovascular deaths, rather than combined as in the Pope et al. (2002) work. Increased O_3 exposure was associated with the risk of death from respiratory causes, and this effect was robust to the inclusion of $PM_{2.5}$. The association between increased O_3 concentrations and increased risk of death from respiratory causes was insensitive to the use of different models and to adjustment for several ecologic variables considered individually. Additionally, a recent multi-city time series study (Zanobetti and Schwartz, 2011), which followed (from 1985 to 2006) four cohorts of Medicare enrollees with chronic conditions that might predispose to O_3-related effects, observed an association between long-term (warm season) exposure to O_3 and elevated risk of mortality in the cohort that had previously experienced an emergency hospital admission due to COPD. A key limitation of this study was the inability to control for $PM_{2.5}$, because data were not available in these cities until 1999.

2.3.1.5 Summary of respiratory effects

The ISA (US EPA, 2012a, section 7.2.8) concludes that taken together, the recent epidemiologic studies of respiratory health effects (including respiratory symptoms, new-onset asthma and respiratory mortality) combined with toxicological studies in rodents and nonhuman primates, provide biologically plausible evidence that there is likely to be a causal relationship between long-term exposure to O_3 and respiratory effects. The strongest epidemiologic evidence for a relationship between long-term O_3 exposure and respiratory effects is provided by studies that demonstrate interactions between exercise or different genetic variants and long-term measures of O_3 exposure on new-onset asthma in children; and increased respiratory symptom effects in asthmatics. Additional studies of respiratory health effects and a study of respiratory mortality provide a collective body of evidence supporting these relationships. Studies considering other pollutants provide data suggesting that the effects related to O_3 are independent from potential effects of the other pollutants. Some studies provide evidence for a positive concentration-response relationship. Short-term studies provide supportive evidence with

increases in respiratory symptoms and asthma medication use, hospital admissions and ED visits for all respiratory outcomes and asthma, and decrements in lung function in children. The recent epidemiologic and toxicological data base provides a compelling case to support the hypothesis that a relationship exists between long-term exposure to ambient O_3 and measures of respiratory health effects.

2.3.2 Other Effects

In contrast to the more extensive bodies of evidence linking long-term O_3 exposures to respiratory effects (discussed above), more limited evidence links long-term O_3 exposures to other health endpoints. Specifically, in recognition of the limitations and uncertainties in the health evidence, the ISA concluded that the evidence is suggestive of a causal relationship with cardiovascular effects, reproductive and developmental effects and CNS effects (US EPA, 2012a, sections 7.3.3, 7.4.11 and 7.5.2, respectively). In addition, the evidence was judged inadequate to determine if a causal relationship exists between ambient O_3 exposures and cancer (US EPA, 2012a, section 7.6.4). The health evidence supporting these conclusions is discussed in detail in the ISA (US EPA, 2012a) and is summarized briefly below for reproductive and developmental effects (2.3.3.1) and CNS effects (2.3.3.2).

2.3.2.1 Cardiovascular effects

Previous AQCDs did not address the cardiovascular effects of long-term O_3 exposure due to limited data availability. The evidence remains limited; however the emerging data is suggestive of a role for O_3 in chronic cardiovascular diseases. Few epidemiologic studies have investigated cardiovascular morbidity after long-term O_3 exposures. The majority evaluated only cardiovascular disease biomarkers such as lipid peroxidation, overall antioxidant capacity, inflammation, coagulation, and blood pressure, with mixed results. However, three new animal studies suggest that long-term O_3 exposure may result in cardiovascular effects. These studies demonstrate O_3-induced atherosclerosis and injury. In addition, evidence is presented for a potential mechanism for the development of vascular pathology that involves increased oxidative stress and proinflammatory mediators and upregulation of genes responsible for proteolysis, thrombosis and vasoconstriction.

A very limited number of epidemiologic studies have assessed the relationship between long-term O_3 exposure and cardiovascular mortality. The 2006 O_3 AQCD concluded that an insufficient amount of evidence existed “to suggest a causal relationship between chronic O_3 exposure and increased risk for mortality in humans” (U.S. EPA, 2006b). Though total and cardio-pulmonary mortality were considered in these studies, cardiovascular mortality was not specifically considered. As noted in section 2.3.1.3 above, in the most recent follow-up analysis

of the ACS cohort (Jerrett et al., 2009), cardiopulmonary deaths were subdivided into respiratory and cardiovascular deaths. While increased exposure to O_3 was associated with the risk of death from cardiopulmonary, cardiovascular, and ischemic heart disease in a single pollutant model, inclusion of $PM_{2.5}$ as a copollutant attenuated the association with exposure to O_3 for all of the cardiovascular endpoints to null. In addition, a recent study (Zanobetti and Schwartz 2011) discussed above, observed an association between long-term exposure to O_3 and elevated risk of mortality among Medicare enrollees that had previously experienced an emergency hospital admission due to congestive heart failure (CHF) or myocardial infarction (MI). Toxicological evidence is also limited, but three strong toxicological studies have been published since the 2006 AQCD. These studies provide evidence for O_3-enhanced atherosclerosis and injury along with the potential mechanisms for vascular pathology. Taking into consideration the findings of toxicological studies and the emerging evidence from epidemiologic studies, the ISA (US EPA, 2012a, section 7.3.3) concludes that the generally limited body of evidence is suggestive of a causal relationship between long-term exposure to O_3 and cardiovascular effects.

2.3.2.2 Reproductive and developmental effects

The 2006 O_3 AQCD concluded that the limited number of studies that investigated O_3 demonstrated no associations between O_3 and birth outcomes, with the possible exception of birth defects. The current review included an expanded body of evidence on the associations between O_3 and reproductive and developmental effects. Recent epidemiologic and toxicological studies provide evidence for an effect of prenatal exposure to O_3 on pulmonary structure and function, including lung function changes in the newborn, incident asthma, ultrastructural changes in bronchiole development, alterations in placental and pup cytokines, and increased pup airway hyper-reactivity. Also, there is limited toxicological evidence for an effect of prenatal and early life exposure on CNS effects, including laterality, brain morphology, neurobehavioral abnormalities, and sleep aberration. Recent epidemiologic studies have begun to explore the effects of O_3 on sperm quality, and provide limited evidence for decrements in sperm concentration, while there is limited toxicological evidence for testicular degeneration associated with O_3. The weight of evidence does not indicate that prenatal or early life O_3 concentrations are associated with infant mortality.

Some of the key challenges to interpretation of these study results include the difficulty in assessing exposure as most studies use existing monitoring networks to estimate individual exposure to ambient air pollution; the inability to control for potential confounders such as other risk factors that affect birth outcomes (e.g., smoking); evaluating the exposure window (e.g., trimester) of importance; integrating the results from both short- and long-term exposure periods;

integrating the results across a variety of reproductive and developmental outcomes; and limited evidence on the physiological mechanism of these effects.

2.3.2.3 CNS effects

The 2006 O_3 AQCD included toxicological evidence that acute exposures to O_3 are associated with alterations in neurotransmitters, motor activity, short and long term memory, and sleep patterns. Additionally, histological signs of neurodegeneration have been observed. However, evidence regarding chronic exposure and neurobehavioral effects was not available. Recent research in the area of O_3-induced neurotoxicity has included several long-term exposure studies. Notably, the first epidemiologic study to examine the relationship between O_3 exposure and neurobehavioral effects observed an association between annual O_3 levels and an aging-related cognitive performance decline in tests measuring attention/short-term memory. This observation is supported by studies in rodents which demonstrate progressive oxidative stress and damage in the brain and associated decrements in behavioral tests, including those measuring memory, after subchronic exposure to 0.25 ppm O_3. Additionally, neurobehavioral changes are evident in animals whose only exposure to O_3 occurred in utero.

2.4 PUBLIC HEALTH IMPLICATIONS

This section discusses the public health implications of O_3 exposures with respect to the adversity of responses (section 2.4.1), the populations at potentially increased risk from exposures (section 2.4.2), the potential effects of averting behavior on reducing O_3 exposures and thereby the incidence of health effects (section 2.4.3), and an estimate of the size of the at-risk population (section 2.4.4). Providing appropriate public health protection requires identification of populations potentially at greater risk from O_3 exposures, and that a distinction is made between those effects that are considered adverse health effects and those that are not adverse. What constitutes an adverse health effect depends not only on the type and magnitude of the effect but also on the population group being affected. While some changes in healthy individuals would not be considered adverse, similar changes in at-risk groups would be seen as adverse. In order to estimate potential overall for public health impacts, it is important to consider not only the adversity of the health effects, but also the populations at greater risk and potential behaviors that may reduce exposure.

2.4.1 Adversity of Responses

In this section we pose the following question:

- **To what extent does the currently available scientific evidence expand our understanding of the adversity of O_3-related health effects?**

In making judgments as to when various O_3-related effects become regarded as adverse to the health of individuals, in previous NAAQS reviews staff has relied upon the guidelines published by the American Thoracic Society (ATS) and the advice of CASAC. While recognizing that perceptions of "medical significance" and "normal activity" may differ among physicians, lung physiologists and experimental subjects, the ATS (1985) defined adverse respiratory health effects as "medically significant physiologic changes generally evidenced by one or more of the following: (1) interference with the normal activity of the affected person or persons, (2) episodic respiratory illness, (3) incapacitating illness, (4) permanent respiratory injury, and/or (5) progressive respiratory dysfunction."

During the 2008 review, it was concluded that for ethical reasons, clear causal evidence from controlled human exposure studies covers only effects in the first category. However, there were results from epidemiologic studies, upon which to base judgments about adversity, for effects in all of the categories. Statistically significant and robust associations were reported in epidemiology studies falling into the second and third categories. These more serious effects included respiratory illness that may require medication (e.g., asthma), but not necessarily hospitalization, as well as respiratory hospital admissions and ED visits for respiratory causes. Less conclusive, but still positive associations have been reported for school absences and cardiovascular hospital admissions. Human health effects for which associations had been suggested through evidence from epidemiologic and animal toxicology studies, but had not been conclusively demonstrated still fell primarily into the last two categories.

In this review, the new evidence strengthens the relationship between O_3 exposure and health effects in all of the categories defined by the ATS in 1985. The ISA judgment that there is a causal relationship between short-term O_3 exposure and a full range of respiratory morbidity effects, including hospital admissions and ED visits, provides support for concluding that short-term O_3 exposure is associated with incapacitating effects. Overall, the evidence supporting an association between short-term O_3 exposures and respiratory mortality is much stronger. And the demonstration of associations between long-term measures of O_3 exposure and new-onset asthma provides evidence of permanent respiratory injury or progressive respiratory decline.

In 2000, the American Thoracic Society (ATS) published an official statement on "What Constitutes an Adverse Health Effect of Air Pollution?" (ATS, 2000), which updated its earlier guidance (ATS, 1985). The revised guidance was intended to address new investigative approaches used to identify the effects of air pollution, and to reflect the concern for the impacts of air pollution on specific groups that had been expressed through the environmental justice movement.

The new guidance builds upon and expands the 1985 definition of adversity in several ways. There is an increased focus on quality of life measures as indicators of adversity. There is also a more specific consideration of population risk. Exposure to air pollution that increases the risk of an adverse effect to the entire population is adverse, even though it may not increase the risk of any individual to an unacceptable level. For example, a population of asthmatics could have a distribution of lung function such that no individual has a level associated with significant impairment. Exposure to air pollution could shift the distribution to lower levels that still do not bring any individual to a level that is associated with clinically relevant effects. However, this would be considered to be adverse because individuals within the population would have diminished reserve function, and therefore would be at increased risk to further environmental insult, if affected by another agent.

Reflecting new investigative approaches, the ATS statement describes the potential usefulness of research into the genetic basis for disease, including responses to environmental agents that will provide insights into the mechanistic basis for susceptibility, and provide markers of risk status. The committee also observed that elevations of biomarkers, such as cell number and types, cytokines and reactive oxygen species, may signal risk for ongoing injury and clinical effects or may simply indicate transient responses that can provide insights into mechanisms of injury, thus illustrating the lack of clear boundaries that separate adverse from nonadverse effects. These newer guidelines, while providing a basis for evaluating new types of scientific evidence with respects to its adversity, do not change the fundamental conclusions that exposure to O_3 at ambient concentrations can cause adverse health effects in the general population, but especially in at-risk groups.

While O_3 has been associated with effects that are clearly adverse, including premature mortality, application of these guidelines, in particular to the least serious category of effects related to ambient O_3 exposures, which are also the most numerous and therefore are also important from a policy perspective, involves judgments about which medical experts on the CASAC panel and public commenters have in the past expressed diverse views. To help frame such judgments, we have defined gradations of individual functional responses (e.g., decrements in FEV_1 and airway responsiveness) and symptomatic responses (e.g., cough, chest pain, wheeze), together with judgments as to the potential impact on individuals experiencing varying degrees of severity of these responses, that have been used in previous NAAQS reviews. These gradations and impacts are summarized in Gradation of Individual Responses to Short-Term O_3 Exposure Tables 2-1 and 2-2, below.

For active healthy people, moderate levels of functional responses (e.g., FEV_1 decrements of >10% but < 20%, lasting up to 24 hours) and/or moderate symptomatic responses

(e.g., frequent spontaneous cough, marked discomfort on exercise or deep breath, lasting up to 24 hours) would likely interfere with normal activity for relatively few sensitive individuals; whereas large functional responses (e.g., FEV_1 decrements > 20%, lasting longer than 24 hours) and/or severe symptomatic responses (e.g., persistent uncontrollable cough, severe discomfort on exercise or deep breath, lasting longer than 24 hours) would likely interfere with normal activities for many sensitive individuals and therefore would be considered adverse under ATS guidelines.

For the purpose of estimating potentially adverse lung function decrements in active healthy people, the CASAC indicated that a focus on the mid to upper end of the range of moderate levels of functional responses is most appropriate (e.g., FEV_1 decrements ≥ 15% but < 20%) (Henderson, 2006). However, for people with lung disease, even moderate functional (e.g., FEV_1 decrements > 10% but < 20%, lasting up to 24 hours) or symptomatic responses (e.g., frequent spontaneous cough, marked discomfort on exercise or with deep breath, wheeze accompanied by shortness of breath, lasting up to 24 hours) would likely interfere with normal activity for many individuals, and would likely result in additional and more frequent use of medication. For people with lung disease, large functional responses (e.g., FEV_1 decrements > 20%, lasting longer than 24 hours) and/or severe symptomatic responses (e.g., persistent uncontrollable cough, severe discomfort on exercise or deep breath, persistent wheeze accompanied by shortness of breath, lasting longer than 24 hours) would likely interfere with normal activity for most individuals and would increase the likelihood that these individuals would seek medical treatment. For the purpose of estimating potentially adverse lung function decrements in people with lung disease, the CASAC indicated that a focus on the lower end of the range of moderate levels of functional responses is most appropriate (e.g., FEV_1 decrements ≥10%) (Henderson, 2006).

Responses measured in controlled human exposure studies indicate that humans exposed to ambient O_3 concentrations include: decreased inspiratory capacity; mild bronchoconstriction; rapid, shallow breathing pattern during exercise; and symptoms of cough and pain on deep inspiration (EPA, 2012a, section 6.2.1.1). Reflex inhibition of inspiration results in a decrease in forced vital capacity and, in combination with mild bronchoconstriction, contributes to a decrease in FEV_1. Some healthy young adults exposed to O_3 concentrations ≥ 60 ppb develop statistically significant reversible, transient decrements in lung function, symptoms of breathing discomfort, and inflammation if minute ventilation or duration of exposure is increased sufficiently. Among healthy subjects there is considerable interindividual variability in the magnitude of the FEV_1 responses. For example, at 60 ppb (EPA, 2012a, p. 6-17), the proportion of healthy subjects with >10% FEV_1 decrements was 20% (n = 30) by Adams (2002), 3% (n =

30) by Adams (2006a), 16% (n = 31) by Schelegle et al. (2009), and 5% (n = 59) by Kim et al. (2011). Based on these studies, the weighted average proportion of individuals with >10% FEV_1 decrements is 10% following 6.6 hour exposure with moderate, quasi-continuous exercise to 60 ppb.[19] Subjects with asthma appeared to be more sensitive to acute effects of O_3 in terms of FEV_1 and inflammatory responses than healthy non-asthmatic subjects, such that controlled human exposure studies of healthy adults may underestimate effects in people with asthma.

As discussed above, relatively small, reversible declines in lung function parameters may be of questionable significance in healthy people. However, a 5 to 15% change in FEV_1 is considered to have clinical importance to asthma morbidity (ATS 1991; Lebowitz et al. 1987; Lippmann, 1988). This is in line with the view expressed by the CASAC that a focus on the lower end of the range of moderate levels of functional responses is most appropriate (e.g., FEV_1 decrements ≥10%) to estimate the risk of potentially adverse lung function responses in people with lung disease.

[19] Due to limited data within the published papers, these proportions were not corrected for responses to FA exposure where lung function typically improves in healthy adults. For example, uncorrected versus O_3-induced (i.e., adjusted for response during FA exposure) proportions of individuals having >10% FEV_1 decrements in the Adams (2006a) study were, respectively, 3% versus 7% at 60 ppb and 17% versus 23% at 80 ppb. Thus, uncorrected proportions underestimate the actual fraction of healthy individuals affected.

Table 2-1. Gradation of Individual Responses to Short-Term Ozone Exposure in Healthy People

Functional Response	**None**	**Small**	**Moderate**	**Large**
FEV_1	Within normal range (±3%)	Decrements of 3 to=10%	Decrements of >10 but <20%	Decrements of =20%
Nonspecific airway responsiveness	Within normal range	Increases of <100%	Increases of =300%	Increases of >300%
Duration of response	None	<4 hours	>4 hours but=24 hours	>24 hours
Symptom Response	**Normal**	**Mild**	**Moderate**	**Severe**
Cough	Infrequent cough	Cough with deep breath	Frequent spontaneous cough	Persistent uncontrollable cough
Chest pain	None	Discomfort just noticeable on exercise or deep breath	Marked discomfort on exercise or deep breath	Severe discomfort on exercise or deep breath
Duration of response	None	<4 hours	>4 hours but=24 hours	>24 hours
Impact of Responses	**Normal**	**Mild**	**Moderate**	**Severe**
Interference with normal activity	None	None	A few sensitive individuals choose to limit activity	Many sensitive individuals choose to limit activity

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Table 2-2. Gradation of Individual Responses to Short-Term Ozone Exposure in People with Respiratory Disease

Functional Response	None	Small	Moderate	Large
FEV_1	Within normal range (±3%)	Decrements of 3 to =10%	Decrements of >10 but <20%	Decrements of =20%
Nonspecific airway responsiveness	Within normal range	Increases of <100%	Increases of =300%	Increases of >300%
Airway resistance (SRaw)	Within normal range (±20%)	SRaw increased <100%	SRaw increased up to 200% or up to 15 cm H2O/s	SRaw increased >200% or more than 15 cm H2O/s
Duration of response	None	<4 hours	>4 hours but =24 hours	>24 hours
Symptom Response	**Normal**	**Mild**	**Moderate**	**Severe**
Wheeze	None	With otherwise normal breathing	With shortness of breath	Persistent with shortness of breath
Cough	Infrequent cough	Cough with deep breath	Frequent spontaneous cough	Persistent uncontrollable cough
Chest pain	None	Discomfort just noticeable on exercise or deep breath	Marked discomfort on exercise or deep breath	Severe discomfort on exercise or deep breath
Duration of response	None	<4 hours	>4 hours but =24 hours	>24 hours
Impact of Responses	**Normal**	**Mild**	**Moderate**	**Severe**
Interference with normal activity	None	None	A few sensitive individuals choose to limit activity	Many sensitive individuals choose to limit activity
Medical Treatment	No change	Normal medication as needed	Increased frequency of medication use or additional medication	Physician or emergency room visit

In judging the extent to which these impacts represent effects that should be regarded as adverse to the health status of individuals, an additional factor that has been considered in previous NAAQS reviews is whether such effects are experienced repeatedly during the course of a year or only on a single occasion. While some experts would judge single occurrences of moderate responses to be a "nuisance," especially for healthy individuals, a more general consensus view of the adversity of such moderate responses emerges as the frequency of occurrence increases. Thus it has been judged that repeated occurrences of moderate responses, even in otherwise healthy individuals, may be considered to be adverse since they could well set the stage for more serious illness (61 FR 65723). The CASAC panel in the 1997 review expressed a consensus view that these "criteria for the determination of an adverse physiological response were reasonable" (Wolff, 1995). In the 2008 review, estimates of repeated occurrences continued to be an important policy factor in judging the adversity of moderate lung function decrements in healthy and asthmatic people.

2.4.2 At-Risk Populations

In this section we pose the following question:

- **To what extent does the currently available scientific evidence expand our understanding of at-risk populations?**

In order to identify populations and lifestages at greater risk for O_3-related health effects, studies have evaluated factors that may contribute to the susceptibility and/or vulnerability of an individual to air pollutants. The definitions of susceptibility and vulnerability have been found to vary across studies, but in most instances "susceptibility" refers to biological or intrinsic factors (e.g., lifestage, sex, preexisting disease/conditions) while "vulnerability" refers to non-biological or extrinsic factors (e.g., socioeconomic status [SES]) (U.S. EPA, 2010c, 2009d). In the ISA and this PA, "at-risk" is the all-encompassing term used for groups with specific factors that increase the risk of O_3-related health effects in a population.

There are multiple avenues by which individuals, and ultimately populations, could experience increased risk for O_3-induced health effects. A population or lifestage[20] may exhibit greater effects with the same concentration or dose as the general population, or they may be at greater risk due to increased exposure to an air pollutant (e.g., time spent outdoors). A group with intrinsically increased risk would have some factor(s) that increases risk through a

[20] Lifestages, which in this case includes children and older adults, are factors that most people go through over the course of a lifetime, unlike the other factors associated with at-risk populations.

biological mechanism and, in general, would have a steeper concentration-risk relationship, compared to those not in the group. Factors that are often considered intrinsic include asthma and genetic background. A group of people could also have extrinsically increased risk, which would be through an external, non-biological factor, including, for example, socioeconomic status (SES) and diet. Some groups are at risk of increased internal dose at a given exposure concentration, for example, because of breathing patterns. This category would include people who work or exercise outdoors. Finally, there are those who might be placed at increased risk for experiencing greater exposures by being exposed at higher concentrations. This would include, for example, groups of people with greater exposure to ambient O_3 due to less availability or use of home air conditioners (i.e., more open windows on high ozone days).

Some factors described above are multifaceted and may influence the risk of O_3-related health effects through a combination of factors. For example, children tend to spend more time outdoors at higher levels of activity than adults, which leads to increased exposure and dose, but they also have biological (i.e., intrinsic) differences when compared to adults.

The following sections discuss factors for which the ISA concludes that there is evidence to support potentially increased risk of O_3-related health effects, and the overall weight of evidence for the factor. This discussion includes factors that potentially increase the risk of O_3-related health effects, regardless of whether the increased risk is due to intrinsic factors, extrinsic factors, or a combination, due to the often connected pathways between factors.

2.4.2.1 Approach to classifying factors that increase risk

To identify factors that potentially lead to some populations being at greater risk to O_3-related health effects, the evidence across relevant scientific disciplines (i.e., exposure sciences, dosimetry, controlled human exposure, toxicology, and epidemiology) was evaluated in Chapter 8 of the ISA. In this systematic approach, the collective evidence is used to examine coherence of effects across disciplines and determine biological plausibility. The ISA first focuses on studies (i.e., epidemiologic or controlled human exposure) that conduct stratified analyses to identify factors that may result in some populations being at greater risk of an air pollutant related health effect. These types of studies allow for an evaluation of populations exposed to similar air pollutant (e.g., O_3) concentrations within the same study design. Experimental studies also provide important lines of evidence in the evaluation of factors that may lead to increased risk of an air pollutant related-health effect. Toxicological studies conducted using animal models of disease and controlled human exposure studies that examine individuals with underlying disease or genetic polymorphisms may provide additional evidence of at-risk populations in the absence of stratified epidemiologic analyses. Experimental and toxicological studies can provide evidence of biological plausibility as well as provide support for coherence

with the health effects observed in epidemiologic studies. The collective results across the scientific disciplines comprise the overall weight of evidence that is used to determine whether a specific factor results in a population being at increased risk of an air pollutant related health effect.

Building on the causal framework discussed the Preamble to the ISA, and discussed in section 2.1 above, conclusions are made regarding the strength of evidence for each factor that may contribute to increased risk of an O_3-related health effect based on the evaluation and synthesis of evidence across scientific disciplines. The conclusions drawn considered the "Aspects to Aid in Judging Causality" discussed in Table 1 of the Preamble to the ISA. The categories considered for evaluating the evidence for potential increased risk of an O_3-related health effect are "adequate evidence," "suggestive evidence," "inadequate evidence," and "evidence of no effect." They are described in more detail in Table 8-1, Classification of Evidence for Potential At-Risk Factors, in the ISA (US EPA, 2012a).

2.4.2.2 Factors that increase risk

Specific groups within the general population, referred to as at-risk populations, are at increased risk of experiencing adverse health effects related to O_3 exposures. As discussed above, these groups can exhibit a greater risk of O_3-related health effects than the general population because of a number of different types of factors, which may be intrinsic or extrinsic in nature. Given the heterogeneity of individual responses to O_3 exposures, the severity of effects experienced by at-risk populations may be much greater than that experienced by the general population. Providing appropriate public health protection requires identification of populations potentially at greater risk from O_3 exposures.

A summarized below, the currently available evidence expands our understanding of populations identified to be at greater risk from the last review (i.e., people who are active outdoors, people with lung disease, children and older adults and people with increased responsiveness to O_3) (US EPA 2006, section 3.6.2) and supports the identification of additional factors that may lead to increased risk. For the purpose of this PA, only the factors for which there is adequate evidence for increased risk (this section) or suggestive evidence for potential increased risk (section 2.4.2.3) of O_3-related health effects will be considered.

<u>Asthma</u>

Previous O_3 AQCDs identified individuals with asthma as a population at increased risk of O_3-related health effects. Within the U.S., approximately 8.2% of adults have reported currently having asthma (Schiller et al., 2012) and 9.5% of children have reported currently

having asthma (Bloom et al., 2011). Table 2-3 below provides more detailed information on prevalence of asthma by age in the U.S.

Table 2-3. Prevalence of asthma by age in the U.S.

Age (years)	N (in thousands)	Percent
0-4	1,285	6.0
5-11	3,020	10.5
12-17	2,672	10.9
18-44	8,902	8.1
45-64	6,704	8.4
65-74	1,849	8.7
75+	1,279	7.4

Asthma prevalence is reported for "still has asthma"

Source: Statistics for adults: Schiller et al. (2012); Statistics for children: Bloom et al. (2011)

Multiple new epidemiologic studies included in the ISA have evaluated the potential for increased risk of O_3-related health effects in people with asthma, including: lung function; symptoms; medication use; airway hyperresponsiveness (AHR); and airway inflammation (also measured as exhaled nitric oxide fraction, or FeNO). A study of lifeguards in Texas reported decreased lung function with short-term O_3 exposure among both individuals with and without asthma, however, the decrease was greater among those with asthma (Thaller et al., 2008). A Mexican study of children ages 6-14 detected an association between short-term O_3 exposure and wheeze, cough, and bronchodilator use among asthmatics but not non-asthmatics, although this may have been the result of a small non-asthmatic population (Escamilla-Nuñez et al., 2008). A study of modification by AHR (an obligate condition among asthmatics) reported greater short-term O_3-associated decreases in lung function in elderly individuals with AHR, especially among those who were obese (Alexeeff et al., 2007). With respect to airway inflammation, in one study, a positive association was reported for airway inflammation among asthmatic children following short-term O_3 exposure, but the observed association was similar in magnitude to that of non-asthmatics (Barraza-Villarreal et al., 2008). Similarly, another study of children in California reported an association between O_3 concentration and FeNO that persisted both among

children with and without asthma as well as those with and without respiratory allergy (Berhane et al., 2011). Finally, Khatri et al. (2009) found no association between short-term O_3 exposure and altered lung function for either asthmatic or non-asthmatic adults, but did note a decrease in lung function among individuals with allergies.

New evidence for difference in effects among asthmatics has been observed in studies that examined the association between O_3 exposure and altered lung function by asthma medication use. A study of children with asthma living in Detroit reported a greater association between short-term O_3 and lung function for corticosteroid users compared with noncorticosteroid users (Lewis et al., 2005). Conversely, another study found decreased lung function among noncorticosteroid users compared to users, although in this study, a large proportion of non-users were considered to be persistent asthmatics (Hernández-Cadena et al., 2009). Lung function was not related to short-term O_3 exposure among corticosteroid users and non-users in a study taking place during the winter months in Canada (Liu et al., 2009a). Additionally, a study of airway inflammation reported a counterintuitive inverse association with O_3 of similar magnitude for all groups of corticosteroid users and non-users (Qian et al., 2009).

Controlled human exposure studies that have examined the effects of O_3 on individuals with asthma and healthy controls are limited. Based on studies reviewed in the 1996 and 2006 O_3 AQCDs, subjects with asthma appeared to be more sensitive to acute effects of O_3 in terms of FEV_1 and inflammatory responses than healthy non-asthmatic subjects. For instance, Horstman et al. (1995) observed that mild-to-moderate asthmatics, on average, experienced double the O_3-induced FEV_1 decrement of healthy subjects (19% versus 10%, respectively, $p = 0.04$). Moreover, a statistically significant positive correlation between FEV_1 responses to O_3 exposure and baseline lung function was observed in individuals with asthma, i.e., responses increased with severity of disease. Minimal evidence exists suggesting that individuals with asthma have smaller O_3-induced FEV_1 decrements than healthy subjects (3% versus 8%, respectively) (Mudway et al., 2001). However, the asthmatics in that study also tended to be older than the healthy subjects, which could partially explain their lesser response since FEV_1 responses to O_3 exposure diminish with age. Individuals with asthma also had significantly more neutrophils in the BALF (18 hours postexposure) than similarly exposed healthy individuals (Peden et al., 1997; Scannell et al., 1996; Basha et al., 1994). Furthermore, a study examining the effects of O_3 on individuals with atopic asthma and healthy controls reported that greater numbers of neutrophils, higher levels of cytokines and hyaluronan, and greater expression of macrophage cell-surface markers were observed in induced sputum of atopic asthmatics compared with healthy controls (Hernandez et al., 2010). Differences in O_3-induced epithelial cytokine expression were noted in bronchial biopsy samples from asthmatics and healthy controls (Bosson

et al., 2003). Cell-surface marker and cytokine expression results, and the presence of hyaluronan, are consistent with O_3 having greater effects on innate and adaptive immunity in these asthmatic individuals. In addition, studies have demonstrated that O_3 exposure leads to increased bronchial reactivity to inhaled allergens in mild allergic asthmatics (Kehrl et al., 1999; Jorres et al., 1996) and to the influx of eosinophils in individuals with pre-existing allergic disease (Vagaggini et al., 2002; Peden et al., 1995). Taken together, these results point to several mechanistic pathways which could account for the enhanced sensitivity to O_3 in subjects with asthma (see Section 5.4.2.2 in the ISA).

Toxicological studies (see section 8.2.2 in the ISA) provide biological plausibility for greater effects of O_3 among those with asthma or AHR. In animal toxicological studies, an asthmatic phenotype is modeled by allergic sensitization of the respiratory tract. Many of the studies that provide evidence that O_3 exposure is an inducer of AHR and remodeling utilize these types of animal models. For example, a series of experiments in infant rhesus monkeys have shown these effects, but only in monkeys sensitized to house dust mite allergen. Similarly, adverse changes in pulmonary function were demonstrated in mice exposed to O_3; enhanced inflammatory responses were in rats exposed to O_3, but only in animals sensitized to allergen. In general, it is the combined effects of O_3 and allergic sensitization which result in measurable effects on pulmonary function. In a pulmonary fibrosis model, exposure O_3 for 5 days increased pulmonary inflammation and fibrosis, along with the frequency of bronchopneumonia in rats. Thus, short-term exposure to O_3 may enhance damage in a previously injured lung.

In the 2006 O_3 AQCD, the potential for individuals with asthma to have greater risk of O_3-related health effects was supported by a number of controlled human exposure studies, evidence from toxicological studies, and a limited number of epidemiologic studies. In section 8.2.2, the ISA reports that in the recent epidemiologic literature some, but not all, studies report greater risk of health effects among individuals with asthma. Studies examining effect measure modification of the relationship between short-term O_3 exposure and altered lung function by corticosteroid use provided limited evidence of O_3-related health effects. However, recent studies of behavioral responses have found that studies do not take into account individual behavioral adaptations to forecasted air pollution levels (such as avoidance and reduced time outdoors), which may underestimate the observed associations in studies that examined the effect of O_3 exposure on respiratory health (Neidell and Kinney, 2010). This could explain some inconsistency observed among recent epidemiologic studies. The evidence from controlled human exposure studies provides support for increased detriments in FEV_1 and greater inflammatory responses to O_3 in individuals with asthma than in healthy individuals without a history of asthma. The collective evidence for increased risk of O_3-related health effects among

individuals with asthma from controlled human exposure studies is supported by recent toxicological studies which provide biological plausibility for heightened risk of asthmatics to respiratory effects due to O_3 exposure. Overall, the ISA finds there is adequate evidence for asthmatics to be an at-risk population.

Children

The 2010 Census reported that 27% of the U.S. population, or more than 83 million people, was under 20 years of age, with 13.1%, or more than 40 million people, under the age of 10 (Howden and Meyer, 2011). Children are considered to be at greater risk from O_3 exposure because their respiratory systems undergo lung growth until about 18-20 years of age and are therefore thought to be intrinsically more at risk for O_3-induced damage (U.S. EPA, 2006b). It is generally recognized that children spend more time outdoors than adults, and therefore would be expected to have higher exposure to O_3 than adults. The ventilation rates also vary between children and adults, particularly during moderate/heavy activity. Children aged 11 years and older and adults have higher absolute ventilation rates than children aged 1 -11 years. However, children have higher ventilation rates relative to their lung volumes, which tends to increase dose normalized to lung surface area. Exercise intensity has a substantial effect on ventilation rate, with high intensity activities resulting in nearly double the ventilation rate during moderate activity among children and those adults less than 31 years of age. For more information on time spent outdoors and ventilation rate differences by age group, see Section 4.X in the ISA.

The 1996 O_3 AQCD reported clinical evidence that children, adolescents, and young adults (<18 years of age) appear, on average, to have nearly equivalent spirometric responses to O_3 exposure, but have greater responses than middle-aged and older adults (U.S. EPA, 1996a). Symptomatic responses (e.g., cough, shortness of breath, pain on deep inspiration) to O_3 exposure, however, appear to increase with age until early adulthood and then gradually decrease with increasing age (U.S. EPA, 1996a). Complete lung growth and development is not achieved until 18-20 years of age in women and the early 20s for men; pulmonary function is at its maximum during this time as well.

Recent epidemiologic studies have examined different age groups and their risk to O_3-related respiratory hospital admissions and emergency department (ED) visits. Evidence for greater risk in children was reported in several studies. A study in Cyprus of short-term O_3 concentrations and respiratory hospital admissions (HA) detected possible effect measure modification by age with a larger association among individuals < 15 years of age compared with those > 15 years of age; the effect was apparent only with a 2-day lag (Middleton et al., 2008). Similarly, a Canadian study of asthma-ED visits reported the strongest O_3-related associations among 5- to 14-year olds compared to the other age groups (ages examined 0-75+) (Villeneuve et al., 2007). Greater O_3-associated risk in asthma-related ED visits were also

reported among children (<15 years) as compared to adults (15 to 64 years) in a study from Finland (Halonen et al., 2009). A study of New York City hospital admissions demonstrated an increase in the association between O_3 exposure and asthma-related hospital admissions for 6- to 18-year olds compared to those < 6 years old and those > 18 years old (Silverman and Ito, 2010). When examining long-term O_3 exposure and asthma HA among children, associations were determined to be larger among children 1 to 2 years old compared to children 2 to 6 years old (Lin et al., 2008b). A few studies reported positive associations among both children and adults and no modification of the effect by age.

The evidence reported in epidemiologic studies is supported by recent toxicological studies which observed O_3-induced health effects in immature animals. Early life exposures of multiple species of laboratory animals, including infant monkeys, resulted in changes in conducting airways at the cellular, functional, ultra-structural, and morphological levels. The studies conducted on infant monkeys are most relevant for assessing effects in children. Carey et al. (2007) conducted a study of O_3 exposure in infant rhesus macaques, whose respiratory tract closely resemble that of humans. Monkeys were exposed either acutely or in episodes designed to mimic human exposure. All monkeys acutely exposed to O_3 had moderate to marked necrotizing rhinitis, with focal regions of epithelial exfoliation, numerous infiltrating neutrophils, and some eosinophils. The distribution, character, and severity of lesions in episodically exposed infant monkeys were similar to that of acutely exposed animals. Neither exposure protocol for the infant monkeys produced mucous cell metaplasia proximal to the lesions, an adaptation observed in adult monkeys exposed in another study (Harkema et al., 1987a). Functional and cellular changes in conducting airways were common manifestations of exposure to O_3 among both the adult and infant monkeys (Plopper et al., 2007). In addition, the lung structure of the conducting airways in the infant monkeys was significantly stunted by O_3 and this aberrant development was persistent 6 months postexposure (Fanucchi et al., 2006).

Age may also affect the inflammatory response to O_3 exposure. Toxicological studies reported that the difference in effects among younger lifestage test animals may be due to age-related changes in antioxidants levels and sensitivity to oxidative stress. Further discussion of these studies may be found in section 8.3.1.1 of the ISA (US EPA, 2012a, p. 8-20).

The previous and recent human clinical and toxicological studies reported evidence of increased risk from O_3 exposure for younger ages, which provides coherence and biological plausibility for the findings from epidemiologic studies. Although there was some inconsistency, generally, the epidemiologic studies reported positive associations among both children and adults or just among children. The interpretation of these studies is limited by the lack of consistency in comparison age groups and outcomes examined. However, overall, the

epidemiologic, controlled human exposure, and toxicological studies provide adequate evidence that children are potentially at increased risk of O_3-related health effects.

Older adults

The ISA notes that older adults are at greater risk of health effects associated with O_3 exposure through a variety of intrinsic pathways (US EPA, 2012a, section 8.3.1.2). In addition, older adults may differ in their exposure and internal dose. Older adults were outdoors for a slightly longer proportion of the day than adults aged 18-64 years. Older adults also have somewhat lower ventilation rates than adults aged 31 - less than 61 years. For more information on time spent outdoors and ventilation rate differences by age group, see Section 4.4 in the ISA (US EPA, 2012a). The gradual decline in physiological processes that occur with aging may lead to increased risk of O_3-related health effects (U.S. EPA, 2006a). Respiratory symptom responses to O_3 exposure appears to increase with age until early adulthood and then gradually decrease with increasing age (U.S. EPA, 1996a); lung function responses to O3 exposure also decline from early adulthood (US EPA, 1996a). The reductions of these responses with age may put older adults at increased risk for continued O_3 exposure. In addition, older adults, in general, have a higher prevalence of preexisting diseases compared to younger age groups and this may also lead to increased risk of O_3-related health effects (see Table 8-3 in the ISA, US EPA, 2012a, p. 8-10). With the number of older Americans increasing in upcoming years (estimated to increase from 12.4% of the U.S. population to 19.7% between 2000 to 2030, which is approximately 35 million and 71.5 million individuals, respectively) this group represents a large population potentially at risk of O_3-related health effects (SSDAN CensusScope, 2010a; U.S. Census Bureau, 2010).

The majority of recent studies reported greater effects of short-term O_3 exposure and mortality among older adults, which is consistent with the findings of the 2006 O_3 AQCD. A study (Medina-Ramón and Schwartz, 2008) conducted in 48 cities across the U.S. reported larger effects among adults ≥65 years old compared to those < 65 years; further investigation of this study population revealed a trend of O_3-related mortality risk that gets larger with increasing age starting at age (Zanobetti and Schwartz, 2008). Another study conducted in 7 urban centers in Chile reported similar results, with greater effects in adults ≥65 years old (Cakmak et al., 2007). More recently, a study conducted in the same area reported similar associations between O_3 exposure and mortality in adults aged < 64 years old and 65 to 74 years old, but the risk was increased among older age groups (Cakmak et al., 2011). A study performed in China reported greater effects in populations ≥45 years old (compared to 5 to 44 year olds), with statistically significant effects present only among those ≥65 years old (Kan et al., 2008). An Italian study reported higher risk of all-cause mortality associated with increased O_3 concentrations among

individuals ≥85 year old as compared to those 35 to 84 years old (Stafoggia et al., 2010). The Air Pollution and Health: A European and North American Approach (APHENA) project examined the association between O_3 exposure and mortality for those <75 and ≥ 75 years of age. In Canada, the associations for all-cause and cardiovascular mortality were greater among those ≥75 years old. In the U.S., the association for all-cause mortality was slightly greater for those <75 years of age compared to those ≥75 years old in summer-only analyses. No consistent pattern was observed for CVD mortality. In Europe, slightly larger associations for all-cause mortality were observed in those <75 years old in all-year and summer-only analyses. Larger associations were reported among those <75years for CVD mortality in all-year analyses, but the reverse was true for summer-only analyses (Katsouyanni et al., 2009).

With respect to epidemiologic studies of O_3 exposure and hospital admissions, a positive association was reported between short-term O_3 exposure and respiratory hospital admissions for adults ≥65 years old but not for those adults aged 15 to 64 years (Halonen et al., 2009). In the same study, no association was observed between O_3 concentration and respiratory mortality among those ≥65 years old or those 15 to 64 years old. No modification by age (40 to 64 year olds versus >64 year olds) was observed in a study from Brazil examining O_3 levels and COPD ED visits.

Although some outcomes reported mixed findings regarding an increase in risk for older adults, recent epidemiologic studies report consistent positive associations between short-term O_3 exposure and mortality in older adults. The evidence from mortality studies is consistent with the results reported in the 2006 O_3 AQCD and is supported by toxicological studies providing biological plausibility for increased risk of effects in older adults. Also, older adults may be experiencing increased exposure compared to younger adults. Overall, the ISA concludes adequate evidence is available indicating that older adults are at increased risk of O_3-related health effects.

Diet

Diet was not examined as a factor potentially affecting risk in previous O_3 AQCDs, but recent studies have examined modification of the association between O_3 and health effects by dietary factors. Because O_3 mediates some of its toxic effects through oxidative stress, the antioxidant status of an individual is an important factor that may contribute to increased risk of O_3-related health effects. Supplementation with vitamins C and E has been investigated in a number of studies as a means of inhibiting O_3-mediated damage.

Two epidemiologic studies have examined effect measure modification by diet and found evidence that certain dietary components are related to the effect O_3 has on respiratory outcomes.

In one recent study the effects of fruit/vegetable intake and Mediterranean diet were examined. Increases in these food patterns, which have been noted for their high vitamins C and E and omega-3 fatty acid content, were positively related to lung function in asthmatic children living in Mexico City, and modified by O_3 exposure (Romieu et al., 2009). Another study examined supplementation of the diets of asthmatic children in Mexico with vitamins C and E (Sienra-Monge et al., 2004). Associations were detected between short-term O_3 exposure and nasal airway inflammation among children in the placebo group but not in those receiving the supplementation.

The epidemiologic evidence is supported by controlled human exposure studies, discussed in section 8.4.1 of the ISA, that have shown that the first line of defense against oxidative stress is antioxidants-rich extracellular lining fluid (ELF) which scavenge free radicals and limit lipid peroxidation. Exposure to O_3 depletes antioxidant levels in nasal ELF probably due to scrubbing of O_3; however, the concentration and the activity of antioxidant enzymes either in ELF or plasma do not appear to be related to O_3 responsiveness. Controlled studies of dietary antioxidant supplementation have demonstrated some protective effects of α-tocopherol (a form of vitamin E) and ascorbate (vitamin C) on spirometric measures of lung function after O_3 exposure but not on the intensity of subjective symptoms and inflammatory responses. Dietary antioxidants have also afforded partial protection to asthmatics by attenuating postexposure bronchial hyperresponsiveness. Toxicological studies discussed in section 8.4.1 of the ISA provide evidence of biological plausibility to the epidemiologic and controlled human exposure studies.

There is adequate evidence that individuals with diets lower in vitamins C and E are at risk for O_3-related health effects. The evidence from epidemiologic studies is supported by controlled human exposure and toxicological studies.

<u>Outdoor workers</u>

Studies included in the 2006 O_3 AQCD reported that individuals who participate in outdoor activities or work outside to be a population at increased risk based on consistently reported associations between O_3 exposure and respiratory health outcomes in these groups (U.S. EPA, 2006b). Outdoor workers are exposed to ambient O_3 concentrations for a greater period of time than individuals who spend their days indoors. As discussed in Section 4.Y of the ISA (US EPA, 2012) outdoor workers sampled during the work shift had a higher ratio of personal exposure to fixed-site monitor concentrations than health clinic workers who spent most of their time indoors. Additionally, an increase in dose to the lower airways is possible during outdoor exercise due to both increases in the amount of air breathed (i.e., minute ventilation) and a shift

from nasal to oronasal breathing. The association between FEV_1 responses to O_3 exposure and minute ventilation is discussed more fully in Section 6.2.3.1 of the 2006 O_3 AQCD.

Previous studies have shown that increased exposure to O_3 due to outdoor work leads to increased risk of O_3-related health effects, specifically decrements in lung function (U.S. EPA, 2006b). The strong evidence from the 2006 O_3 AQCD which demonstrated increased exposure, dose, and ultimately risk of O_3-related health effects in this population supports the conclusion that there is adequate evidence to indicate that increased exposure to O_3 through outdoor work increases the risk of O_3-related health effects.

2.2.4.3 Factors that potentially increase risk

There were four factors for which the ISA concludes that there is suggestive evidence for potential increased risk of O_3-related health effects. These include genetic factors, sex, SES and obesity. Each factor is discussed briefly below.

For variants in multiple genes there is suggestive evidence for potential increased risk to some populations from O_3 exposure. Controlled human exposure and epidemiologic studies have reported some evidence of O_3-related increases in respiratory symptoms or decreases in lung function with variants including GSTM1, GSTP1, HMOX1 and NQO1, although the results are not consistent across studies and gene variants. Future studies of these and other genes in human populations will be important for determining the role of each genotype and its effect on risk as well as finding coherence across the disciplines.

With respect to effect measure modification by sex, most studies examining the associations O_3 and mortality report females to be at greater risk than males, but minimal evidence is available regarding a difference between the sexes for other outcomes. Inconsistent findings were reported for respiratory and cardiovascular hospital admissions and ED visits, although there is some indication that females are at increased risk of O_3-related respiratory hospital admissions and ED visits. While O_3-related effects may occur in both men and women, there is suggestive evidence exists indicating that females are at potentially increased risk of O_3-related health effects as there are consistent findings among epidemiologic studies of mortality.

Overall, most studies have reported that individuals with low SES and those living in neighborhoods with low SES are more at risk for O_3-related health effects, resulting in increased risk of respiratory hospital admissions and ED visits. Inconsistent results have been observed in the few studies examining effect modification of associations between O_3 exposure and mortality and reproductive outcomes. Also, a controlled human exposure study does not support evidence of increased risk of respiratory morbidity among individuals with lower SES. Overall, evidence is suggestive of SES as a factor affecting risk of O_3-related health outcomes based on collective

evidence from epidemiologic studies of respiratory hospital admissions, but there is inconsistency among studies of mortality and reproductive outcomes. Further studies are needed to confirm this relationship, especially in populations within the U.S.

Multiple epidemiologic, human clinical and toxicological studies have reported suggestive evidence for increased O_3-related respiratory health effects among obese individuals. Future research of the effect modification by body mass index on the relationship between O_3 and nonrespiratory-related health outcomes, and studies examining the role of physical conditioning will advance understanding of obesity as a factor potentially increasing risk.

2.4.2.4 Summary of factors that increase or potentially increase risk

In this section, epidemiologic, controlled human exposure and toxicological studies have been discussed which indicate that various factors may lead to increased risk of O_3-related health effects. The populations identified in chapter 8 of the ISA that have "adequate" evidence for O_3-related health effects are individuals with asthma, younger and older age groups, individuals with certain dietary deficiencies, and outdoor workers, based on consistency in findings across studies and evidence of coherence in results from different scientific disciplines. Asthma as a factor affecting risk was supported by controlled human exposure and toxicological studies, as well as some evidence from epidemiologic studies. Generally, studies of age groups reported positive associations for respiratory hospital admissions and ED visits among children. Biological plausibility for this increased risk is supported by toxicological and clinical research. Children have higher exposure and dose due to increased time spent outdoors and ventilation rate, their lungs are still developing, and they are more likely than adults to have asthma. Most studies comparing age groups reported greater effects of short-term O_3 exposure on mortality among older adults, although studies of other health outcomes had inconsistent findings regarding whether older adults were at increased risk. Older adults may also withstand greater O_3 exposure and not seek relief as quickly as younger adults. Multiple epidemiologic, controlled human exposure and toxicological studies reported that diets deficient in vitamins E and C are associated with risk of O_3-related health effects. Previous studies have shown that increased exposure to O_3 due to outdoor work leads to increased risk of O_3-related health effects and it is clear that outdoor workers have higher exposures, and possibly greater internal doses, of O_3, which may lead to increased risk of O_3-related health effects.

In some cases, it is difficult to determine a factor that results in increased risk of effects. For example, previous assessments have included controlled human exposure studies in which some healthy individuals demonstrate greater O_3-related health effects compared to other healthy individuals. Intersubject variability has been observed for lung function decrements, symptomatic responses, pulmonary inflammation, AHR, and altered epithelial permeability in

healthy adults exposed to O_3 and these results tend to be reproducible within a given individual over a period of several months indicating differences in the intrinsic responsiveness. In many cases the reasons for the variability is not clear. This may be because one or some of the factors described above have not been evaluated in studies, or it may be that additional, unidentified factors influence individual responses to O_3.

As discussed in chapter 8 of the ISA, the challenges and limitations in evaluating the factors that can increase risk for experiencing O_3-related health effects may contribute to a lack of information about the factors that may increase risk from O_3 exposures. This lack of information may contribute to conclusions that evidence for some factors, such as genetic factors, sex, SES, and obesity provided "suggestive" evidence of increased risk, or that for a number of factors the evidence was inadequate to draw conclusions about potential increase in risk of effects. Overall, the factors most strongly supported as contributing to increased risk of populations for experience O_3-related effects were related to asthma, lifestage (children and older adults), dietary factors, and working outdoors.

2.4.3 Averting Behavior

The activity pattern of individuals is an important determinant of their exposure. Variation in O_3 concentrations among various microenvironments means that the amount of time spent in each location, as well as the level of activity, will influence an individual's exposure to ambient O_3. Activity patterns vary both among and within individuals, resulting in corresponding variations in exposure across a population and over time. Individuals can reduce their exposure to O_3 by altering their behaviors, such as by staying indoors, being active outdoors when air quality is better, and by reducing their activity levels or reducing the time being active outdoors on high-O_3 days. This is a topic that was not discussed in the 2006 AQCD. The evidence discussed below is new in this review.

The EPA has developed the Air Quality Index (AQI) to provide the public information about ambient levels of common air pollutants and associated health effects, if any (www.airnow.gov). The AQI describes the potential for health effects from O_3 (and other individual pollutants) in six color-coded categories of air-quality, ranging from Good (green), Moderate (yellow), Unhealthy for Sensitive Groups (orange), Unhealthy (red), and Very Unhealthy (purple), and Hazardous (maroon). Levels in the unhealthy ranges (i.e., Unhealthy for Sensitive Groups and above) come with recommendations about reducing exposure. Forecasted and actual AQI values for O_3 are reported to the public during the O_3 season.

The AQI advisories explicitly state that children, older adults, people with lung disease, and people who are active outdoors, may be at greater risk from exposure to O_3. People are advised to reduce exposure depending on the predicted O_3 levels and the likelihood of risk. This

advice includes being active outdoors when air quality is better, and reducing activity levels or reducing the time being active outdoors on high-O_3 days. Staying indoors to reduce exposure is not recommended until air quality reaches the Very Unhealthy or Hazardous categories.

Evidence of individual averting behaviors in response to AQI advisories has been found in several studies, including activity pattern and epidemiologic studies, especially for the at-risk populations, such as children, older adults, and people with asthma, who are targeted by the advisories. Such effects are less pronounced in the general population, possibly due to the opportunity cost of behavior modification. Epidemiologic evidence from a study (Neidell and Kinney, 2010) conducted in the 1990's in Los Angeles, CA reports increased asthma hospital admissions among children and older adults when O_3 alert days (1-hour max O_3 concentration >200 ppb) were excluded from the analysis of daily hospital admissions and O_3 concentrations (presumably thereby eliminating averting behavior based on high O_3 forecasts). The lower rate of admissions observed when alert days were included in the analysis suggests that estimates of health effects based on concentration-response functions that do not account for averting behavior may be biased towards the null.

2.4.4 Size of At-Risk Populations in the United States

One consideration in the assessment of potential public health impacts is the size of various population groups for which there is adequate evidence of increased risk for health effects associated with O_3-related air pollution exposure. The factors for which the ISA (EPA, 2012a, section 8.5, p. 8-36) judged the evidence to be "adequate" with respect to contributing to increased risk of O_3-related effects among various populations and lifestages included: asthma; age group (children and older adults); dietary factors; and, working outdoors.

With regard to asthma, Table 2.3 above summarizes information on the prevalence of current asthma by age in the U.S. adult population in 2010 (Schiller et al. 2012; children - Bloom et al., 2011). Individuals with current asthma constitute a fairly large proportion of the population, including more than 25 million people. Asthma prevalence tends to be higher in children than adults.

With regard to lifestages, based on U.S. census data from 2010 (Howden and Meyer, 2011), about 74 million people, or 24% of the U.S. population, are under 18 years of age and more than 40 million people, or about 13% of the U.S. population, are 65 years of age or older. Hence, large proportions of the U.S. population are included in age groups that are considered likely to be at increased risk for health effects from ambient O_3 exposure.

With regard to dietary factors, no statistics are available to estimate the size of an at-risk population based on nutritional status. However, in order to get an approximate estimate of the

potential size of this population, inference can be made that people living below the poverty level would be more likely to have reduced nutritional status. Based on data from the 2010 Census, about 46 million people (about 15% of the total population) live below the poverty level (DeNavas-Walt et al., 2011). Of these, about 26 million people were in the age range of 18 to 64 years (about 14 % of the people in that age range), and therefore would not be included in the groups (i.e., children and older adults) considered to be at increased risk from O_3 exposure simply because of their age.

With regard to outdoor workers, in 2010 approximately 11.7% of the total number of people (143 million people) employed, or about 16.8 million people, worked outdoors one or more day per week (O*NetOnline: http://www.onetonline.org/find/descriptor/result/4.C.2.a.1.c?a=1). Of these approximately 7.4% of the workforce, or about 7.8 million people, worked outdoors three or more days per week.

The health statistics data illustrate what is known as the "pyramid" of effects. At the top of the pyramid, there are approximately 2.5 million deaths from all causes per year in the U.S. population, with about 250 thousand respiratory-related deaths (CDC-WONDER, 2008). For respiratory health diseases, there are nearly 3.3 million hospital discharges per year (HCUP, 2007), 8.7 million respiratory ED visits (HCUP, 2007), 112 million ambulatory care visits (Woodwell and Cherry, 2004), and an estimated 700 million restricted activity days per year due to respiratory conditions (Adams et al., 1999). Combining small risk estimates with relatively large baseline levels of health outcomes can result in quite large public health impacts. Thus, even a small percentage reduction in O_3 health impacts on cardiopulmonary diseases would reflect a large number of avoided cases.

2.5 INTEGRATED DISCUSSION OF THE EVIDENCE

In this section, we revisit the overarching question for this chapter:

- **To what extent has scientific information become available that alters or substantiates our understanding of the health effects that occur following short-term or long-term exposures to O_3, and our understanding of the O_3 concentrations at which such effects occur?**

As in the last review, the clearest evidence for health effects associated with exposure to O_3 is provided by studies of respiratory effects. Collectively, there is a vast amount of evidence spanning several decades that supports a causal association between exposure to O_3 and a continuum of respiratory effects (US EPA, 2012a, section 2.5). The majority of this evidence is derived from studies investigating short-term exposures (i.e., hours to weeks) to O_3, although

animal toxicological studies and recent epidemiologic evidence demonstrate that long-term exposure (i.e., months to years) may also be detrimental to the respiratory system.

The 2006 O_3 AQCD concluded that there was clear, consistent evidence of a causal relationship between short-term exposure to O_3 and respiratory health effects (U.S. EPA, 2006). This causal relationship was substantiated by the coherence of effects observed across controlled human exposure, epidemiologic, and toxicological studies indicating associations of short-term O_3 exposures with a range of respiratory health endpoints. Across disciplines, short-term O_3 exposures induced or were associated with statistically significant declines in lung function. An equally strong body of evidence from controlled human exposure and toxicological studies demonstrated O_3-induced inflammatory responses, increased epithelial permeability, and airway hyperresponsiveness. Toxicological studies provided additional evidence for O_3-induced impairment of host defenses. Combined, these findings from experimental studies provided support for epidemiologic evidence, in which short-term O_3 exposure was consistently associated with increases in respiratory symptoms and asthma medication use in asthmatic children, respiratory-related hospital admissions, and asthma-related emergency department visits. Although O_3 was consistently associated with non-accidental and cardiopulmonary mortality, the contribution of respiratory causes to these findings was uncertain. The combined evidence across disciplines supported a causal relationship between short-term O_3 exposure and respiratory effects (US EPA, 2006).

Studies conducted since the last review have generally supported the conclusions of the 2006 AQCD regarding the strength of the evidence for respiratory effects following short-term O_3 exposures, with more recent studies reporting such effects following exposures to lower O_3 concentrations than previously reported. Specifically, as discussed above (section 2.2.1), recent controlled human exposure studies have reported lung function decrements, respiratory symptoms, and airway inflammation following exposures to O_3 concentrations from 60 to 80 ppb and recent epidemiologic studies have reported O_3-associated airway inflammation in locations with ambient O_3 concentrations below 75 ppb. These recent studies reinforce the large body of existing experimental and epidemiologic evidence for respiratory effects following exposures to somewhat higher O_3 concentrations.

The frequency of emergency department visits and hospital admissions due to respiratory symptoms, asthma exacerbations and other respiratory diseases is associated with short- and long-term exposure to ambient O_3 (US EPA, 2012a, section 2.5.3). Summertime daily hospital admissions for respiratory causes in various locations of eastern North America were consistently associated with ambient levels of O_3 in studies reviewed in the 1996 O_3 AQCD. The 2006 O_3 AQCD concluded that aggregate population time-series studies demonstrate a

positive and robust association between ambient O_3 concentrations and respiratory-related hospitalizations and asthma emergency department visits during the warm season. Recent epidemiologic time-series studies that include additional multicity studies and a multicontinent study further support that short-term exposures to ambient O_3 concentrations are consistently associated with increases in respiratory hospital admissions and emergency department visits specifically during the warm/summer months in multiple geographic locations and across a range of O_3 concentrations (Section 6.2.7). Recent evidence from several multicity studies and a multicontinent study also demonstrate consistent positive associations between short-term exposure to ambient O_3 concentrations and increases in respiratory mortality (Section 6.6.2.5). Evidence from recent mortality studies is consistent and coherent with the evidence from epidemiologic, controlled human exposure, and animal toxicological studies for the respiratory effects of O_3 exposures. Additionally, the evidence for respiratory morbidity after short- and long-term exposure provides biological plausibility for mortality due to respiratory disease.

In addition, recent epidemiologic studies provide greater insight into factors that may increase susceptibility to O_3-associated respiratory morbidity (e.g., presence of asthma and respiratory infection; presence of airway hyperresponsiveness or elevated body mass index, particularly in older adults; and groups with diminished antioxidant capacity). Across endpoints, recent studies indicate that groups with diminished antioxidant capacity or comorbidities such as atopy, AHR, or elevated body mass index may have increased susceptibility to respiratory morbidity associated with O_3 exposure. The potential susceptibility of these populations identified in recent epidemiologic studies are strongly supported by findings from experimental studies that demonstrated O_3-induced decreases in intracellular antioxidant levels, increases in airway responses with co-exposures to allergens, and increases in airway responses in animal models of obesity. By demonstrating O_3-induced airway hyperresponsiveness, decreased pulmonary function, allergic responses, lung injury, impaired host defense, and airway inflammation, recent toxicological studies have characterized O_3 modes of action and have provided biological plausibility for epidemiologic associations of ambient O_3 exposure with lung function and respiratory symptoms, hospital admissions, emergency department visits, and mortality. Together, the evidence integrated across controlled human exposure, epidemiologic, and toxicological studies and across the spectrum of respiratory health endpoints continues to demonstrate that there is a causal relationship between short-term O_3 exposure and respiratory health effects (US EPA, 2012a, section 6.2.1).

The strongest evidence for a relationship between long-term O_3 exposure and respiratory morbidity is contributed by recent studies from a single cohort demonstrating associations between long-term measures of O_3 exposure and new-onset asthma in children and increased

respiratory symptom effects in asthmatics. While the evidence is limited, this U.S. multi-community prospective cohort demonstrates that asthma risk is affected by interactions among genetic variability, environmental O_3 exposure, and behavior. Other recent studies provide coherent evidence for long-term O_3 exposure and respiratory morbidity effects such as first asthma hospitalization and respiratory symptoms in asthmatics. Generally, the epidemiologic and toxicological evidence provides a compelling case that supports the hypothesis that a relationship exists between long-term exposure to ambient O_3 and measures of respiratory morbidity. The evidence for short-term exposure to O_3 and effects on respiratory endpoints provides coherence and biological plausibility for the effects of long-term exposure to O_3. Building upon that evidence, the more recent epidemiologic evidence, combined with toxicological studies in rodents and non-human primates, provides biologically plausible evidence that there is likely to be a causal relationship between long-term exposure to O_3 and respiratory health effects.

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3. ASSESSMENT OF O_3-RELATED EXPOSURES AND RISKS

To put judgments about O_3-related health effects into a broader public health context, the first draft REA has developed and applied models to estimate human exposures to O_3 and O_3-associated health risks across the United States, with a specific focus on several urban study areas (US EPA, 2012b). Using such models, the first draft REA has estimated the O_3 exposures and health risks that are associated with recent air quality and with air quality adjusted to simulate just meeting the current O_3 standard (US EPA, 2012b). The second draft and final REA will also include estimates of O_3 exposures and health risks associated with air quality adjusted to simulate just meeting potential alternative O_3 standards.[1] The first draft REA has identified the following goals for the exposure and risk assessments: (1) to provide estimates of the number of people in the general population and in sensitive populations with O_3 exposures above short-term benchmark levels; (2) to provide estimates of the number of people in the general population and in sensitive populations with impaired lung function resulting from short-term exposures to O_3; (3) to provide estimates of the potential magnitude of premature mortality and/or selected morbidity health effects in the population, including sensitive populations, associated with recent short-term ambient concentrations of O_3 and with just meeting the current O_3 NAAQS in selected urban study areas; (4) to develop a better understanding of the influence of various inputs and assumptions on the risk estimates to more clearly differentiate alternative standards that might be considered including potential impacts on various sensitive populations; (5) to gain insights into the distribution of risks and patterns of risk reduction and uncertainties in those risk estimates, and (6) to understand the national mortality burden associated with recent ambient O_3, and how well the risk estimates for the set of urban areas modeled reflect the national distribution of mortality risk (US EPA, 2012b, section 1.2).

Air quality inputs to the exposure and risk assessments include: (1) recent air quality data for O_3 from selected urban study areas; (2) simulated air quality for the selected urban areas that reflects changes in the distribution of O_3 air quality estimated to occur when an area just meets the current O_3 NAAQS, and (3) O_3 air quality surfaces for recent years covering the entire continental U.S. for use in the national scale assessment. The exposure and risk analyses are based on the five most recent years of air quality data available at this time, 2006-2010, in order to reflect the considerable variability in meteorological conditions and the variation in O_3

[1]Air quality simulations are meant to provide perspective on the O_3-associated exposures and health risks under different air quality scenarios. These simulations do not reflect any consideration of specific control programs or strategies designed to achieve the reductions in emissions required to meet the specified standards. Further, these simulations do not represent predictions of when, whether, or how areas might meet the specified standards.

precursor emissions that have occurred in recent years.[2] The analyses in the draft REA focus primarily on the months of May to September, when O_3 concentrations are likely to be highest in urban areas (US EPA, 2012b, section 3.2.1).

Simulation of just meeting the current O_3 standard is accomplished in this first draft REA using a quadratic rollback method, similar to that used in the previous risk and exposure analysis for the 2008 O_3 NAAQS review (US EPA, 2007). In evaluating just meeting the current standard, the first draft REA focused on air quality changes that were likely to occur as the U.S. puts in place programs to meet the standard. As such, the REA used U.S. background concentrations as a floor for the quadratic rollback. The first draft REA also explored alternative simulation approaches based on modeled sensitivities of ozone to U.S. emissions. These alternative approaches, which will be evaluated more fully in the second draft REA,[3] will remove the need for imposing a specific floor to prevent adjustments beyond those likely to occur due to U.S. emissions reductions.

In selecting health endpoints on which to base estimates of O_3-related health impacts, the first draft REA considers the weight-of-evidence conclusions from the ISA. Specifically, the first draft REA notes the ISA conclusions that there is a causal relationship between short-term O_3 exposures and respiratory effects and a likely causal relationship between short-term O_3 exposures and all-cause mortality. In light of these conclusions, the first draft REA estimates respiratory effects and all-cause mortality following short-term O_3 exposures (section 2.1, above).[4] The remainder of this chapter discusses the assessment of O_3 exposures (section 3.1) and O_3-associated health risks (section 3.2) for recent O_3 air quality concentrations and for O_3 air quality adjusted to simulate just meeting the current 8-hour O_3 NAAQS.

3.1 EXPOSURE ASSESSMENT

The exposure assessment, which provides estimates of the number of people exposed to different concentrations of ambient O_3 while at specified exertion levels, serves two purposes.

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[2] The national-scale risk analyses are based on air quality data from 2006-2008, given available air quality modeling data for that time period.

[3] In the second draft, the REA will evaluate approaches for simulating attainment of current and alternative standards that are based on modeling the response of O_3 concentrations to reductions in anthropogenic NOx and VOC emissions, using the Higher-order Decoupled Direct Method (HDDM) capabilities in the Community Multi-scale Air Quality (CMAQ) model. This modeling incorporates all known emissions, including emissions from nonanthropogenic sources and anthropogenic emissions from sources in and outside of the U.S. As a result, the need to specify values for U.S. background is not necessary, as it is incorporated in the modeling directly. The evaluation of this new approach is presented in Chapter 4 of the draft REA (US EPA, 2012b) and in Simon et al. (2012).

[4] The first draft REA does not evaluate risks associated with long-term exposures, but notes that such risks could be assessed in the second draft REA (US EPA, 2012b, section 7.7).

First, the entire range of modeled personal exposures to ambient O_3 is an essential input to the portion of the health risk assessment based on exposure-response functions from controlled human exposure studies, discussed in the next section (i.e., section 3.2).[5] Second, estimates of personal exposures (both the number and percent of total populations and sensitive subpopulations) to ambient O_3 concentrations at and above specific health benchmark levels provide perspective on the potential public health impacts of O_3-related health effects, including effects that cannot currently be evaluated in a quantitative risk assessment.

As part of the 2008 review of the O_3 NAAQS, the EPA conducted exposure analyses in 12 metropolitan areas representing different regions of the United States where the then-current 8-hour O_3 standard was not met. For each of these metropolitan areas, O_3 exposures were estimated for the general population, for school age children (ages 5–18), and for school age children with asthma. The emphasis on children reflected the finding of the 1997 O_3 NAAQS review that children are an important at-risk group. The 12 modeled areas included 89 million people, including 18 million school age children, 2.6 million of whom had asthma. The selection of urban areas to include in the exposure analysis took into consideration the location of O_3 epidemiological studies, the availability of ambient O_3 monitoring data, and the desire to represent a range of geographic areas, population demographics, and O_3 climatology. These selection criteria are discussed further in chapter 5 of the 2007 Staff Paper (EPA, 2007).

The exposure analysis conducted for the current review in the first draft REA builds upon the methodology and lessons learned from the exposure analyses conducted in previous reviews, as well as information provided in the third draft ISA (US EPA, 2012a). EPA will be conducting exposure modeling for 16 urban areas located across the United States (US EPA, 2012b). In the first draft REA, results are presented for four of these areas, Atlanta, Denver, Los Angeles, and Philadelphia. The criteria and considerations that went into selection of these urban areas for the O_3 risk assessment included the following:

- The overall set of urban locations should represent a range of geographic areas, urban population demographics, and climatology.
- The locations should be focused on areas that do not meet or are close to not meeting the current 8-hr O_3 NAAQS and should include the largest areas with major O_3 nonattainment problems.
- There must be sufficient O_3 air quality data for the recent 2006-2010 period.

[5]As noted in the first draft REA, the quantitative assessment of respiratory health risks based on controlled human exposure studies is under development and will be made available along with this first draft Policy Assessment. Therefore, the characterization of such respiratory health risks will be considered in the second draft Policy Assessment.

- The areas should include the 12 cities modeled in the epidemiologic-based risk assessment.

In considering exposure estimates, the draft REA noted that there are several sources of variability and uncertainty inherent in assessment inputs and that there is uncertainty in the resulting O_3 exposure estimates. The exposure modeling approach accounts for variability in ambient O_3 concentrations, demographic characteristics, physiological attributes, activity patterns, and factors affecting microenvironmental (e.g., indoor) concentrations. Among the most important uncertainties affecting the exposure estimates are those related to the modeling of human activity patterns over an O_3 season, the modeling of variations in ambient concentrations across urban areas, the modeling of air exchange rates that affect the amount of O_3 that penetrates indoors, and the characterization of energy expenditure and breathing rates for children engaged in various activities. These uncertainties will be characterized more fully in the second draft REA (US EPA, 2012b, section 5.5.2).

The remainder of this section discusses the approach taken in the draft REA to assess O_3 exposures (3.1.1) and the key observations from the REA analyses of O_3 exposures (section 3.1.2).

3.1.1 Approach to Assessing O_3 Exposures

Population exposures to O_3 are driven primarily by exposures to ambient concentrations, which vary by time of day, location, and peoples' activities. In the absence of large scale exposure studies that encompass the overall population as well as at-risk subpopulations, exposure modeling is the preferred approach to estimating population exposures to O_3. In the first draft REA, population exposures to ambient ozone concentrations were evaluated using the current version of the Air Pollutants Exposure (APEX) model. The APEX model simulates the movement of individuals through time and space and estimates their exposures to a given pollutant in indoor, outdoor, and in-vehicle microenvironments (US EPA, 2011c, section 3.2). APEX takes into account the most significant factors that contribute to total human O_3 exposure, including the temporal and spatial distribution of people and O_3 concentrations throughout an urban area, the variation of O_3 concentrations within each microenvironment, and the effects of exertion on breathing rate in exposed individuals.

The first draft REA developed exposure estimates for four urban areas for recent O_3 concentrations during the O_3 season, based on 2006-2010 air quality data, and for ozone concentrations adjusted to simulate just meeting the current 8-hour ozone NAAQS, based on adjusting 2006-2010 air quality data to simulate attainment for the 2006-2008 and 2008-2010

periods, reflecting the 3-year average period over which the current standard is evaluated. Exposure estimates based on adjusted air quality allow consideration of the extent to which O_3-related exposures and associated health impacts might be reduced by meeting the current O_3 NAAQS. Multiple years were modeled in order to reflect the substantial year-to-year variability that occurs in ambient O_3 concentrations and related meteorological conditions, and because the standard is specified in terms of a three-year period. The year-to-year variability observed in O_3 levels is due to a combination of different weather patterns and the variation in emissions of O_3 precursors. For each year and in each urban location, the O_3 season was modeled in order to characterize the period of the year where the highest O_3 concentrations tend to occur. Exposures were estimated for the general population, school-age children (ages 5 to 18), and asthmatic school-age children. This choice of population groups includes a strong emphasis on children, which reflects the findings of the last O_3 NAAQS review (EPA, 2007) and the third draft ISA in the current review (EPA, 2012a, Chapter 8) that children are an important at-risk group. Children breathe more air per pound of body weight, are more likely than adults to have asthma, and their lungs continue to develop until they are fully grown.

As noted above, one of the main purposes of O_3 exposure estimates is to provide information on population exposures to O_3 concentrations exceeding health benchmarks, which are based on the available evidence for respiratory effects following exposures to specific O_3 concentrations, as assessed in the third draft ISA (US EPA, 2012a, section 6.2). Estimates of exposures at or above discrete benchmark concentrations provide some perspective on the public health impacts of O_3-related health effects that have been demonstrated in controlled human exposure and toxicological studies but that cannot be evaluated in quantitative risk assessments, such as lung inflammation, increased airway responsiveness, and changes in lung host defenses. They also help in understanding the extent to which such impacts have the potential to be reduced by meeting the current and potential alternative standards. Identification of O_3 benchmark concentrations for analysis are based on consideration of the range of health effects reported in controlled human exposure and epidemiologic studies, including effects that are not assessed in the quantitative health risk assessment discussed in section 3.2 below.

Though this analysis is conducted using discrete benchmark concentrations, health-relevant exposures are more appropriately viewed as a continuum with greater confidence and less uncertainty about the existence of health effects at higher O_3 exposure concentrations and less confidence and greater uncertainty as one considers increasingly lower exposure concentrations. In considering these results, it is important to balance concerns about the potential for health effects and their severity with the increasing uncertainty associated with our understanding of the likelihood of such effects following exposures to lower O_3 concentrations.

The draft REA evaluates specific benchmark concentrations from 60 to 80 ppb (i.e., 60, 70, 80 ppb) (US EPA, 2012b, section 5.5), based on controlled human exposure studies that report respiratory effects following O_3 exposures in healthy exercising adults. As discussed above (section 2.2.1) and in more detail in the ISA (US EPA, 2012a, section 6.2), there is a substantial body of evidence from controlled human exposure studies reporting that prolonged (e.g., 6.6 hour) exposures to O_3 concentrations from 60 to 80 ppb during moderate levels of exertion result in a range of respiratory effects in healthy adult subjects. These effects include decrements in lung function, increased airway inflammation, increased respiratory symptoms, and increased airway responsiveness (section 2.2.1, above). As O_3 exposure concentrations decrease from 80 to 60 ppb, the breadth of reported O_3-induced effects decrease, the magnitudes of those effects decrease, and the consistency and statistical precision of those effects decrease, with 60 ppb the lowest exposure concentration for which such respiratory effects have been reported.

3.1.2 Key Observations: Exposures to O_3 Concentrations Above Health Benchmarks

The first draft REA presents a series of figures and tables characterizing the percents and numbers of school-age children who experience at least one 8-hour average O_3 exposure above the different benchmark concentrations (60, 70, 80 ppb), while at the same time undergoing exercise of moderate or greater intensity (US EPA, 2012b, Figures 5-1 through 5-15), in four cities (Atlanta, Denver, Los Angeles, Philadelphia). In characterizing the results of these analyses, the REA noted that the APEX model is not proficient at modeling activity patterns that lead to repeated exposures to elevated ozone concentrations. As a result, while the REA reported the numbers and percentages of children with at least one exposure greater than the alternative exposure benchmarks, the REA did not report the numbers or percentages of children estimated to experience more than one exposure. Children with repeated exposures may be at greater risk of significant health effects, an issue that could be explored more fully in the second draft REA. Key observations from the REA exposure analyses are discussed below.

Across the years included in the analysis (2006-2010), the pattern of exposures differed. For example, in the worst O_3 year (2006) the percent of children exposed to 8-hour O_3 concentrations at or above 60 ppb while at moderate or greater exertion ranged from 30 to 37% across the 4 study areas; the percent exposed to 8-hour concentrations at or above 70 ppb ranged from 10 to 21%; and the percent exposed to 8-hour concentrations at or above 80 ppb ranged from 1 to 10%. In the year with the lowest O_3 concentrations (2009), the percent of children exposed to 8-hour O_3 concentrations at or above 60 ppb while at moderate or greater exertion ranged from 9 to 32%; the percent exposed to 8-hour concentrations at or above 70 ppb ranged from 1 to 15%; and the percent exposed to 8-hour concentrations at or above 80 ppb ranged from

0 to 5%. With unadjusted air quality, the average (i.e., average across years 2006 to 2010) percentages of school age children estimated to experience one or more exposures per year to 8-hour O_3 concentrations above 60, 70, or 80 ppb, while at moderate or greater exertion, were as follows (US EPA, 2012b, Figures 5-1 to 5-15, Tables 4-5 to 4-6, and section 9.1):

- For Denver, approximately 20% above 60 ppb (corresponding to 109,000 children), 4% above 70 ppb (corresponding to approximately 22,000 children), and 0.4% above 80 ppb (corresponding to approximately 2,200 children)

- For Atlanta, approximately 22% above 60 ppb (corresponding to 189,000 children), 9% above 70 ppb (corresponding to approximately 75,000 children), and 3% above 80 ppb (corresponding to approximately 24,000 children)

- For Philadelphia, approximately 26% above 60 ppb (corresponding to 297,000 children), 10% above 70 ppb (corresponding to 117,000 children), and 2% above 80 ppb (corresponding to approximately 28,000 children)

- For Los Angeles, approximately 32% above 60 ppb (corresponding to 1,150,000 children), 15% above 70 ppb (corresponding to 559,000 children), and 6% above 80 ppb (corresponding to approximately 218,000 children)

When air quality was adjusted to simulate just meeting the current O_3 NAAQS, these estimated benchmark exceedances decreased. Specifically, for adjusted air quality, the average percentages of school age children estimated to experience one or more exposures per year to 8-hour O_3 concentrations above 60, 70, or 80 ppb, while at moderate or greater exertion, were as follows[6] (US EPA, 2012b, Figures 5-1 to 5-15, Tables 4-5 to 4-6):

- For Denver, approximately 9-11% above 60 ppb (corresponding to approximately 51,000-61,000 children), 0.6-0.7% above 70 ppb (corresponding to approximately 3,300-4,200 children), and 0.0% above 80 ppb

- For Atlanta, approximately 8-10% above 60 ppb (corresponding to approximately 72,000-83,000 children), 1% above 70 ppb (corresponding to approximately 9,600-11,200 children), and 0.1% above 80 ppb (corresponding to approximately 700-900 children)

- For Philadelphia, approximately 9-13% above 60 ppb (corresponding to approximately 105,000-145,000 children), 1-2% above 70 ppb (corresponding to approximately 10,000-26,000 children), and 0.0-0.1% above 80 ppb (corresponding to approximately 500-1,600 children)

[6]The ranges presented represent the range of estimates across each of the 3-year periods for which air quality was adjusted to simulate just meeting the current O_3 NAAQS (i.e., 2006-2008, 2008-2010).

- For Los Angeles, approximately 4% above 60 ppb (corresponding to approximately 126,000-148,000 children), 0.2-0.3% above 70 ppb (corresponding to approximately 7,500-11,300 children), and 0.0% above 80 ppb

When considering exposures above benchmark concentrations in asthmatic children at moderate or greater exertion, the results were similar in term of percentages (US EPA, 2012b, Tables 5-11 and 5-12). When air quality was adjusted to simulate just meeting the current O_3 NAAQS, the numbers of asthmatic children estimated to be exposed one or more times per year to 8-hour O_3 concentrations at or above 60 ppb, while at moderate exertion, ranged from approximately 5,000 to 17,000 across these four cities; the numbers of asthmatic children estimated to be exposed to O_3 concentrations at or above 70 ppb ranged from approximately 300 to 3,000 across cities; and the numbers of asthmatic children estimated to be exposed to O_3 concentrations at or above 80 ppb ranged from 0 to approximately 200 across cities (US EPA, 2012b, Tables 5-11 and 5-12).

3.2 RISK ASSESSMENT

For some health endpoints, there is sufficient scientific evidence and information available to support the development of quantitative estimates of O_3-related health risks. In the last review of the O_3 NAAQS, the quantitative health risk assessment estimated the risks of lung function decrements in all children and in asthmatic school age children, of respiratory symptoms in asthmatic children, of respiratory-related hospital admissions, and of non-accidental and cardiorespiratory-related mortality. Both controlled human exposure and epidemiologic studies were used for the quantitative assessment of O_3-related human health risks.

In the current review, the health risk assessments in the first draft REA estimated O_3-attributable all-cause mortality; hospital admissions and emergency department visits for respiratory causes; and respiratory symptoms in asthmatics. The first draft REA will also estimate O_3-attributable lung function decrements, though these analyses will be made available in conjunction with the release of this first draft Policy Assessment and, therefore, will be fully considered in the second draft Policy Assessment (US EPA, 2012b, chapter 6). Ozone-attributable health effects have been estimated for recent ambient O_3 concentrations, based on 2006-2010 air quality data, as well as for ambient concentrations associated with just attaining the current 8-hour ozone NAAQS, based on adjusting 2006-2010 air quality data.[7]

[7]As with the exposure assessment, the second draft REA will also estimate O_3 health risks associated with just meeting different potential alternative O_3 standards.

Section 3.2.1 below discusses the risk assessment based on concentration-response relationships from epidemiologic studies, which are used as the health basis for assessing all-cause mortality; respiratory-related hospital admissions and emergency room visits; and respiratory symptoms. Section 3.2.2 provides a placeholder for the discussion of the risk assessment based on exposure-response relationships for lung function derived from controlled human exposure studies.

3.2.1 Risk Assessment Based on Epidemiologic Studies

As discussed in the third draft ozone ISA (EPA, 2012a, chapter 6), a number of O_3 epidemiologic studies have evaluated associations between short-term O_3 concentrations and mortality or morbidity in different locations across the United States. The first draft REA evaluated risks of mortality and morbidity from short-term exposures to O_3 based on application of concentration-response functions derived from such epidemiologic studies. The analyses included both a set of urban area case studies and a national scale assessment.

The urban case study analyses evaluated mortality and morbidity risks, including emergency department visits, hospitalizations, and respiratory symptoms associated with recent O_3 concentrations (2006-2010) and with O_3 concentrations adjusted to simulate just meeting the current O_3 standard. Mortality and hospital admissions (HA) were evaluated in 12 urban areas, while emergency department visits and respiratory symptoms were evaluated in subsets of these 12 areas. The 12 urban areas were: Atlanta, GA; Baltimore, MD; Boston, MA; Cleveland, OH; Denver, CO; Detroit, MI; Houston, TX; Los Angeles, CA; New York, NY; Philadelphia, PA; Sacramento, CA; and St. Louis, MO. The urban case study analyses focused on risk estimates for the middle year of each three-year attainment simulation period (2006-2008 and 2008-2010) in order to provide estimates of risk for a year with generally higher O_3 levels (2007) and a year with generally lower O_3 levels (2009) (US EPA,2012b, section 9.3).

The national scale assessment evaluated only mortality associated with recent O_3 concentrations across the entire U.S for 2006-2008. The national scale assessment is a complement to the urban scale analysis, providing both a broader assessment of O_3-related health risks across the U.S., as well as an evaluation of how well the 12 urban study areas represented the full distribution of ozone-related health risks in the U.S.

Both the urban area and national scale assessments provided the absolute incidence and percent of incidence attributable to O_3. In modeling risks, the REA employed continuous non-threshold concentration-response functions, reflecting the conclusions reached in the ISA (US EPA, 2012a, sections 6.2.7 and 6.6.2.4). However, the draft REA also recognized that confidence is increased in the concentration-response function as it is applied to O_3

concentrations closer to the central mass of O_3 measurements used in the underlying epidemiological study. Specifically, the REA noted that estimates of risk associated with O_3 concentrations below the lowest measured level (LML) for the underlying epidemiological study would be associated with reduced confidence since these estimates involve applying the concentration-response function outside of the range of data used in its derivation. In light of this, the REA has characterized mortality risks in excess of lowest measured O_3 concentrations[8] as well as total risks associated with O_3 concentrations down to zero (US EPA, 2012b, sections 7.3.3 and 8.1.1.4).[9] In considering these different approaches, the REA concluded that the two sets of estimates provide a reasonable bound on estimated total risks, reflecting uncertainties about the concentration-response functions below the lowest ozone concentrations evaluated in the studies.

The remainder of this section discusses the key observations from the analyses in the REA with regard to O_3-attributable all-cause mortality (section 3.2.1.1) and O_3-attributable morbidity effects, including hospital admissions, emergency department visits, and respiratory symptoms (section 3.2.1.2). Section 3.2.1.3 identifies key sources of variability and uncertainty in these risk assessments, as discussed in the REA.

3.2.1.1 All-cause mortality

As noted above, the REA estimated O_3-attributable mortality in a national assessment for 2006-2008 air quality and in 12 specific urban areas for 2007 and 2009 air quality and, in the case of the 12 urban areas, for 2007 and 2009 air quality adjusted to simulate just meeting the current standard. Mortality estimates were based on concentration-response relationships from two studies (Bell et al., 2004; Zanobetti and Schwartz, 2008). For the 12 urban area risk analysis, estimates of mortality attributable to short-term O_3 exposures under recent conditions varied widely across urban study areas, reflecting differences in ambient O_3 concentrations and populations, as well as differences in city-specific effect estimates. The estimates based on Zanobetti and Schwartz (2008) showed the largest O_3-associated mortality risks in Boston, Detroit, Los Angeles, and New York, while the estimates based on Bell et al (2004) showed the largest risks in Atlanta, Boston, Houston, Los Angeles, and New York (US EPA, 2012b, section 9.3).

Across the 12 study cities, and using estimates based on both Bell et al. (2004) and Zanobetti and Schwartz (2008), O_3-attributable mortality risk estimates for unadjusted air quality

[8] Due to data limitations, the REA did not identify the actual LMLs from the epidemiologic studies used in the risk assessment. Rather, as a surrogate for the study-based LMLs, the REA used the lowest O_3 concentrations from the composite monitor O_3 distributions used to model health risks (US EPA, 2012b, section 7.1.1).

[9] For morbidity endpoints, risks were estimated down to the LML but not for total O_3 concentrations down to zero (US EPA, 2012b, chapter 7).

ranged from approximately 20 to 930 deaths, accounting for approximately 0.5 to 4.9% of total baseline all-cause mortality (for 2007 air quality). When risk estimates were focused on O_3 concentrations above the LML, risk estimates were somewhat smaller (i.e., approximately 10 to 730 deaths across the different cities). For 2009 unadjusted air quality, the O_3-attributable mortality risk estimates ranged from 20 to approximately 980 deaths across the 12 cities, accounting for approximately 0.6 to 4.3% of total baseline all-cause mortality. When risk estimates were focused on O_3 concentrations above the LML, these risk estimates ranged from approximately 10 to 780 deaths across cities, accounting for approximately 0.4 to 3.0% of total baseline all-cause mortality. Mortality estimates based on O_3 effect estimates from Bell et al. (2004) were generally larger than estimates based on effect estimates from Zanobetti and Schwartz (2008), likely due to the larger effect estimates reported by Bell et al. and to the longer O_3 season modeled in Bell et al. (US EPA, 2012b, Table 7-4).

After simulating just meeting the current standard, estimates of O_3-attributable mortality decreased across the 12 study cities, as noted in Table 4-1 of the first draft REA (US EPA, 2012b, section 7.5). Specifically, in considering estimates based on effect estimates from both epidemiologic studies, we note that reductions in O_3-attributable mortality upon simulation of just meeting the current O_3 NAAQS were estimated to range from approximately 10 to 50% for 2007 air quality and approximately 0.1 to 35% for 2009 air quality. Although this suggests the potential for important risk reductions as precursor emissions are reduced to meet the current NAAQS, particularly when these percentages are considered within the context of national estimates of O_3-attributable mortality, estimates also suggest that substantial O_3-attributable risks will remain after meeting the current NAAQS. With regard to the O_3-attributable mortality risks estimated to remain after air quality was adjusted to simulate just meeting the current O_3 NAAQS, we specifically note the following:

- Using effect estimates from Zanobetti and Schwartz (2008) for the 2007 simulation year, the REA estimated that the range of remaining O_3-attributable deaths in the 12 U.S. study cities was approximately 20-850, based on estimates with no O_3 concentration cutoff, and 10-630, based on estimates down to the LML. The cities with the largest remaining O_3-attributable mortality risks were New York City [849 (no cutoff), 626 (LML)], Detroit [212 (no cutoff), 122 (LML)], and Boston [209 (no cutoff), 110 (LML)].

- Using effect estimates from Zanobetti and Schwartz (2008) for the 2009 simulation year, the REA estimated that the range of remaining O_3-attributable deaths in the 12 U.S. study cities was approximately 20-780, based on estimates with no O_3 concentration cutoff, and 10-520, based on estimates down to the LML. The cities with the largest remaining O_3-attributable mortality risks were New York City [777 (no cutoff), 521 (LML)], Detroit [178 (no cutoff), 127 (LML)], Boston [180 (no cutoff), 93 (LML)], and Los Angeles [175 (no cutoff), 83 (LML)].

- Using effect estimates from Bell et al. (2004) for the 2007 simulation year, the REA estimated that the range of remaining O_3-attributable deaths in the 12 U.S. study cities was approximately 30-830, based on estimates with no O_3 concentration cutoff, and 30-590, based on estimates down to the LML. The cities with the largest remaining O_3-attributable mortality risks were New York City [827 (no cutoff), 585 (LML)], Los Angeles [786 (no cutoff), 567 (LML)], Boston [404 (no cutoff), 282 (LML)], Atlanta [415 (no cutoff), 260 (LML)], Houston [270 (no cutoff), 217 (LML)], and St. Louis [193 (no cutoff), 157 (LML)].

- Using effect estimates from Bell et al. (2004) for the 2009 simulation year, the REA estimated that the range of remaining O_3-attributable deaths in the 12 U.S. study cities was approximately 30-820, based on estimates with no O_3 concentration cutoff, and 20-630, based on estimates down to the LML. The cities with the largest remaining O_3-attributable mortality risks were Los Angeles [821 (no cutoff), 628 (LML)], New York City [764 (no cutoff), 576 (LML)], Atlanta [364 (no cutoff), 315 (LML)], Boston [369 (no cutoff), 250 (LML)], and Houston [272 (no cutoff), 211 (LML)].

In the national analysis of O_3-attributable mortality for the years 2006 to 2008, the REA estimated 18,000 O_3-attributable deaths based on O_3 effect estimates from Bell et al. (2004) and 15,000 O_3-attributable deaths based on O_3 effect estimates from Zanobetti and Schwartz (2008), accounting for approximately 1.9 to 2.5% of total mortality (US EPA, 2012b, chapter 8, Tables 1.2 and 1.3). Of these O_3-attributable deaths, the first draft REA estimated that 85-90% occur in locations where the seasonal average 8-hr daily maximum or 8-hr daily mean (10am-6pm) O_3 concentration is greater than 40 ppb, corresponding to 4th high 8-hour daily maximum O_3 concentrations ranging from approximately 50 ppb to 100 ppb. In addition, the national analysis showed that the 12 urban study areas considered in the city-specific risk assessment represent the overall distribution of risk across the nation well, with a potential for better characterization of the high end of the risk distribution.

3.2.1.2 Respiratory morbidity

As noted above, the REA also estimated O_3-attributable respiratory hospital admissions for the 12 urban study areas, and emergency department visits and asthma exacerbations for subsets of the 12 cities, based on availability of data. These estimates were based on concentration-response relationships from several available epidemiologic studies, using different statistical approaches (US EPA, 2012b, section 7.5, Table 7-4), and they characterized risks for O_3 concentrations down to the LML. With regard to these estimates, we specifically note the following:

- In Atlanta for 2007 unadjusted air quality, using different studies and statistical models, the REA estimated approximately 3,000 to 6,000 respiratory emergency department visits attributable to O_3. Upon simulating just meeting the current O_3 NAAQS, the REA estimated that O_3-attributable emergency department visits decreased by approximately 20%, but that approximately 2,000 to 5,000 O_3-attributable emergency department visits remained. For 2009, the REA estimated that approximately 3,000 to 7,000 O_3-attributable emergency department visits remained (US EPA, 2012b, Table 7-21).

- In New York City for 2007 unadjusted air quality, using different statistical models, the REA estimated approximately 7,000 to 11,000 asthma emergency department visits attributable to O_3. Upon simulating just meeting the current O_3 NAAQS, the REA estimated that O_3-attributable emergency department visits decreased by approximately 10%, but that approximately 6,000 to 10,000 O_3-attributable asthma emergency department visits remained. (US EPA, 2012b, Table 7-21). For 2009, the REA estimated that approximately 8,000 to 13,000 O_3-attributable emergency department visits remained (US EPA, 2012b, Table 7-21).

- In New York City for 2007 unadjusted air quality, using different statistical models, the REA estimated approximately 500 to 700 O_3-attributable asthma hospital admissions. Upon simulating just meeting the current O_3 NAAQS, the REA estimated that O_3-attributable hospital admissions decreased by approximately 10%, but that approximately 500 to 600 O_3-attributable asthma hospital admissions remained. For 2009, the REA estimated that approximately 600 to 800 O_3-attributable asthma hospital admissions remained (US EPA, 2012b, Tables 7-22 and 7-23).

- Across the 12 urban study cities for 2007 unadjusted air quality, the REA estimated up to approximately 100 O_3-attributatble hospital admissions for respiratory causes. Upon simulating just meeting the current O_3 NAAQS, the REA estimated that O_3-attributable hospital admissions decreased by approximately 10 to 40% across cities, but that up to approximately 60 O_3-attributable hospital admissions remained. For 2009, the REA estimated that up to approximately 250 O_3-attributable hospital admissions remained (US EPA, 2012b, Tables 7-22 and 7-23).

- In Boston for 2007 unadjusted air quality, the REA estimated approximately 54,000 incidents of O_3-attributable wheezing and approximately 20,000 to 30,000 incidents of O_3-attributable chest tightness or shortness of breath among asthmatics. Upon simulating just meeting the current O_3 NAAQS, the REA estimated that the number of such O_3-attributable events decreased by approximately 8%, but that approximately 50,000 incidents of O_3-attributable wheezing and approximately 18,000 to 27,000 incidents of chest tightness or shortness of breath remained for Boston (US EPA, 2012b, Table 7-24).

3.2.1.3 Key sources of variability and uncertainty

As discussed in the first draft REA (US EPA, 2012a, section 7.4), an important component of a population risk assessment is the characterization of both variability and uncertainty in risk estimates. Variability refers to the heterogeneity of a variable of interest within a population or across different populations while uncertainty refers to the lack of knowledge regarding the actual values of inputs to an analysis. Key sources of variability in the REA risk assessments, as identified in section 7.4.1 of the first draft REA (US EPA, 2012b), include heterogeneity in O_3-related health effects across different urban areas; intra-urban variability in ambient O_3 concentrations; variability in the patterns of ambient O_3 reductions across urban areas (i.e., for rollback to current standard); co-pollutant concentrations; demographics and socioeconomic status-related factors; and baseline incidence of disease (US EPA, 2012b, section 7.4.1). Key sources of uncertainty include the use of ambient O_3 concentrations measured by existing monitors as surrogates for population exposures; characterizing U.S. background O_3 concentrations; characterizing intra-urban population exposures; shape and statistical fit of concentration-response functions; surrogate LML concentrations used in risk assessment; potential for co-pollutant confounding; appropriate lag structure; using studies from a particular geographic area to estimate risks for locations outside study area (US EPA, 2012b, Table 7-6). The potential implications of these sources of variability and uncertainty are discussed in section 7.4.1 of the first draft REA (US EPA, 2012b).

3.2.2 Risk Assessment Based on Controlled Human Exposure Studies

As noted above, the risk assessment of O_3-induced lung function decrements will be released in parallel with this first draft Policy Assessment. The results of this assessment will be fully considered in the second draft Policy Assessment.

3.3 REFERENCES

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4. PRELIMINARY STAFF CONCLUSIONS REGARDING THE PRIMARY O_3 NAAQS

The purpose of this chapter is to present staff's preliminary considerations and conclusions regarding the adequacy of the current primary O_3 standard and additional analyses that would be appropriate to inform consideration of potential alternative standards in the second draft PA, including additional exposure and risk analyses. Our preliminary conclusions in this first draft chapter are based on the assessment and integrative synthesis of the scientific evidence presented in the third draft O_3 ISA and the exposure and risk analyses presented in the first draft Health REA (discussed above in chapters 2 and 3, respectively). In the final PA, this chapter will present staff's final considerations and conclusions for the Administrator to consider regarding the adequacy of the current primary O_3 standard and, if appropriate, staff's considerations and conclusions regarding the range of potential alternative standards that could be supported by the scientific evidence and exposure/risk information available in this review.

In this first draft PA, we consider the following overarching questions:

- **To what extent does the available scientific evidence and exposure/risk information support or call into question the adequacy of the public health protection afforded by the current O_3 primary standard?**

- **What additional analyses would be appropriate to help inform consideration of potential alternative standards in the second draft of the PA?**

In considering our approach to developing preliminary conclusions regarding the primary O_3 standard, we first note that the CAA charges the Administrator with setting primary NAAQS that are "requisite" (i.e., neither more nor less stringent than necessary) to protect public health with an adequate margin of safety. In light of this requirement, we note that a decision on the adequacy of the public health protection provided by the current O_3 standard, and by potential alternative standards, will be a public health policy judgment in which the Administrator weighs the available evidence, exposure/risk information, and the uncertainties and limitations inherent in that evidence and information. Therefore, in developing preliminary conclusions in this first draft PA, we are mindful that the Administrator's ultimate judgments on the current and potential alternative standards will most appropriately reflect an interpretation of the available scientific evidence and exposure/risk information that neither overstates nor understates the strengths and limitations of that evidence and information.

Section 4.1 discusses the approach to reviewing the O_3 NAAQS in the last review and provides a general overview of the preliminary approach to reviewing the current O_3 primary NAAQS. Section 4.2 presents staff's preliminary considerations and conclusions regarding the

adequacy of the current 8-hour O_3 primary standard. Section 4.3 presents staff's views regarding additional analyses that would be appropriate to inform consideration of potential alternative standards in the second draft PA, including additional exposure and risk analyses for the second draft Health REA. In the second draft PA, section 4.4 will present a summary of staff's conclusions on the current standard and, if appropriate, on alternative standards for the Administrator's consideration. Section 4.5 will be added to outline areas for future research and data collection to address key uncertainties identified in this review.

4.1 APPROACH TO REVIEWING THE PRIMARY O_3 NAAQS

This section discusses the approach taken to reviewing the primary O_3 NAAQS in the review completed in 2008 (section 4.1.1) and the approach being taken in the current review (section 4.1.2).

4.1.1 Approach Taken in 2008 Review

In the last review of the O_3 NAAQS, the Administrator revised the level of the 8-hour O_3 primary standard to 75 ppb.[1] In making this decision, the Administrator placed primary emphasis on the body of available scientific evidence, while viewing the results of exposure and risk assessments as providing information in support of the decision. Specifically, the Administrator judged that a standard set at 75 ppb would be appreciably below 80 ppb, the level in controlled human exposure studies at which adverse effects had been demonstrated at the time, and would provide a significant increase in protection compared to the then-current standard. Based on results of the exposure assessment, he also noted that exposures to O_3 concentrations at and above a benchmark level of 80 ppb would be essentially eliminated with a standard level of 75 ppb, and that exposures at and above a 70 ppb benchmark level would be substantially reduced or eliminated for the vast majority of people in at-risk groups. In addition, the Administrator concluded that the body of evidence did not support setting a lower standard level, specifically judging that the available evidence for effects following exposures to O_3 concentrations of 60 ppb was "too limited to support a primary focus at this level" (FR 75 2938). In light of this conclusion regarding the evidence, the Administrator did not emphasize quantitative estimates of exposures to O_3 concentrations at or above a 60 ppb benchmark level.

In making his final decision about the level of the primary O_3 standard, the Administrator noted that the level of 75 ppb was above the range recommended by the CASAC (*i.e.,* 70 to 60 ppb). The Administrator concluded that "CASAC's recommendation appeared to be a mixture

[1]The level of the O_3 standard is specified as 0.075 ppm rather than 75 ppb. However, in this draft PA we refer to ppb, which is most often used in the scientific literature and in the ISA, in order to avoid the confusion that could result from switching units when discussing the evidence versus the standard level.

of scientific and policy considerations" (FR 75 2938). The Administrator reached a different policy judgment than the CASAC Panel based on placing less weight than CASAC on the available controlled human exposure studies reporting effects following exposures to 60 ppb O_3 (Adams, 2002; 2006) and less weight on the results from exposure and risk assessments, particularly on estimates of exposures to O_3 concentrations at or above 60 ppb.

4.1.2 Approach in the Current Review

In this review our approach to considering the adequacy of the current primary O_3 standard and to identifying a range of potential alternative primary standards for consideration, draws from the approaches used in previous reviews. As discussed above, past approaches have been based most fundamentally on using information from O_3 health studies and exposure/risk analyses in order to inform the selection of O_3 standards that, in the Administrator's judgment, protect the public health with an adequate margin of safety. As in past reviews, staff's approach in this review relies most heavily on consideration of the health evidence, including the controlled human exposure, epidemiologic, and animal toxicological evidence as assessed in the ISA and on consideration of the O_3 exposure/risk information, as assessed in the Health REA.

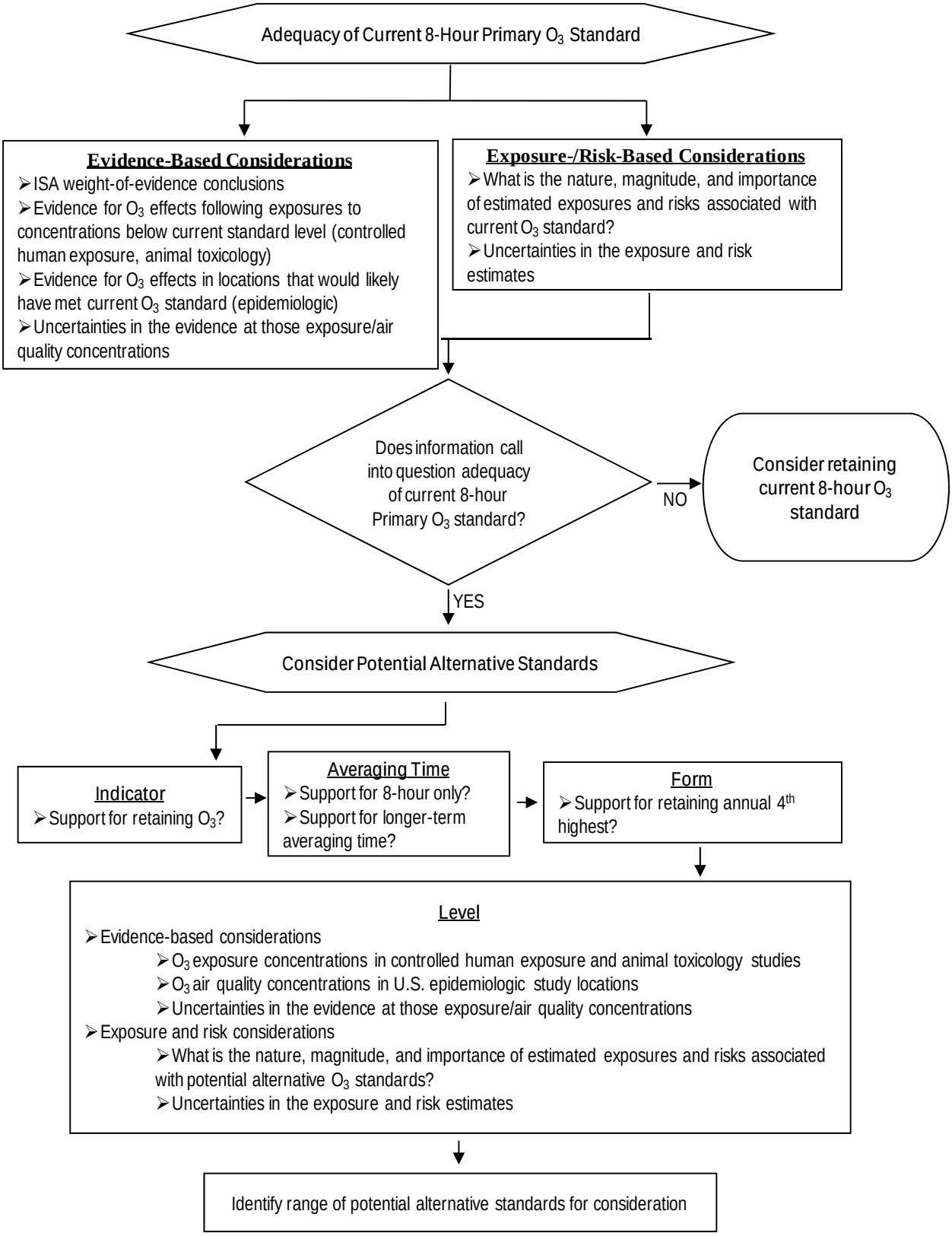
In considering our approach in this review, we note that using the available scientific evidence and technical information to inform conclusions on the adequacy of the current primary O_3 standard and on potential alternative standards appropriate for consideration is complicated by the recognition that no population threshold, below which it can be concluded with confidence that O_3-related effects do not occur, can be discerned within the range of O_3 concentrations commonly observed during the O_3 season in the U.S. (US EPA, 2012a, section 2.5.4.4). As a result, any approach that uses the available scientific evidence and exposure/risk information to inform decisions on the primary O_3 NAAQS would most appropriately require judgments to be made about how to consider the evidence and information, including consideration of how to weigh associated uncertainties.

In light of the above, staff's consideration of the adequacy of the current primary O_3 standard in this first draft PA and of potential alternative standards in the second draft PA recognizes that the available health effects evidence reflects a continuum from relatively high O_3 exposure concentrations, at which scientists generally agree that adverse health effects are likely to occur, through lower exposure concentrations, at which the likelihood and magnitude of a response become increasingly uncertain. Therefore, in considering the evidence and information we consider the likelihood that particular O_3 exposure concentrations will result in one or more health effects, as well as the likely magnitude and severity of such effects. In this first draft PA, such considerations include the nature, magnitude, and statistical precision of O_3-related effects, as well as the O_3 exposure concentrations reported in controlled human exposure studies and the

O_3 air quality concentrations in locations where epidemiologic studies have been conducted. The second draft PA will further refine these considerations, particularly consideration of the approach to using epidemiologic evidence to inform decisions on the primary O_3 NAAQS, in reaching preliminary conclusions regarding the current and potential alternative primary standards.

The approach described above for considering the evidence and information on O_3-related health effects in this review is consistent with setting standards that are neither more nor less stringent than necessary, recognizing that a zero-risk standard is not required by the CAA. This approach is outlined below in Figure 4-1.

Figure 4-1. Overview of Approach to Reviewing Primary O_3 NAAQS



4.2 PRELIMINARY STAFF CONCLUSIONS REGARDING THE ADEQUACY OF THE CURRENT PRIMARY O_3 STANDARD

In this section, we consider the extent to which the available O_3 health evidence and exposure/risk information, as discussed in detail in the third draft ISA and first draft REA respectively, and as summarized above (chapters 2 and 3), supports or calls into question the adequacy of the protection afforded by the current 8-hour O_3 standard against effects that have been linked to short-term or long-term O_3 exposures. Section 4.2.1 presents evidence-based considerations, section 4.2.2 presents exposure- and risk-based considerations, section 4.2.3 presents the advice and recommendations from CASAC in the last review of the O_3 NAAQS, and section 4.2.4 presents an integrated synthesis of staff's preliminary conclusions regarding the adequacy of the current O_3 primary NAAQS.

4.2.1 Evidence-Based Considerations

In translating information from controlled human exposure, epidemiologic, and animal toxicological studies into the basis for reaching preliminary staff conclusions on the adequacy of the current O_3 standard, we apply the policy framework outlined in Figure 4-1 above. In so doing, we consider the strength of the evidence for O_3-related health effects, the O_3 concentrations at which such health effects have been reported, and the potential public health implications of exposures in at-risk populations to O_3 concentrations that would be allowed by the current O_3 standard.

In first considering the strength of the evidence, we note the weight-of-evidence conclusions in the ISA. Specifically, as discussed above (section 2.1), we note the ISA conclusions that there is a causal relationship between short-term O_3 exposures and respiratory effects, including respiratory-related morbidity and mortality; there is likely to be a causal relationship between short-term O_3 exposures and all-cause mortality; and there is likely to be a causal relationship between long-term O_3 exposures and respiratory effects (including morbidity and mortality). These conclusions were based on extensive bodies of scientific evidence reporting coherent and consistent results using different approaches and study designs to evaluate O_3-related health effects. For other health endpoints, we note that the more limited bodies of scientific evidence were judged in the ISA to be either suggestive of a causal relationship or inadequate to infer a causal relationship (US EPA, 2012a, Table 1-1). Specifically, the evidence for cardiovascular and central nervous system effects following short-term exposures; the evidence for cardiovascular, reproductive and developmental, and central nervous system effects following long-term exposures; and the evidence for mortality following long-term exposures was judged to be suggestive of a causal relationship. The evidence for cancer was judged inadequate to determine whether a causal relationship exists. In light of these conclusions in the

ISA, which reflect the strength of the available evidence for different health endpoints, our evidence-based consideration of the current O_3 primary standard places emphasis on studies that have evaluated respiratory effects, including an array of respiratory-related morbidity endpoints and respiratory-related mortality following short- and long-term exposures, and on studies that have evaluated total mortality following short-term exposures.

In considering such O_3-related health effects within the context of the adequacy of the current O_3 NAAQS, we specifically consider the following question:

- **To what extent does the available scientific evidence support the occurrence of respiratory-related morbidity and mortality effects or total mortality following exposures to O_3 concentrations that would be allowed by the current O_3 standard?**

In evaluating this question, we consider the O_3 exposure concentrations at which respiratory effects have been reported in experimental studies (i.e., controlled human exposure and animal toxicological studies) and the ambient O_3 concentrations in locations where O_3-related morbidity or mortality has been reported in epidemiologic studies. The following sections consider the evidence for O_3-induced lung function decrements, respiratory symptoms, airway inflammation, and other respiratory effects (section 4.2.1.1); O_3-related respiratory hospital admissions, emergency department visits, and mortality (section 4.2.1.2); and O_3-related total mortality (section 4.2.1.3). Section 4.2.1.4 discusses other health endpoints and section 4.2.1.5 presents an integrated synthesis of staff's evidence-based considerations.

4.2.1.1 Lung function, respiratory symptoms, airway inflammation, and other respiratory effects

As discussed above (section 2.2.1), and as assessed and discussed in detail in the ISA (US EPA, 2012a, Chapter 6), controlled human exposure, animal toxicological, and epidemiologic studies provide strong evidence that short-term exposures to O_3 result in a variety of respiratory effects, including lung function decrements, respiratory symptoms, airway inflammation, increased airway responsiveness, and decreased lung host defense. When considering studies of these O_3-induced respiratory effects within the context of the adequacy of the current O_3 NAAQS, we consider (1) the extent to which controlled human exposure studies have reported such effects following exposures to O_3 concentrations below the level of the current standard and (2) the extent to which O_3 epidemiologic studies have reported associations with such effects in locations likely to have met the current O_3 standard. In considering such studies, we also note the extent to which effects reported following exposures to O_3 concentrations below the current standard level are plausibly linked to the larger body of evidence for effects following exposures to higher O_3 concentrations.

In first considering controlled human exposure studies of O_3-induced lung function decrements within the context of the current O_3 standard, we note that such studies have consistently reported decrements in group mean lung function in healthy exercising adults following 6.6-hour exposures to O_3 concentrations ranging from 60 to 120 ppb (US EPA, 2012a, Figure 6-1). When data were combined across a number of studies, group mean decrements were approximately 3% following exposures to 60 ppb O_3, 6% to 8% following exposures to 80 ppb O_3, 8% to 14% following exposures to 100 ppb O_3, and 13% to 16% following exposures to 120 ppb O_3. In addition, a study that evaluated exposures to 70 ppb O_3 (Schelegle et al., 2009) reported a 6% decrement in group mean FEV_1 (section 2.2.1.1, above). In considering these studies as a whole, we note that reported group mean decrements have consistently been statistically significant following exposures at or above 70 ppb O_3. Following exposures to 60 ppb O_3, decrements have been reported to be statistically significant in a study by Kim et al. (2011) and in an analysis of existing data by Brown et al. (2008), though not in the original study that generated the data used by Brown et al. (Adams, 2006) or in a study by Schelegle et al. (2009) (US EPA, 2011b, section 6.2.1.1). Statistically significant lung function decrements have not been reported following exposures to O_3 concentrations below 60 ppb (i.e., 40 ppb) (US EPA, 2012a, Figure 6-1).

In further considering these controlled human exposure studies of O_3-induced lung function decrements, we note that while it is important to consider the statistical precision of group mean decrements when evaluating whether reported effects are due to O_3 exposures rather than chance alone, when considering the potential public health implications of study results it is also important to consider the potential for some individuals to experience larger decrements than average (US EPA, 2012a, section 6.2.1.1). Such inter-individual variability in lung function responses is relevant when evaluating the proportion of the population that might experience clinically meaningful effects during an O_3 exposure.

As noted in the ISA (US EPA, section 6.2.1.1), for individuals with relatively normal lung function, a within-day change in FEV_1 of 5% or larger is clinically meaningful and a 10% reduction in FEV_1 has been generally accepted as an abnormal response (Dryden et al., 2010; American Thoracic Society, 2000). In addition, in the last review of the O_3 standard CASAC recommended that EPA focus on FEV_1 decrements at or above 10% when estimating potentially adverse lung function decrements in people with lung disease. The CASAC noted that while such moderate levels of lung function impairment would likely not interfere with normal activity for most healthy individuals, even moderate functional impairment would likely interfere with normal activity for many individuals with lung disease (Henderson, 2006).

In light of the above, in considering the potential for some individuals to experience potentially adverse O_3-induced lung function decrements (as defined by CASAC in the last review) following exposures to O_3 concentrations below the level of the current standard, we consider the extent to which exposures to O_3 concentrations below 75 ppb result in FEV_1 decrements of 10% or more. With regard to this, we note that following 6.6-hour exposures to an average O_3 concentration of 60 ppb, the proportion of healthy adult study subjects at intermittent, moderate exertion, with such potentially adverse FEV_1 decrements ranged from 3% to 20% across several studies (US EPA, 2012a, section 6.2.1.1). When the results from such studies were combined, the ISA noted that 10% of healthy subjects experienced such FEV_1 decrements following exposures to an average O_3 concentration of 60 ppb (US EPA, 2012a, section 6.2.1.1). In addition, in a study that evaluated the exposure-response relationship in the percentage of subjects experiencing FEV_1 decrements greater than or equal to 10%, the percentage increased with increasing O_3 exposure concentrations such that no subjects experienced such decrements following exposures to filtered air, 16% of subjects experienced such decrements following exposures to 60 ppb O_3; 19% experienced such decrements following exposures to 70 ppb O_3; and 29% experienced such decrements following exposures to 80 ppb O_3 (US EPA, 2012a, Figure 6-2). Taken together these results indicate that, although group mean lung function decrements are relatively small following exposures to O_3 concentrations below the level of the current standard, on average more than 10% of healthy individuals experience O_3-induced decrements that are potentially adverse for those with lung diseases such as asthma.

With regard to the O_3-induced FEV_1 decrements reported in controlled human exposure studies, we also note that these studies were conducted in healthy adults, while individuals in at-risk groups could experience larger O_3-induced decrements. Specifically, the ISA concludes that there is adequate evidence to identify several groups as particularly at-risk for O_3-related effects, including asthmatics and children (US EPA, 2012a, section 2.4.5.1). Several studies have reported larger O_3-induced FEV_1 decrements in asthmatics than non-asthmatics (US EPA, 2012a, section 8.2.2), with one study reporting that decrements increased with increasing disease severity (Horstman et al., 1995). In addition, children experience higher O_3 exposures and doses, compared to adults, due to increased time spent outdoors and increased ventilation rates (US EPA, 2012a, section 2.4.5.1). In light of this evidence, we note that studies conducted in healthy adults may underestimate O_3-induced lung function decrements in asthmatics and children (US EPA, 2012a, Preamble).

In further considering the potential clinical implications of O_3-induced effects reported in controlled human exposure studies, we note that a number of such studies have also evaluated

respiratory symptoms. Statistically significant increases in respiratory symptoms (which includes pain on deep inspiration, shortness of breath, and cough) have been consistently reported in healthy volunteers engaged in intermittent, moderate exertion following 6.6 hour exposures to average O_3 concentrations at or above 80 ppb (US EPA, 2012a, section 6.2.1.1). In addition, in a recent study Schelegle et al. (2009) reported a statistically significant increase in respiratory symptoms following 6.6 hour exposures to an average O_3 concentration of 70 ppb. With regard to lower exposure concentrations, we note that two studies, Adams (2006) and Schelegle et al. (2009), reported a tendency for increased respiratory symptoms in healthy volunteers during 6.6 hour exposure protocols with average O_3 exposure concentrations of 60 ppb. For one of the exposure protocols tested in the study by Adams (i.e., the triangular exposure protocol), the increase in symptoms was reported to be statistically different from initial respiratory symptoms, though neither study reported the increase in symptoms to be statistically significant relative to filtered air controls.

Consistent with the results of the controlled human exposure studies in healthy adults, we note the large number of O_3 epidemiologic studies that have reported positive and statistically significant associations with lung function decrements and respiratory symptoms in a variety of populations including children attending summer camps, adults exercising outdoors, outdoor workers, and asthmatic children living in urban areas (US EPA, 2012a, section 6.2.1). Consistent with controlled human exposure studies, O_3-related group mean decrements in lung function were often small in magnitude, though some individuals experienced decrements in excess of 10%. When studies of O_3-associated lung function decrements or respiratory symptoms have evaluated the potential for confounding by co-pollutants, meteorological factors, or pollen counts, we note that associations with O_3 generally remained robust (sections 2.2.1.1 and 2.2.1.4, above). In considering these studies within the context of the adequacy of the current O_3 standard, we take particular note of studies that have been conducted in locations likely to have met the current O_3 standard, though we also note that the results of such studies are consistent with the larger body of epidemiologic studies reporting O_3-induced lung function decrements and respiratory symptoms in locations that would not have likely met the current O_3 standard (US EPA, 2012a, section 6.2).[2]

As discussed above (section 2.2.1), associations with lung function decrements and respiratory symptoms typically remained, and in several studies remained statistically significant,

[2]Because attainment status is based on ambient O_3 concentrations measured at individual monitors, with the highest relevant monitored concentration in an area determining whether that area meets or violates the NAAQS, it is most appropriate to use O_3 concentrations from individual monitoring sites when drawing conclusions about whether a study area would likely have met or violated the O_3 NAAQS. Therefore, in considering ambient O_3 concentrations in epidemiologic study locations, we focus on locations with data available from individual monitoring sites.

in analyses restricted to ambient O_3 concentrations near or below the level of the current O_3 standard (US EPA, 2012a, section 6.2.1.2 and Table 6-6). For example, O_3-associated lung function decrements in children remained statistically significant in an analysis restricted to 1-hour average O_3 concentrations below 60 ppb (Spektor et al., 1988) and remained, though were not statistically significant, in a separate analysis restricted to concentrations below 61 ppb (Brunekreef et al., 1994). In studies of outdoor workers, O_3-associated lung function decrements have been reported in analyses restricted to maximum hourly concentrations below 40 ppb (Brauer et al., 1996); in a location where the highest 8-hour concentration was 65 ppb (Chan and Wu, 2005); and in a location with a maximum 30-minute concentration of 77 ppb[3] (Hoppe et al., 1995). In addition, positive associations with respiratory symptoms were statistically significant in asthmatic children in Denver, a location with a maximum 1-hour O_3 concentration of 70 ppb during the study period (Rabinovitch et al., 2004). Considered together, we note that these epidemiologic results, combined with the results of the controlled human exposure studies discussed above, provide strong support for the conclusion that short-term exposures to ambient O_3 concentrations can result in direct and independent effects on respiratory function in healthy children and adults, and in asthmatics, even when ambient O_3 concentrations remain below the level of the current standard.

In further considering O_3-induced decrements in lung function and increases in respiratory symptoms, we note the American Thoracic Society (ATS) conclusions that (1) reversible loss of lung function in combination with respiratory symptoms should be considered adverse and that (2) a downward shift in the population distribution of lung function should be considered adverse, even in the absence of overt illness, because individuals within that population would have diminished reserve function placing them at increased risk from other agents such as viral infections (ATS, 2000, p. 672). Consistent with these conclusions, the ISA states the following (US EPA, 2011b, section 6.2.1.2, pp. 6-54 to 6-55):

> "In considering the clinical significance of more subtle health outcomes such as lung function changes, it is important to note that a small shift in the population mean likely will have a disproportionate effect in the extreme ends of the distribution of lung function where these small magnitudes of decrease lead to clinically-significant airway resistance or obstruction and where individuals likely have concurrent symptoms. Several epidemiologic studies have demonstrated the clinical significance of O_3-associated lung function decrements, primarily in individuals with asthma, by finding concomitant increases in respiratory symptoms."

[3]While it is not possible to conclude definitively that the maximum 8-hour concentration would have been at or below 75 ppb in the study by Hoppe et al. (1995), it would have been somewhat lower than 77 ppb, the maximum 30-minute concentration.

In light of these conclusions, and in considering the controlled human exposure and epidemiologic studies discussed above, we note that exposures to O_3 concentrations below the level of the current standard can result in respiratory effects that meet ATS criteria for adversity, given that (1) controlled human exposure and epidemiologic studies have reported lung function decrements and respiratory symptoms in healthy adults following exposures to O_3 concentrations below 75 ppb, 8-hour average, with one controlled human exposure study reporting both lung function decrements and respiratory symptoms following exposures to 70 ppb. and (2) controlled human exposure and epidemiologic studies have reported a downward shift in the population distribution of lung function (e.g., as indicated by decrements in group mean FEV_1) following exposures to O_3 concentrations below 75 ppb, including 8-hour average concentrations as low as 60 ppb in some controlled human exposure studies.

In addition to O_3-induced lung function decrements and respiratory symptoms, controlled human exposure, epidemiologic, and animal toxicological studies have reported airway inflammation following O_3 exposures. Although there is little quantitative information available to relate changes in markers of airway inflammation to specific clinical effects, inflammation is the host response to injury and the induction of inflammation is evidence that injury has occurred (US EPA, 2011b, section 6.2.3). Animal toxicology studies suggest that continued airway inflammation could have a variety of important respiratory consequences, including (1) the development of a chronic inflammatory state; (2) altered structure and function of pulmonary tissues; (3) alteration of the body's host defense response to inhaled microorganisms; and (4) alteration of the lung's response to other agents such as allergens or toxins (US EPA, 2012a, section 6.2.3). Some controlled human exposure studies have reported more pronounced O_3-induced inflammatory responses in asthmatics than non-asthmatics and some studies have reported that tissue damage persists for days or weeks following repeated O_3 exposures (US EPA, 2011b, sections 6.2.1.3, 6.2.3.1). Ozone-induced airway inflammation is generally reproducible within individuals over time (Holz et al., 1999), and some individuals are intrinsically more susceptible to increased inflammatory responses following O_3 exposures (Holz et al., 2005).

We note that several controlled human exposure studies have reported O_3-induced airway inflammation in humans following exposures to O_3 concentrations of 80 and 100 ppb (Alexis et al., 2010; Peden et al., 1997; Devlin et al., 1991), and that the only controlled human exposure study to have evaluated airway inflammation following exposures below the level of the current O_3 standard (Kim et al., 2011) reported a statistically significant increase in neutrophilic inflammation following 6.6 hour exposures to 60 ppb O_3 in healthy adults engaged in intermittent,moderate exertion (section 2.2.1.2, above). Relative to clean air, exposures to 60

ppb O_3 resulted in a 16% increase in inflammation, on average across subjects. While information is not available to quantitatively link markers of airway inflammation with specific clinical effects, given evidence that asthmatics can experience larger O_3-induced airway inflammation than non-asthmatics and evidence supporting the potential for clearly adverse respiratory effects with continued airway inflammation, these findings in healthy humans further support the potential for important respiratory effects following exposures to O_3 concentrations below the level of the current standard.

In addition to lung function decrements, respiratory symptoms, and airway inflammation, we note that several additional O_3-induced respiratory effects have been reported in controlled human exposure and animal toxicological studies, including airway hyperresponsiveness, impaired lung host defense, and structural changes in the respiratory system. However, few studies have evaluated these endpoints following exposures to O_3 concentrations below 75 ppb. With regard to studies evaluating these respiratory effects, we specifically note the following:

- Airway hyperresponsiveness has been reported following short-term exposures of humans to O_3 concentrations at or above 80 ppb and in animals following exposures to O_3 concentrations as low as 50 ppb (US EPA, 2011b, section 6.2.2). Airway hyperresponsiveness following O_3 exposures is more pronounced in asthmatics than non-asthmatics and can exacerbate asthma by placing allergic asthmatics at greater risk for prolonged bouts of breathing difficulties due to airway constriction.

- Impaired lung host defenses have been reported in healthy humans following short-term exposures to O_3 concentrations as low as 80 ppb, and a number of human and animal studies have reported immune cell alterations following exposures to O_3 concentrations at or above 80 ppb (US EPA, 2011b, section 6.2.5). Such impairments could increase the susceptibility of exposed individuals to respiratory infections.

- Animal toxicological studies in rodents and non-human primates have reported that long-term (i.e, chronic or repeated exposures to O_3 with typical concentrations ranging from 120 to 500 ppb) during gestation or development resulted in irreversible morphological changes in the lung, which in turn can influence pulmonary function (US EPA, 2011b, section 7.2.3).

While studies of most of these additional endpoints have not evaluated exposures to O_3 concentrations at or below the level of the current O_3 standard, they do provide insight into the range of O_3-related respiratory effects and into the potential for at-risk individuals (e.g., asthmatics) to experience more severe effects.

Controlled human exposure studies of O_3-induced lung function decrements, respiratory symptoms, and airway inflammation provide strong evidence that exposures to O_3 concentrations below those allowed by the current O_3 standard (i.e., 60-70 ppb) can impair respiratory function.

As noted above, members of at-risk groups, including asthmatics and children, would likely experience larger O_3-induced respiratory effects than indicated by controlled human exposure studies, most of which have been conducted in healthy adults. Based on available evidence from controlled human exposure studies, the weighted average proportion of healthy individuals with >10% FEV_1 decrements is 10% following exposure to 60 ppb O_3. For the purpose of estimating potentially adverse lung function decrements in people with lung disease, the CASAC indicated that a focus on the lower end of the range of moderate levels of functional responses is most appropriate (i.e., FEV_1 decrements ≥10%) (Henderson, 2006). Thus the proportion of healthy individuals experiencing >10% FEV_1 decrements in these controlled human exposure studies may be viewed as important from a public health perspective, and the results are important to consider in assessing the overall public health impacts associated with exposures to O_3. In addition, controlled human exposure and animal toxicological studies of airway hyperresponsiveness, impaired host defense, and structural changes in the respiratory system provide perspective on the broad range of O_3-related respiratory effects. In some individuals, the types of O_3-induced respiratory responses reported in controlled human exposure studies could become severe enough that they result in increased use of medication, emergency room visits, and/or hospital admissions. Thus, the strong evidence for lung function decrements, respiratory symptoms, airway inflammation, and other respiratory effects following exposures to O_3 concentrations commonly encountered in U.S. urban locations supports the biological plausibility of the conclusions that exposures to ambient O_3 concentrations can result in respiratory-related hospital admissions and emergency department visits, as well as the most severe O_3-associated effect, premature mortality. Studies of these O_3-related effects are discussed below, within the context of considering the adequacy of the current O_3 standard.

4.2.1.2 Respiratory-related hospital admissions, emergency department visits, and mortality

Ozone-related respiratory hospital admissions, emergency department visits, and mortality have been reported in a number of epidemiologic studies conducted in the United States and around the world. In translating information from these epidemiologic studies into the basis for reaching preliminary conclusions on the adequacy of the current O_3 standard, we consider available information on the extent to which the current standard provides protection against health effects that have been reported to be associated with both short- and long-term O_3 concentrations. Our general approach to considering epidemiologic studies with regard to the adequacy of the current standard is to characterize our degree of confidence in associations reported for O_3 concentrations that would likely be allowed by the current standard. In doing so, we note the ambient O_3 concentrations in study locations and, where available, we note information on the concentration-response relationship between O_3 and morbidity or mortality.

In placing relative weight on specific epidemiologic studies, we take several factors into account. These factors include the geographic coverage provided by the study, the extent to which analyses control for potential confounders, and the statistical precision of results. In considering specific epidemiologic studies, we place considerable weight on information from U.S. multi-city studies. These studies have a number of advantages compared to single-city studies, including representing ambient O_3 concentrations and potential health impacts across a range of diverse locations, providing spatial coverage for different regions reflecting differences in O_3 exposure patterns and co-pollutants; lack of publication bias; consideration of larger study populations that afford the possibility of generalizing to the broader national population; and providing increased statistical power.

While we emphasize multi-city studies, we also take into account relevant information from single-city studies, where appropriate. Specifically, although multi-city studies have more power to detect associations and provide broader geographic coverage, the extent to which effects reported in multi-city studies are associated with the specific O_3 air quality in any particular location is less clear than in single-city studies. Regional heterogeneity in O_3-associated health risks has led some researchers (e.g., Smith et al., 2009) to question the appropriateness of using multi-city approaches to generate national O_3 effect estimates. Therefore, while single-city studies are more limited than multi-city studies in terms of power and geographic coverage, the link between reported health effects and the air quality in a given study area is more straightforward to establish. In light of this, we consider relevant information from single-city studies, where appropriate.

In light of the above considerations, and given the weight-of-evidence conclusions in the ISA as discussed above, in considering multi-city and single-city epidemiologic studies within the context of the adequacy of the current O_3 standard, we consider studies that have evaluated associations between short-term O_3 concentrations and respiratory effects or total mortality, as well as studies that have evaluated associations between long-term O_3 concentrations and respiratory effects.

<u>Short-term exposure studies</u>

In considering the available epidemiologic evidence for associations with short-term O_3 concentrations within the context of considering the adequacy of the current O_3 standard, we first take into account the O_3 air quality concentrations in the locations where U.S. studies have reported associations with respiratory-related hospital admissions, respiratory-related emergency department visits, respiratory-related mortality, and total mortality. In order to facilitate

consideration of this issue, we have used EPA's Air Quality System (AQS)[4] to identify O_3 design values[5] for the locations where U.S. studies have been conducted.

With regard to U.S. multi-city studies that evaluated O_3-associated respiratory hospital admissions, emergency department visits, or mortality (i.e., Medina-Ramon et al., 2006; Lin et al., 2008; Katsouyanni et al., 2009; Zanobetti and Schwartz, 2008) (US EPA, 2012a, Chapter 6; sections 2.2.1 and 2.2.2, above), we note that 50th percentiles of the distributions of O_3 design values across cities ranged from 83 to 94 ppb (Table 4-1). These median concentrations indicate that most of the cities included in available U.S. multi-city O_3 studies would likely not have met the current O_3 standard over the study periods. In considering design values for individual cities evaluated in these studies we note the following: (1) For Medina-Ramon et al. (2006) 21 of the 27 cities evaluated had average (i.e., averaged over the time periods of the studies) O_3 design values above 75 ppb; (2) for Lin et al. (2008) 22 of the 26 cities evaluated had average O_3 design values above 75 ppb;[6] (3) for Katsouysanni et al. (2009) 9 of the 14 cities evaluated for hospital admissions and 79 of the 90 cities evaluated for respiratory mortality had average O_3 design values above 75 ppb; and (4) for Zanobetti and Schwartz (2008) 42 of the 48 cities evaluated had average O_3 design values above 75 ppb (Wells et al., 2012). Given this, we note that the large majority of the cities included in U.S. multi-city studies of O_3-related respiratory hospital admissions, emergency department visits, or mortality would likely not have met the current O_3 standard during the study periods. Therefore, we note that while U.S. multi-city epidemiologic studies provide strong support for the occurrence of clearly adverse O_3-related respiratory effects, consideration of the O_3 design values for the cities included in these studies does not provide insight into the appropriateness of the degree of public health protection provided by the current O_3 standard.

Of the U.S. single-city studies evaluating O_3-related respiratory effects, only the study by Mar and Koenig (2009) was conducted in a location with an O_3 design value lower than 75 ppb. As discussed in section 2.2.1.6 above and as indicated in Table 4-1, this study reported positive and statistically significant associations with asthma emergency department visits in both children and adults in Seattle. The average (i.e., over the years of the study) O_3 design value for Seattle during the study period was 71 ppb (Table 4-1), and the highest design value for any three-year period during the study was 75 ppb (Wells et al., 2012), indicating that the study area

[4]Accessible at http://www.epa.gov/ttn/airs/airsaqs/

[5]A design value is a statistic that describes the air quality status of a given area relative to the level of the NAAQS (http://www.epa.gov/airtrends/values.html). In the case of O_3, the design value for an area is based on the 3-year average of the annual 4th highest 8-hour daily maximum concentration in an O_3 season, measured at the monitor recording the highest such concentration.

[6]The study by Lin et al. (2008) identified regions rather than specific cities. In identifying design values for the study area, we considered the cities that were encompassed by the regions evaluated in the study (Wells et al., 2012).

would have met the current O_3 standard during the entire study period. Average design values for other U.S. single-city studies ranged from 104 ppb to 107 ppb (Table 4-1).

Although most of the U.S. O_3 epidemiologic studies of respiratory-related hospital admissions, emergency department visits, and mortality have not been conducted in locations likely to have met the current O_3 standard, a study conducted in New York City (Silverman and Ito, 2010) has evaluated the concentration-response relationship between O_3 and asthma hospital admissions (US EPA, 2012a, Figure 6-15), potentially providing insight into O_3-associated health risks at air quality concentrations that would have been allowed by the current standard.[7] In considering such concentration-response relationships, we take note of the statistical precision of estimates of that relationship at different O_3 concentrations across the air quality distribution. We specifically note the O_3 concentrations below which confidence bounds indicate appreciably less confidence in the nature of the association. In taking this approach to evaluating concentration-response relationships we acknowledge that the decreasing precision in effect estimates reported as concentrations approach the lower extreme of the air quality distribution, as indicated by notable widening of confidence bounds, is intrinsically related to data density and is not necessarily indicative of an absence of O_3-associated health effects.

As discussed in section 2.2.1.6 above, Silverman and Ito (2010) evaluated the concentration-response relationship for O_3 and asthma hospital admissions in New York City using a co-pollutant model that also included $PM_{2.5}$. The authors concluded that a linear relationship between O_3 and hospital admissions is a reasonable approximation of the concentration-response function throughout much of the range of ambient O_3 concentrations. Based on the 95% confidence intervals around the concentration-response function (US EPA, 2012a, Figure 6-15), the most precise estimates of this relationship were reported for average (i.e., averaged across monitors in the study area) 8-hour daily maximum O_3 concentrations around 40 ppb (the 50th percentile of the distribution was 41 ppb), with confidence intervals becoming progressively wider at average 8-hour daily maximum O_3 concentrations below and above this concentration. As noted above, this broadening of the confidence intervals is likely due to the decreasing amounts of data at the lower and upper ends of the air quality distribution.

[7]In addition, the study by Strickland et al. (2010) evaluated the concentration-response relationship with asthma emergency department visits in Atlanta. To the extent it is judged appropriate, based on advice received from CASAC on this first draft Policy Assessment, the second draft Policy Assessment could also consider the concentration-response relationship reported in the study by Strickland et al. (2010) within the context of the current O_3 NAAQS in a manner analogous to our consideration in this section of the study by Silverman and Ito (2010).

Table 4-1. Average Ozone Design Values in U.S. Cities where Epidemiologic Studies have Evaluated Associations between Short-Term O_3 and Respiratory-Related Hospital Admissions (HA), Emergency Department (ED) Visits, and Mortality

Study	Endpoint	Location	Age	Lag	Avg Time	% Increase (95% CI)	Design Values (ppb)[8]
All-year							
Strickland et al. (2010)	Asthma ED	Atlanta	Children	0-2	8-h max	6.38 (3.19, 9.57)	107
Medina-Ramon et al. (2006)	COPD HA	36 U.S. cities	65+	0-1	8-h max	0.24 (-0.78, 1.21)	94
Katsouyanni et al. (2009)	Respiratory HA	14 U.S. cities	65+	0-1	1-h max	2.38 (0.00, 4.89)	92
Katsouyanni et al. (2009)	Respiratory mortality	90 U.S. cities	All	DL 0-2	1-h max	2.54 (-3.32, 8.79)	89
Warm Season							
Ito et al. (2007)	Asthma ED	New York City	All	0-1	8-h max	16.9 (10.9, 23.4)	112
Darrow et al. (2011)	Respiratory ED	Atlanta	All	1	8-h max	2.08 (1.25, 2.91)	107
Tolbert et al. (2007)	Respiratory ED	Atlanta	All	0-2	8-h max	3.90 (2.70, 5.20)	107
Strickland et al. (2010)	Asthma ED	Atlanta	Children	0-2	8-h max	8.43 (4.42, 12.7)	107
Silverman and Ito (2010)	Asthma HA	New York City	6 to 18	0-1	8-h max	28.2 (15.3, 41.5)	104
Silverman and Ito (2010)	Asthma HA	New York City	All	0-1	8-h max	12.5 (8.27, 16.7)	104
Medina-Ramon et al. (2006)	COPD HA	36 U.S. cities	65+	0-1	8-h max	1.63 (0.48, 2.85)	94
Katsouyanni et al. (2009)	Respiratory HA	14 U.S. cities	65+	0-1	1-h max	2.14 (-0.63, 4.97)	92
Zanobetti and Schwartz (2008)	Respiratory mortality	48 U.S. cities	All	0-3	8-h max	2.51 (1.14, 3.89)	92
Katsouyanni et al. (2009)	Respiratory mortality	90 U.S. cities	All	DL 0-2	1-h max	4.40 (-2.10, 11.3)	89
Katsouyanni et al. (2009)	Respiratory mortality	90 U.S. cities	75+	DL 0-2	1-h max	4.07 (-4.23, 13.0)	89
Lin et al. (2008)	Respiratory HA	New York State (11 regions)					83
Mar and Koenig (2009)	Asthma ED	Seattle, WA	18+	2	8-h max	19.1 (3.00, 40.5)	71
Mar and Koenig (2009)	Asthma ED	Seattle, WA	< 18	0	8-h max	33.1 (3.00, 68.5)	71

[8]For each study city and each study year, 4th highest 8-hour daily maximum O_3 concentrations were identified. To provide some perspective on whether these cities would likely have met or violated the current O_3 NAAQS during the study period, these concentrations were averaged over the years of the study, resulting in the study average design value. For multi-city studies, the median of the distribution of average design values was identified. Design values for each of the cities included in these multi-city studies are included in Wells et al. (2012).

While we recognize that there is no single air quality concentration that unambiguously identifies the portion of the concentration-response function in which it is appropriate to place the greatest confidence, we note that confidence intervals are smallest around 40 ppb (averaged across monitors), become somewhat wider at O_3 concentrations below about 30 ppb (31 ppb was the 25th percentile concentration reported by Silverman and Ito) and above about 50 ppb (53 ppb was the 75th percentile reported in the study), and become dramatically wider below about 20 ppb (24 ppb was the 10th percentile reported in the study) and above about 70 ppb (68 ppb was the 90th percentile reported in the study). In light of this, we reach the preliminary conclusion that confidence is greatest that a linear concentration-response relationship exists for O_3 and asthma hospital admissions in New York City for average 8-hour daily maximum O_3 concentrations around 40 ppb, with confidence in the nature of the concentration-response relationship decreasing notably for concentrations lower than approximately 20 ppb.

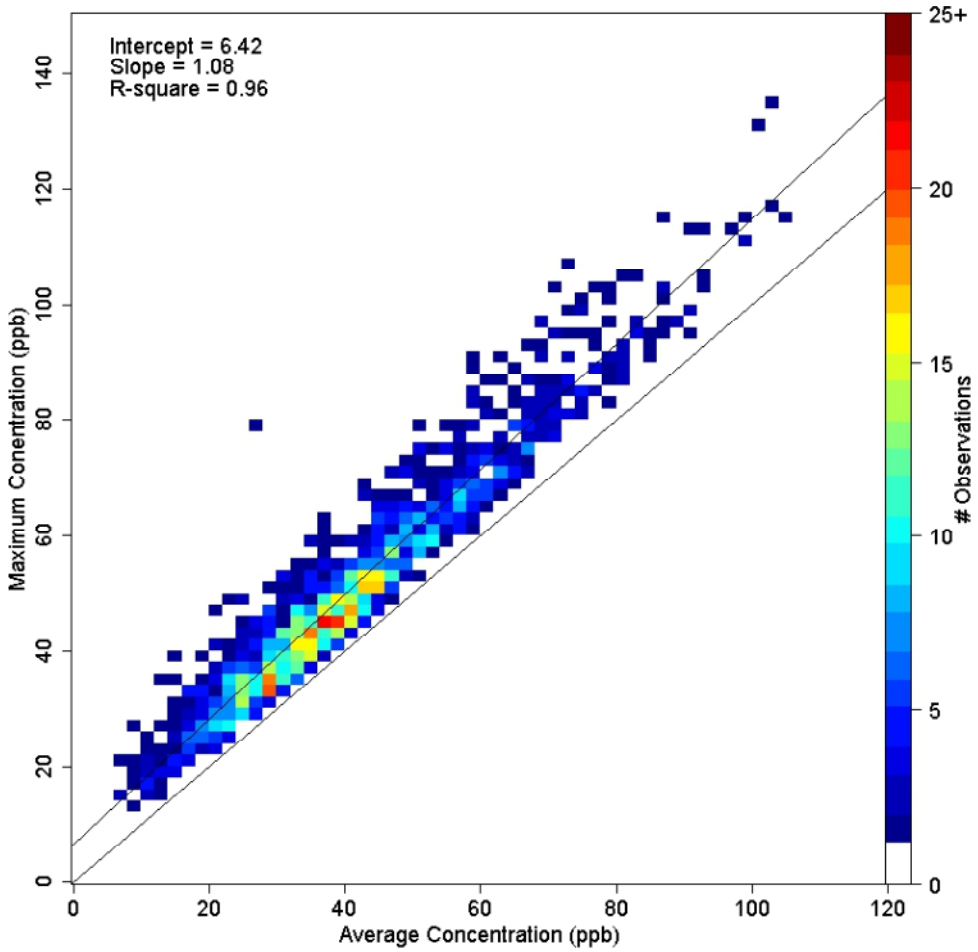
As noted above, the 8-hour O_3 concentrations reported in the analysis by Silverman and Ito (2010) were based on averaging across multiple monitors in the study area. Because attainment of the current standard is based on the annual 4th highest 8-hour daily maximum O_3 concentration measured at the monitor recording the highest such concentration, the average 8-hour concentrations reported by Silverman and Ito (2010) are not directly comparable to the level of the current O_3 standard. Therefore, it is not clear from the data presented in the study whether particular average 8-hour daily maximum O_3 concentrations, based on averaging across monitors, would reflect ambient O_3 concentrations likely to be above or below those allowed by the current O_3 standard. To gain insight into the relationship between average 8-hour daily maximum O_3 concentrations (i.e., based on averaging across monitors) and the highest 8-hour daily maximum concentrations (i.e., from the individual monitor recording the highest such concentration), we have considered available air quality information from EPA's AQS for the monitors used in the study by Silverman and Ito (2010) over the time period of the study (Wells et al., 2012, section 1.3.3; Figure 4-2, below).

In considering the range of average O_3 concentrations for which we have the greatest confidence in the concentration-response relationship, we first note that for the New York City study area over the period of the study, 742 days had average (i.e., averaged across monitors) 8-hour daily maximum O_3 concentrations around 40 ppb (i.e., 30 to 50 ppb) (Wells et al., 2012). On these days with average 8-hour daily maximum O_3 concentrations from 30 to 50 ppb, the highest 8-hour daily maximum O_3 concentrations (i.e., from the monitors recording the highest such concentrations) ranged from approximately 55 ppb (i.e., for average concentrations from 30 to 35 ppb) to just below 75 ppb (i.e., 72 ppb for average concentrations from 45 to 50 ppb) (Figure 4-2). In addition, we note that 996 days had average 8-hour daily maximum O_3

concentrations from 20 to 50 ppb (Wells et al., 2012). The highest 8-hour daily maximum O_3 concentrations on these days ranged from approximately 50 ppb (i.e., 49 ppb for average concentrations from 20 to 25 ppb) to just below 75 ppb (Figure 4-2).

In considering this analysis within the context of the current standard we note that, of the days with average 8-hour daily maximum O_3 concentrations from approximately 20 to 50 ppb (i.e., corresponding to the majority of the range over which we have reasonable confidence in the linearity of the concentration-response relationship), virtually none had highest 8-hour concentrations (i.e., from the highest monitor) greater than 75 ppb. In light of this, we note that the linear relationship between ambient O_3 concentrations and asthma hospital admissions in New York City, as reported by Silverman and Ito (2010), persisted for O_3 air quality concentrations likely to have been well below those allowed by the current O_3 standard.

Figure 4-2. Average Versus Highest 8-hour Daily Maximum O_3 Concentrations in New York City, 1999-2006



Long-term exposure studies

In considering the available epidemiologic evidence for associations with long-term O_3 concentrations within the context of considering the adequacy of the current O_3 standard, as with the short-term studies discussed above, we take into account O_3 design values in the locations where U.S. studies have reported associations with respiratory effects, including new onset asthma, asthma hospital admissions, and respiratory mortality. These design values are presented in Table 4-2, below. The approach to identifying design values is discussed in Wells et al. (2012).

Table 4-2. Ozone Design Values in U.S. Cities where Epidemiologic Studies have Evaluated Associations between Long-Term O_3 and Respiratory Effects

Study	Location	Reported Results	Design Value (ppb)[9]
Moore et al. (2008)	Southern California Communities	Increases in quarterly average O_3 concentrations were associated with increases in hospitalization for asthma	178
Islam et al. (2008)	12 California Communities	Apparent genetic protective effect against developing new onset asthma disappeared in high O_3 communities	123
Islam et al. (2009)	12 California Communities	Apparent genetic susceptibility to developing new onset asthma was accentuated in high O_3 communities	123
Salam et a. (2009)	12 California Communities	Apparent genetic protective effect against developing new onset asthma for children in high O_3 communities	123
Meng et al. (2010)	San Joaquin Valley	Positive and statistically significant association between annual average O_3 and asthma emergency department visits or hospitalizations	100[10]
Jerrett et al. (2009)	96 U.S. MSAs	Positive and statistically significant association between long-term O_3 and respiratory mortality	91
Zanobetti and Schwartz (2011)	105 U.S. cities	Positive and statistically significant association between summer-time average O3 and mortality in people with COPD	88
Lin et al. (2008)	Communities across New York State	Positive and statistically significant associations between asthma hospital admissions long-term O_3 concentrations	83

[9]For each study city and each study year, 4th-highest 8-hour daily maximum O_3 concentrations were identified. To provide some perspective on whether these cities would likely have met or violated the current O_3 NAAQS during the study period, these concentrations were averaged over the years of the study, resulting in the study average design value. For multi-city studies, the median of the distribution of design values was identified. Design values for each of the cities included in these multi-city studies are included in Wells et al. (2012).

[10]The study period for the study by Meng et al. (2010) was November 1999 to September 2000. The design value reported in Table 4-2 reflects all 3-year periods that include 1999 and 2000.

With regard to the long-term studies in Table 4-2, we note that 50th percentiles of the distributions of O_3 design values across cities ranged from 83 to 178 ppb. These median concentrations indicate that most of the cities included in available U.S. multi-city studies of long-term O_3 would likely not have met the current O_3 standard over the study periods. In considering the broader distributions of design values across study cities, we note that even in the study with the lowest O_3 concentrations, the 25th percentile of the design values was above the level of the current O_3 standard (i.e., 79 ppb for the study by Lin et al., 2008) (Wells et al., 2012). In light of this, we note that the large majority of the cities included in U.S. multi-city studies of long-term O_3-related respiratory effects would likely not have met the current O_3 standard during the study periods. While U.S. epidemiologic studies provide strong support for the association between long-term O_3 concentrations and clearly adverse respiratory effects, consideration of the O_3 design values for the cities included in these studies does not provide insight into the appropriateness of the degree of public health protection provided by the current O_3 standard.

Beyond looking at design values in long-term exposure studies, we note that several U.S. epidemiologic studies provide information about annual or seasonal mean 8-hour average concentrations used to differentiate low and high O_3 communities or that characterized the range of O_3 concentrations over which positive concentration-response relationships were observed. As discussed above in chapter 2, section 2.3, key new studies include longitudinal studies of serious effects such as new-onset asthma and first asthma hospital admission, as well as cross-sectional studies of current asthma and respiratory school absences.

For example, recent longitudinal studies from the CHS provide evidence for gene-environment interactions in effects on new-onset asthma by indicating that the lower risks associated with specific genetic variants are found in children who live in lower O_3 communities. In two studies (Islam et al., 2008; Islam et al., 2009), low ozone communities were defined by an annual mean 8-hour average O_3 concentrations of 38.4 ppb. In another study (Salam et al., 2009), the median annual mean 8-hour average concentration used differentiate high and low O_3 communities was 50 ppb. A cross-sectional study (Wenton et al., 2009) from the CHS provides evidence of gene-environment interactions in effects on respiratory school absences indicating that the lower risks associated with specific genetic variants are found in children who live in lower O_3 communities, in which a median annual mean 8-hour average O_3 concentration of 46.9 ppb was used to differentiate high and low O_3 communities.

Evidence associating long-term O_3 exposure to first asthma hospital admission in a concentration-response relationship is provided in a retrospective cohort study (Lin et al., 2008b) that followed a birth cohort of more than 1.2 million babies born in New York State to first asthma admission. A positive concentration-response relationship between exposure to O_3 and

childhood asthma hospital admissions was observed across the annual mean 8-hour O_3 concentrations which ranged from 37.51 to 47.78 ppb. In a cross-sectional analysis, Akinbami et al. (2010) examined the association between chronic exposure to O_3 and asthma outcomes in a national sample of children ages 3-17 years living in U.S. metropolitan areas. A positive association for both currently having asthma and for having at least 1 asthma attack in the previous year was observed, with a median value for 12-month average O_3 levels of 39.5 ppb and an IQR of 35.9-43.7 ppb, with a positive concentration-response relationship apparent from the lowest quartile to the highest.

Such air quality information can help inform consideration of the adequacy of the current primary O_3 standard, or lower 8-hour average levels that may be considered, in providing protection to children against the effects of long-term O_3 exposures. We plan to conduct additional air quality analyses in the second draft PA, relating annual or seasonal 8-hour average O_3 concentrations in areas across the country with 4th-highest 8-hour daily maximum O_3 concentrations, to further inform such considerations.

4.2.1.3 Total mortality

In addition to the morbidity studies discussed above, we consider studies linking short-term O_3 concentrations to all-cause total mortality.[11] As is the case with most of the U.S. epidemiologic studies of respiratory-related hospital admissions, emergency department visits, and mortality (see above), U.S. epidemiologic studies of total mortality have not been conducted in locations likely to have met the current O_3 standard during the study periods (Table 4-3). The medians of the distributions of average O_3 design values ranged from 88 to 96 ppb.

[11]The evidence linking long-term O_3 concentrations with mortality was judged in the ISA to be suggestive of a causal relationship (US EPA, 2012a, section 2.5.2). Therefore, unlike for morbidity, our consideration of mortality focuses on studies of short-term O_3 concentrations.

Table 4-3. Ozone Design Values in U.S. Cities where Epidemiologic Studies have Evaluated Associations between Short-Term O_3 and Non-Accidental Mortality

Study	Location	Lag	Averaging Time	% Increase (95% CI)	Median Design Value (ppb)
All-year					
Schwartz (2005)	14 U.S. cities	0	1-h max	0.76 (0.13, 1.40)	96
Bell et al. (2007)	98 U.S. communities	0-1	24-h	0.64 (0.34, 0.92)	89
Bell and Dominici (2008)	98 U.S. communities	0-6	24-h avg	1.04 (0.56, 1.55)	89
Katsouyanni et al. (2009)	APHENA-U.S. (90 cities)	DL (0-2)	1-h max	3.02 (1.10, 4.89)	89
Bell et al. (2004)	95 U.S. communities	0-6	24-h avg	1.04 (0.54, 1.55)	88
Warm Season					
Schwartz (2005)	14 U.S. cities	0	1-h max	1.00 (0.30, 1.80)	96
Zanobetti and Schwartz (2008)	48 U.S. cities	0	8-h max	1.51 (1.14, 1.87)	92
Zanobetti and Schwartz (2008)	48 U.S. cities	0-3	8-h max	1.60 (0.84, 2.33)	92
Medina-Ramon and Schwartz (2008)	48 U.S. cities	0-2	8-h max	1.96 (1.14, 2.82)	92
Franklin and Schwartz (2008)	18 U.S. communities	0	24-h avg	1.79 (0.90, 2.68)	91
Katsouyanni et al. (2009)	APHENA-U.S.	DL (0-2)	1-h max	3.83 (1.90, 5.79)	89
Bell et al. (2004)	95 U.S. communities	0-6	24-h avg	0.78 (0.26, 1.30)	88

However, several epidemiologic studies have evaluated the nature of the concentration-response relationship with mortality and the possibility that a threshold concentration exists, below which O_3 is no longer associated with mortality (US EPA, 2012a, section 6.6.2.4). In one of the largest U.S. studies to address this issue, Bell et al. (2006) used different statistical approaches to evaluate the potential for a threshold in the O_3-mortality relationship in the 98 cities in the NMMAPS dataset. As discussed above (section 2.2.2), the authors reported positive and statistically significant associations with mortality in a variety of restricted analyses, including analyses restricted to days with 24-hour average O_3 concentrations (i.e., averaged across monitors in cities with multiple monitors) below 60, 55, 50, 45, 40, 35, and 30 ppb. In these restricted analyses O_3 effect estimates were of similar magnitude and had similar statistical precision. In the analysis restricted to days with 24-hour average O_3 concentrations below 25 ppb, the O_3 effect estimate was similar in magnitude to the effect estimates resulting from analyses with the higher cutoffs, but had somewhat lower statistical precision, with the estimate approaching statistical significance (i.e., based on observation of Figure 2 in Bell et al., 2006).

In analyses restricted to days with lower 24-hour average O_3 concentrations (i.e., below 20 and 15 ppb), effect estimates were similar in magnitude to analyses with higher cutoffs, but with notably less statistical precision (i.e., confidence intervals included no O_3-associated mortality) (i.e., based on observation of Figure 2 in Bell et al., 2006). Ozone was no longer positively associated with mortality when the analysis was restricted to days with 24-hour O_3 concentrations below 10 ppb.

In considering the results of Bell et al. (2006) within the context of the adequacy of the current O_3 standard we note that, as with the study by Silverman and Ito (2010) discussed above, it is not appropriate to compare O_3 concentrations based on averaging across monitors (i.e., which in the case of the study by Bell reflect 24-hour concentrations averaged across monitors for cities with multiple monitors) directly to the level of the current standard (for which attainment is based on the 4th highest 8-hour daily maximum concentration from the single monitor recording the highest such concentration). Therefore, we have used EPA's AQS to relate average 24-hour O_3 concentrations in the 98 study cities (i.e., averaged across monitors in cities with multiple monitors) to the highest 8-hour daily maximum concentrations (i.e., from the individual monitors in each city recording the highest such concentrations) (Wells et al., 2012).[12]

Specifically, we first used AQS to identify average 24-hour O_3 concentrations in each of the 98 study cities for each day during the study period. We then used the cutoff values identified by Bell to restrict the distribution of average 24-hour concentrations. Specifically, for each city we restricted the distribution of O_3 air quality to days with average 24-hour O_3 concentrations at or below 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, and 5 ppb (i.e., the cutoffs evaluated by Bell). From these restricted air quality distributions, we then identified the highest 8-hour O_3 concentrations (i.e., from a single monitor) in each city for each year. These highest 8-hour daily maximum O_3 concentrations were then used to provide insight into whether the restricted air quality distributions used by Bell et al. (2006) would have reflected O_3 concentrations likely to have been allowed by the current O_3 standard.

In considering these restricted analyses, we first focus on the lowest cutoff value that resulted in a positive and statistically significant association with mortality in Bell et al. (2006) (i.e., 30 ppb). In considering only days with average 24-hour O_3 concentrations at or below 30 ppb, we note that the 50th percentile of the distribution of highest 8-hour daily maximum O_3 concentrations[13] was approximately 70 ppb (25th percentile was approximately 64 ppb; 75th

[12]As noted in Wells et al. (2012), the MSA was used as a surrogate for the study area boundaries. We recognize that this does not exactly match the study area definitions used by Bell et al. (2006). Further refinement of this approach may be explored in the 2nd draft Policy Assessment.

[13]Percentiles were identified from the distribution of the study period averages of highest 8-hour daily maximum O_3 concentrations within each city.

percentile was approximately 78 ppb). In light of this, we note that ambient O_3 concentrations across most of the cities evaluated by Bell et al. (2006) would likely have been allowed by the current O_3 standard for the restricted analysis with a 30 ppb cutoff (Wells et al., 2012).

In further considering the restricted analyses by Bell et al. (2006), we also consider lower cutoff values. Specifically, we consider the analysis with a 24-hour average cutoff of 25 ppb, which resulted in a positive association with mortality that approached statistical significance (i.e., based on confidence intervals in figure 2 of Bell et al., 2006), and the analysis with a 24-hour average cutoff of 15 ppb, which resulted in a positive association with mortality but with notably wider confidence intervals (The 15 ppb cutoff was the lowest cutoff value that resulted in a positive association with mortality).[14]

In considering days with average 24-hour O_3 concentrations at or below 25 ppb, we note that the 50th percentile of the distribution of highest 8-hour daily maximum O_3 concentrations (i.e., the distribution across cities) was approximately 60 ppb (25th percentile was approximately 55 ppb; 75th percentile was approximately 67 ppb). In addition, cities had fewer than one day per year, on average, with highest 8-hour daily maximum O_3 concentrations greater than 75 ppb (i.e., average was 0.4 days per year). In light of this, we note that ambient O_3 concentrations across most of the cities evaluated by Bell et al. (2006) would likely have been well below those allowed by the current O_3 standard for the restricted analysis with a 25 ppb cutoff (Wells et al., 2012).

In considering the days with average 24-hour O_3 concentrations at or below 15 ppb, we note that the 50th percentile of the distribution of highest 8-hour daily maximum O_3 concentrations (i.e., the distribution across cities) was approximately 40 ppb (25th percentile was approximately 37 ppb; 75th percentile was approximately 46 ppb). In addition, all cities had far fewer than one day per year, on average, with highest 8-hour daily maximum O_3 concentrations greater than 75 ppb (i.e., average across cities was 0.008 days per year). In light of this, we note that ambient O_3 concentrations across all of the cities evaluated by Bell et al. (2006) would likely have been well-below those allowed by the current O_3 standard for the restricted analysis with a 15 ppb cutoff (Wells et al., 2012).

In considering the restricted analyses by Bell et al. (2006) within the context of the adequacy of the current O_3 standard, we note that Bell reported positive and statistically significant associations between O_3 and mortality in analyses restricted to O_3 concentrations that would likely have been allowed by the current O_3 standard in most of the cities evaluated. In

[14]As discussed above, the decreasing precision in effect estimates as concentrations approach the lower extreme of the air quality distribution, as indicated by notable widening of confidence bounds, is intrinsically related to data density and is not necessarily indicative of an absence of O_3-associated health effects.

addition, positive, though not statistically significant associations were reported in analyses restricted to lower O_3 concentrations, likely to have been well-below those allowed by the current standard across most or all cities.

4.2.1.4 Other health endpoints

In addition to our above consideration of the health effects judged in the ISA to be caused or likely caused by O_3 exposures, we also note that evidence continues to emerge for a broader range of O_3-related health effects. Specifically, we note the ISA conclusions that the evidence is "suggestive of a causal relationship" between short-term O_3 exposures and cardiovascular effects and central nervous system effects and between long-term O_3 exposures and cardiovascular effects, reproductive and developmental effects, central nervous system effects, and mortality (US EPA, 2011b, Table 2-1). Although the bodies of evidence for these O_3-related effects have generally expanded since the last review, important uncertainties remain regarding the contribution of O_3 to such effects and the extent to which such effects can result from exposures to O_3 concentrations that would be allowed by the current standard. Therefore, while these studies provide important information on the breadth of health effects potentially attributable to O_3 exposures, they provide little additional information to inform a judgment as to the adequacy of the public health protection provided by the current O_3 standard.

4.2.1.5 Integrated consideration of health evidence

There is much new evidence available in this review that supports and builds upon key health-related conclusions drawn in previous reviews of the O_3 standard, including important new controlled human exposure studies and a large number of new epidemiologic studies, including new epidemiologic studies of effects associated with short-term as well as long-term O_3 exposures. The staff believes that this body of scientific evidence is very robust, recognizing that it includes large numbers of various types of studies, including toxicological studies, controlled human exposure studies, and community epidemiological studies, that provide consistent and coherent evidence of an array of O_3-related effects associated with short-term exposures including respiratory morbidity effects and mortality effects, both respiratory and total non-accidental mortality, as well as evidence associating long-term O_3 exposures with respiratory morbidity and mortality effects, and new onset asthma. Further, the available evidence provides increased confidence that (1) the full range of O_3-related respiratory effects, including emergency department visits, hospital admissions, and respiratory mortality, are caused by short-term O_3 exposures; and that (2) total non-accidental mortality is likely to be caused by short-term exposures.

In particular, we note that recent controlled human exposure and epidemiologic studies reinforce the conclusion that the types of O_3-related effects considered in previous reviews

extend to O_3 concentrations that would be allowed by the current standard. In looking broadly at the available evidence from controlled human exposure, epidemiologic, and animal toxicological studies, we note that the controlled human exposure studies have reported a variety of health effects, including lung function decrements, respiratory symptoms and pulmonary inflammation in healthy subjects, following exposures to O_3 concentrations (i.e., 60-70 ppb) below the level of the current O_3 standard. With respect to epidemiologic studies, a limited number have been conducted at ambient O_3 concentrations below those allowed by the current standard, or have examined subsets of data that include only days with ambient O_3 concentrations below the level of the current standard and continue to report associations with respiratory mortality. Importantly, there are also many epidemiologic studies done in areas that likely would not have met the current standard but which nonetheless report statistically significant associations that generally extend down to ambient O_3 concentrations that are below the level of the current standard; in most studies such effects have not shown evidence for a threshold across the range of O_3 concentrations typically observed in the United States during the O_3 season. These include the most severe O_3-related effects (i.e., emergency department visits, hospital admissions, premature mortality) as well as a variety of other respiratory effects (i.e., lung function decrements, respiratory symptoms, and airway inflammation). The evidence from controlled human exposure and epidemiologic studies is supported by a very large body of toxicological studies which provides additional biological plausibility and coherence to those results. In this section, we draw preliminary conclusions regarding the extent to which this evidence supports or calls into question the adequacy of the public health protection provided by the current O_3 standard.

The clearest evidence that the health effects discussed above can plausibly result from exposures to O_3 concentrations below those allowed by the current O_3 standard comes from a number of new controlled human exposure studies reporting O_3-induced lung function decrements, respiratory symptoms, and airway inflammation following exposures of healthy adults to O_3 concentrations below 75 ppb. As discussed above, controlled human exposure studies that evaluate only healthy, nonasthmatic subjects likely underestimate the effects of O_3 exposure on asthmatics and other susceptible populations. Therefore, relative to the healthy, nonasthmatic subjects used in most controlled human exposure studies, a greater proportion of people with asthma may be affected, and those who are affected may have larger responses following exposures to O_3 concentrations below 75 ppb. This suggests that the lowest observed effects levels demonstrated in controlled human exposure studies that use only healthy subjects (i.e., 60 ppb) may not reflect the lowest levels at which people with asthma or other lung diseases can respond. In support of this, as discussed above we note that epidemiologic studies have

reported O_3-associated lung function decrements in children and outdoor workers at O_3 concentrations below 60 ppb.

A limited number of epidemiologic studies report that O_3-related mortality, hospital admissions, and emergency department visits occur in areas with ambient O_3 concentrations below those allowed by the current O_3 standard. This includes studies of short-term O_3 concentrations reporting O_3-related asthma emergency department visits in children and adults in Seattle, a location that would likely have met the current O_3 standard during the study period (Mar and Koenig, 2009); a study reporting relatively high confidence in a linear concentration-response relationship between short-term O_3 concentrations and asthma hospital admissions in New York City at ambient O_3 concentrations likely to have been allowed by the current standard (Silverman and Ito, 2010); and a multi-city study reporting positive and statistically significant associations between short-term O_3 concentrations and mortality in analyses restricted to ambient O_3 concentrations likely to have been allowed by the current standard (Bell et al., 2006). Moreover, many short-term exposure epidemiologic studies done in areas that likely would not have met the current standard report statistically significant associations that generally extend down to ambient O_3 concentrations that are below the level of the current standard. With respect to epidemiologic evidence regarding the effects of long-term exposures to O_3, we note that while U.S. epidemiologic studies provide strong support for the association between long-term O_3 concentrations and clearly adverse respiratory effects, consideration of the O_3 design values for the cities included in these studies does not provide insight into the appropriateness of the degree of public health protection provided by the current O_3 standard.

In considering the overall body of evidence for O_3-related respiratory effects and mortality, including evidence for such effects following exposures to O_3 concentrations below those that would be allowed by the current O_3 standard, we first conclude that the available evidence provides strong support for a standard at least as protective as the current O_3 standard. In addition, we reach the further preliminary conclusion that the available evidence calls into question the adequacy of the current standard and provides support for considering potential alternative standards to increase public health protection against the effects related to short-term O_3 exposures, especially for at-risk groups. This preliminary conclusion places considerable weight on the array of O_3-related respiratory effects that have been reported following exposures to short-term O_3 concentrations below the level of the current standard. In emphasizing such effects, this preliminary conclusion also places considerable weight on the plausibility of the linkages between the body of evidence for respiratory effects and mortality following exposures to O_3 concentrations below those allowed by the current O_3 standard and the broader body of experimental and epidemiologic evidence for O_3-related respiratory effects and mortality

reported following exposures to higher concentrations. In reaching this preliminary conclusion, we acknowledge that uncertainties persist in the health evidence; however, in staff's view the broad array of health effects reported following short-term exposures to O_3 concentrations below those allowed by the current standard (i.e., respiratory effects and mortality), combined with the plausible linkages between these effects and the much larger body of epidemiologic and controlled human exposure evidence at higher O_3 concentrations, supports the appropriateness of revising the current O_3 standard in order to increase public health protection, particularly for people with asthma, children and other at-risk groups.

4.2.2 Exposure- and Risk-Based Considerations

In this section, we consider the following question:

- **To what extent do the O_3 exposure and risk analyses presented in the first draft REA support or call into question the adequacy of the public health protection provided by the current O_3 primary standard?**

In addressing this question, we consider the first draft REA assessments of O_3-related exposures and risks associated with recent air quality and with air quality adjusted to simulate just meeting the current O_3 standard. More specifically, we consider estimates from the REA of the number of people in at-risk populations with O_3 exposures above health benchmark levels (section 4.2.2.1); estimates of the number of people in at-risk populations with impaired lung function resulting from exposures to O_3 (section 4.2.2.2);[15] and estimates of the potential magnitude in the population of premature mortality and selected morbidity effects (section 4.2.2.3). Section 4.2.2.4 provides an integrated consideration of the exposure and risk information within the context of the adequacy of the current O_3 standard.

4.2.2.1 Exposures above health benchmark concentrations

As part of the last O_3 NAAQS review, EPA conducted exposure analyses for the general population, all school-age children (ages 5-18), active school-age children, and asthmatic school-age children (US EPA, 2007a, b). Exposure estimates were generated for 12 urban areas for recent years of air quality and for just meeting the existing 8-hr standard and several alternative 8-hr standards.

The exposure analysis conducted in the first draft REA in the current review builds upon the methodology and lessons learned from the exposure analyses conducted in previous reviews, as well as information provided in the third draft ISA (US EPA, 2012a). In the second draft REA, EPA will be conducting exposure modeling for 16 urban areas located across

[15] As noted in section 4.2.2.2, quantitative estimates of O_3-induced lung function impairment are being developed in parallel with this first draft Policy Assessment. Therefore, these estimates will be considered in the second draft Policy Assessment.

the U.S. (US EPA, 2012b). In the first draft REA, results are presented for four of these areas, Atlanta, Denver, Los Angeles, and Philadelphia.

Population exposures to ambient O_3 levels were modeled using the Air Pollutants Exposure (APEX) model (U.S. EPA, 2012b,c). Exposure estimates were developed for O_3 concentrations in recent years, based on 2006 to 2010 ambient air quality measurements, and for O_3 concentrations adjusted to simulate just meeting the current 8-hr O_3 standard. Exposures were modeled for 1) the general population, 2) school-age children (ages 5-18), and 3) asthmatic school-age children. The strong emphasis on children reflects the finding of the last O_3 NAAQS review (EPA, 2007a) and the ISA (EPA, 2012a, Chapter 8) that children are an important at-risk group.

Benchmark levels used in the first draft REA were 60, 70, and 80 ppb, 8-hour average. These levels are based on the evidence from controlled human exposures studies that were conducted using 6.6 hour exposures of healthy adults while at intermittent, moderate exertion. Although the analysis of these exposures was conducted using three discrete benchmark levels, the concept is more appropriately viewed as a continuum, with greater confidence and less uncertainty about the existence of health effects at the upper end and less confidence and greater uncertainty as one considers increasingly lower O_3 exposure levels. Estimating exposures to ambient O_3 concentrations at and above these benchmark levels, while at moderate or greater exertion, was intended to provide some perspective on the public health impacts of O_3-related health effects that have been demonstrated in controlled human exposure studies, but that cannot currently be evaluated in quantitative risk assessments, such as lung inflammation, increased airway responsiveness, and decreased resistance to infection. As discussed in detail in the ISA (US EPA, 2012a, section 6.2), and above (sections 2.2.1 and 4.2.1), the 80 ppb benchmark represents an exposure concentration at which there is a substantial amount of human clinical evidence demonstrating a range of O_3-related effects in healthy exercising adults, including lung function decrements, respiratory symptoms, airway inflammation, impaired lung host defense, and airway hyperresponsiveness. The 70 ppb benchmark reflects an O_3 exposure concentration that has been reported to result in lung function decrements and respiratory symptoms in healthy exercising adults. As discussed above (sections 2.2.1 and 4.2.1), the 60 ppb benchmark reflects consideration of the lowest exposure concentration for which O_3-induced respiratory effects have been reported in controlled human exposure studies of healthy exercising adults. Effects at both of these levels reflect the broader range of effects reported following exposures to 80 ppb O_3 that have been reported in healthy adults. And the effects reported in healthy adults at 60 and 70 ppb O_3 could result in underestimating the health impacts of O_3 exposures, as discussed above (section 2.4)

As discussed above in section 3, the first draft REA (US EPA, 2012b, section 5) estimated the number and percentage of school-age children who experience at least one 8-hour average O_3 exposure above each benchmark concentration while at the same time engaged in activities resulting in moderate or greater exertion. Across the years included in the analysis (2006-2010), the pattern of exposures differed. For example, in the worst O_3 year (2006), the percentage of children exposed to 8-hour O_3 concentrations at or above 60 ppb while at moderate or greater exertion ranged from 30 to 37% across the 4 study areas; the percentage exposed to 8-hour concentrations at or above 70 ppb ranged from 10 to 21%; and the percentage exposed to 8-hour concentrations at or above 80 ppb ranged from 1 to 10%. In the year with the lowest O_3 concentrations (2009), the percentage of children exposed to 8-hour O_3 concentrations at or above 60 ppb while at moderate or greater exertion ranged from 9 to 32%; the percentage exposed to 8-hour concentrations at or above 70 ppb ranged from 1 to 15%; and the percentage exposed to 8-hour concentrations at or above 80 ppb ranged from 0 to 5%.

In specifically considering these exposure results within the context of the adequacy of the current standard, we consider estimated exposures associated with recent unadjusted air quality and with air quality adjusted to simulate just meeting the current O_3 standard. With unadjusted air quality, the average (i.e., average across years 2006 to 2010) percentages of school age children estimated to experience one or more exposures per year to 8-hour O_3 concentrations above 60, 70, or 80 ppb, while at moderate or greater exertion, were as follows (US EPA, 2012b, Figures 5-1 to 5-15, Tables 4-5 to 4-6, and section 9.1):

- For Denver, approximately 20% above 60 ppb (corresponding to 109,000 children), 4% above 70 ppb (corresponding to approximately 22,000 children), and 0.4% above 80 ppb (corresponding to approximately 2,200 children)

- For Atlanta, approximately 22% above 60 ppb (corresponding to 189,000 children), 9% above 70 ppb (corresponding to approximately 75,000 children), and 3% above 80 ppb (corresponding to approximately 24,000 children)

- For Philadelphia, approximately 26% above 60 ppb (corresponding to 297,000 children), 10% above 70 ppb (corresponding to 117,000 children), and 2% above 80 ppb (corresponding to approximately 28,000 children)

- For Los Angeles, approximately 32% above 60 ppb (corresponding to 1,150,000 children), 15% above 70 ppb (corresponding to 559,000 children), and 6% above 80 ppb (corresponding to approximately 218,000 children)

When air quality was adjusted to simulate just meeting the current O_3 standard, these estimated benchmark exceedances decreased. Specifically, for adjusted air quality, the average

percentages of school age children estimated to experience one or more exposures per year to 8-hour O_3 concentrations above 60, 70, or 80 ppb, while at moderate or greater exertion, were as follows[16] (US EPA, 2012b, Figures 5-1 to 5-15, Tables 4-5 to 4-6):

- For Denver, approximately 9-11% above 60 ppb (corresponding to approximately 51,000-61,000 children), 0.6-0.7% above 70 ppb (corresponding to approximately 3,300-4,200 children), and 0.0% above 80 ppb

- For Atlanta, approximately 8-10% above 60 ppb (corresponding to approximately 72,000-83,000 children), 1% above 70 ppb (corresponding to approximately 9,600-11,200 children), and 0.1% above 80 ppb (corresponding to approximately 700-900 children)

- For Philadelphia, approximately 9-13% above 60 ppb (corresponding to approximately 105,000-145,000 children), 1-2% above 70 ppb (corresponding to approximately 10,000-26,000 children), and 0.0-0.1% above 80 ppb (corresponding to approximately 500-1,600 children)

- For Los Angeles, approximately 4% above 60 ppb (corresponding to approximately 126,000-148,000 children), 0.2-0.3% above 70 ppb (corresponding to approximately 7,500-11,300 children), and 0.0% above 80 ppb

When considering exposures above benchmark concentrations in asthmatic children at moderate or greater exertion, the results were similar in term of numbers, with decreased exposures estimated for air quality adjusted to simulate just meeting the current O_3 standard (US EPA, 2012b, Tables 5-11 and 5-12). For example, when air quality was adjusted to simulate just meeting the current O_3 standard, the numbers of asthmatic children estimated to be exposed one or more times per year to 8-hour O_3 concentrations at or above 60 ppb, while at moderate exertion, ranged from approximately 5,000 to 17,000 across these four cities; the numbers of asthmatic children estimated to be exposed to O_3 concentrations at or above 70 ppb ranged from approximately 300 to 3,000 across cities; and the numbers of asthmatic children estimated to be exposed to O_3 concentrations at or above 80 ppb ranged from 0 to approximately 200 across cities (US EPA, 2012b, Tables 5-11 and 5-12).

4.2.2.2 Estimates of O_3-induced lung function impairment

As noted in the first draft of the REA (US EPA, 2012b), quantitative estimates of lung function impairment are under development and will be released with this first draft PA. Therefore, estimates of lung function impairment will be considered in the second draft PA.

[16]The ranges presented represent the range of estimates across each of the 3-year periods for which air quality was adjusted to simulate just meeting the current O_3 NAAQS (i.e., 2006-2008, 2008-2010).

4.2.2.3 Estimates of O_3-associated mortality and morbidity

The first draft REA evaluated risks of mortality and morbidity from short-term exposures to O_3 based on application of concentration-response functions derived from epidemiology studies. The analysis included both a set of urban area case studies and a national scale assessment. The urban case study analyses evaluated mortality and morbidity risks, including emergency department visits, hospitalizations, and respiratory symptoms associated with recent O_3 concentrations (2006-2010) and with O_3 concentrations adjusted to simulate just meeting the current O_3 standard. Mortality and hospital admissions (HA) were evaluated in 12 urban areas, while emergency department visits and respiratory symptoms were evaluated in a subset of areas. These 12 urban areas were: Atlanta, GA; Baltimore, MD; Boston, MA; Cleveland, OH; Denver, CO; Detroit, MI; Houston, TX; Los Angeles, CA; New York, NY; Philadelphia, PA; Sacramento, CA; and St. Louis, MO. The urban case study analyses focus on risk estimates for the middle year of each three-year attainment simulation period (2006-2008 and 2008-2010) in order to provide estimates of risk for a year with generally higher O_3 concentrations (2007) and a year with generally lower O_3 concentrations (2009).

As discussed above (section 1.3.4), in past reviews of the O_3 NAAQS, O_3-related health risks have been estimated using non-threshold concentration-response functions. The use of non-threshold functions was consistent with the lack of a discernible threshold in the concentration-response relationship. Further, in past reviews health risks were estimated for O_3 concentrations above estimates of policy-relevant background concentrations (referred to as North American background in the third draft ISA and in Chapter 1, section 1.3.4). The estimation of risks above background concentrations, rather than estimation of total risks, was employed in past reviews to focus policy decisions on the portion of risk attributable to ambient O_3 that can be controlled either through regulation of domestic sources or through international agreements within North America.

Consistent with the approach in the last review, the first draft REA employed continuous non-threshold concentration-response functions relating ozone exposures to health effect incidence. The use of non-threshold functions reflects the conclusion reached in the ISA that the available evidence supports a linear, no-threshold concentration-response relationship across the range of daily O_3 concentrations commonly observed in the United States during the O_3 season (US EPA, 2012a, section 2.5.4.4). However, there are also some key differences in the approach taken in the first draft REA, compared to the approach taken in the previous review.

For example, in contrast to the approach used in the last review, the first draft REA has estimated total risks attributable to O_3 exposure, not risks in excess of background concentrations. In taking this approach, the REA noted the advice of CASAC members, who

recommended in the last review that EPA move away from using background in calculating risks (Henderson, 2007). This approach recognizes that health risks result from O_3 exposures, regardless of the source of the O_3.

In estimating total O_3-related health risks, the REA concluded that the approach most consistent with the statistical models reported in the epidemiological studies is to apply the concentration-response functions to all ozone concentrations down to zero. However, consistent with the conclusions of the ISA that the available evidence indicates less certainty in the shape of the concentration-response curve at the lower end of the distribution of ambient O_3 concentrations, the REA also recognized that confidence in the nature of the concentration-response function and the magnitude of the risks associated with very low concentrations of ozone is reduced because there are few ozone measurements at the lowest levels in many of the urban areas included in the studies. Specifically, the REA noted that estimates of risk associated with O_3 concentrations below the lowest measured level (LML) for the underlying epidemiological study would be associated with reduced confidence since these estimates involve applying the concentration-response function outside of the range of data used in its derivation. In light of this, the REA has characterized mortality risks in excess of lowest measured O_3 concentrations[17] as well as total risks associated with O_3 concentrations down to zero (US EPA, 2012b, sections 7.3.3 and 8.1.1.4).[18] In considering these different approaches, the REA concluded that the two sets of estimates provide a reasonable bound on estimated total risks, reflecting uncertainties about the concentration-response functions below the lowest ozone concentrations evaluated in the studies.

In the remainder of this section, we consider the first draft REA estimates of O_3-related health risks within the context of considering the adequacy of the current standard. Specifically, we consider risk estimates for all-cause mortality and respiratory morbidity, which includes respiratory-related hospital admissions, emergency department visits, and symptoms.

<u>All-cause mortality</u>

As noted above, the REA estimated O_3-associated mortality in a national assessment and in 12 specific urban areas for 2006-2008 and 2008-2010 air quality and, in the case of the 12 urban areas, for air quality adjusted to simulate just meeting the current standard. Mortality estimates were based on concentration-response relationships from two studies (Zanobetti and

[17]As discussed above (section 3.2.1), due to data limitations, the REA did not identify the actual LMLs from the epidemiologic studies used in the risk assessment. Rather, as a surrogate for the study-based LMLs, the REA used the lowest O_3 concentrations from the composite monitor O_3 distributions used to model health risks (US EPA, 2012b, section 7.1.1).

[18]For morbidity endpoints, risks were estimated down to the LML but not for total O_3 concentrations down to zero (US EPA, 2012b, chapter 7).

Schwartz, 2008; Bell et al., 2004). Estimates of mortality attributable to short-term O_3 exposures under recent conditions varied widely across urban study areas, reflecting differences in ambient O_3 concentrations and populations, as well as differences in city-specific effect estimates. The estimates based on Zanobetti and Schwartz (2008) showed the largest O_3-associated mortality risks in Boston, Detroit, Los Angeles, and New York, while the estimates based on Bell et al (2004) showed the largest risks in Atlanta, Boston, Houston, Los Angeles, and New York (US EPA, 2012b, section 9.3).

In the national analysis of O_3-attributable mortality for the years 2006 to 2008, the REA estimated 18,000 O_3-attributable deaths based on O_3 effect estimates from Bell et al. (2004) (corresponding to approximately 1.9% of total mortality) and 15,000 O_3-attributable deaths based on O_3 effect estimates from Zanobetti and Schwartz (2008) (corresponding to approximately 2.5% of total mortality) (US EPA, 2012b, chapter 8, Tables 1.2 and 1.3). Of these O_3-attributable deaths, the first draft REA estimated that 85-90% occur in locations where the seasonal average 8-hr daily maximum or 8-hr daily mean (10am-6pm) O_3 concentration is greater than 40 ppb, corresponding to 4th high 8-hour daily maximum O_3 concentrations ranging from approximately 50 ppb to 100 ppb. In considering the potential implications of estimates of O_3-attributable mortality for evaluation of the adequacy of the current O_3 standard, we consider the analyses in the 12 urban study cities, for which the first draft REA analyzed both unadjusted O_3 air quality and O_3 air quality adjusted to simulate just meeting the current standard.

Across the 12 study cities, and using estimates based on both Bell et al. (2004) and Zanobetti and Schwartz (2008), O_3-attributable mortality risk estimates for unadjusted air quality ranged from approximately 20 to 930 deaths, accounting for approximately 0.5 to 4.9% of total baseline all-cause mortality (for 2007 air quality). When risk estimates were focused on O_3 concentrations above the LML, risk estimates were somewhat smaller (i.e., approximately 10 to 730 deaths across the different cities). For 2009 unadjusted air quality, the O_3-attributable mortality risk estimates ranged from 20 to approximately 980 deaths across the 12 cities, accounting for approximately 0.6 to 4.3% of total baseline all-cause mortality. When risk estimates were focused on O_3 concentrations above the LML, these risk estimates ranged from approximately 10 to 780 deaths across cities, accounting for approximately 0.4 to 3.0% of total baseline all-cause mortality. Mortality estimates based on O_3 effect estimates from Bell et al. (2004) were generally larger than estimates based on effect estimates from Zanobetti and

Schwartz (2008), likely due to the larger effect estimates reported by Bell and to the longer O_3 season modeled for the study by Bell (US EPA, 2012b, Table 7-4).

Upon simulating just meeting the current standard, estimates of O_3-attributable mortality decreased across the 12 study cities, as noted in Table 4-1 of the first draft REA (US EPA, 2012b, section 7.5). Specifically, using effect estimates from both epidemiologic studies, that the estimated reductions in O_3-attributable mortality upon simulation of just meeting the current O_3 standard were approximately 10 to 50% for 2007 air quality and approximately 0.1 to 35% for 2009 air quality. Although this suggests the potential for important risk reductions as precursor emissions are reduced to meet the current standard, particularly when these percentages are considered within the context of national estimates of O_3-attributable mortality, estimates also suggest that substantial O_3-attributable risks will remain after meeting the current standard. With regard to the O_3-attributable mortality risks estimated to remain after air quality was adjusted to simulate just meeting the current O_3 standard, we specifically note the following:

- Using effect estimates from Zanobetti and Schwartz (2008) for the 2007 simulation year, the REA estimated that the range of remaining O_3-attributable deaths in the 12 U.S. study cities was approximately 20-850, based on estimates with no O_3 concentration cutoff, and 10-630, based on estimates down to the LML. The cities with the largest remaining O_3-attributable mortality risks were New York City [849 (no cutoff), 626 (LML)], Detroit [212 (no cutoff), 122 (LML)], and Boston [209 (no cutoff), 110 (LML)].

- Using effect estimates from Zanobetti and Schwartz (2008) for the 2009 simulation year, the REA estimated that the range of remaining O_3-attributable deaths in the 12 U.S. study cities was approximately 20-780, based on estimates with no O_3 concentration cutoff, and 10-520, based on estimates down to the LML. The cities with the largest remaining O_3-attributable mortality risks were New York City [777 (no cutoff), 521 (LML)], Detroit [178 (no cutoff), 127 (LML)], Boston [180 (no cutoff), 93 (LML)], and Los Angeles [175 (no cutoff), 83 (LML)].

- Using effect estimates from Bell et al. (2004) for the 2007 simulation year, the REA estimated that the range of remaining O_3-attributable deaths in the 12 U.S. study cities was approximately 30-830, based on estimates with no O_3 concentration cutoff, and 30-590, based on estimates down to the LML. The cities with the largest remaining O_3-attributable mortality risks were New York City [827 (no cutoff), 585 (LML)], Los Angeles [786 (no cutoff), 567 (LML)], Boston [404 (no cutoff), 282 (LML)], Atlanta [415 (no cutoff), 260 (LML)], Houston [270 (no cutoff), 217 (LML)], and St. Louis [193 (no cutoff), 157 (LML)].

- Using effect estimates from Bell et al. (2004) for the 2009 simulation year, the REA estimated that the range of remaining O_3-attributable deaths in the 12 U.S. study cities was approximately 30-820, based on estimates with no O_3 concentration cutoff, and 20-630, based on estimates down to the LML. The cities with the largest remaining O_3-attributable mortality risks were Los Angeles [821 (no cutoff), 628 (LML)], New York City [764 (no cutoff), 576 (LML)], Atlanta [364 (no cutoff), 315 (LML)], Boston [369 (no cutoff), 250 (LML)], and Houston [272 (no cutoff), 211 (LML)].

Respiratory Morbidity

The REA also estimated O_3-attributable respiratory hospital admissions, emergency department visits, and asthma exacerbations for subsets of the 12 cities. These estimates were based on concentration-response relationships from several available epidemiologic studies, using different statistical approaches (US EPA, 2012b, section 7.5, Table 7-4). With regard to these estimates, we specifically note the following:

- In Atlanta for 2007 unadjusted air quality, using different studies and statistical models, the REA estimated approximately 3,000 to 6,000 respiratory emergency department visits attributable to O_3. Upon simulating just meeting the current O_3 standard, the REA estimated that O_3-attributable emergency department visits decreased by approximately 20%, but that approximately 2,000 to 5,000 O_3-attributable emergency department visits remained. For 2009, the REA estimated that approximately 3,000 to 7,000 O_3-attributable emergency department visits remained (US EPA, 2012b, Table 7-21).

- In New York City for 2007 unadjusted air quality, using different statistical models, the REA estimated approximately 7,000 to 11,000 asthma emergency department visits attributable to O_3. Upon simulating just meeting the current O_3 standard, the REA estimated that O_3-attributable emergency department visits decreased by approximately 10%, but that approximately 6,000 to 10,000 O_3-attributable asthma emergency department visits remained. (US EPA, 2012b, Table 7-21). For 2009, the REA estimated that approximately 8,000 to 13,000 O_3-attributable emergency department visits remained (US EPA, 2012b, Table 7-21).

- In New York City for 2007 unadjusted air quality, using different statistical models, the REA estimated approximately 500 to 700 O_3-attributable asthma hospital admissions. Upon simulating just meeting the current O_3 standard, the REA estimated that O_3-attributable hospital admissions decreased by approximately 10%, but that approximately 500 to 600 O_3-attributable asthma hospital admissions remained. For 2009, the REA estimated that approximately 600 to 800 O_3-attributable asthma hospital admissions remained (US EPA, 2012b, Tables 7-22 and 7-23).

- Across the 12 urban study cities for 2007 unadjusted air quality, the REA estimated up to approximately 100 O_3-attributatble hospital admissions for respiratory causes. Upon

simulating just meeting the current O_3 standard, the REA estimated that O_3-attributable hospital admissions decreased by approximately 10 to 40% across cities, but that up to approximately 60 O_3-attributable hospital admissions remained. For 2009, the REA estimated that up to approximately 250 O_3-attributable hospital admissions remained (US EPA, 2012b, Tables 7-22 and 7-23).

- In Boston for 2007 unadjusted air quality, the REA estimated approximately 54,000 incidents of O_3-attributable wheezing and approximately 20,000 to 30,000 incidents of O_3-attributable chest tightness or shortness of breath among asthmatics. Upon simulating just meeting the current O_3 standard, the REA estimated that the number of such O_3-attributable events decreased by approximately 8%, but that approximately 50,000 incidents of O_3-attributable wheezing and approximately 18,000 to 27,000 incidents of chest tightness or shortness of breath remained for Boston (US EPA, 2012b, Table 7-24).

4.2.2.4 Integrated consideration of the exposure and risk information

In this section, we revisit the following question:

- **To what extent do the O_3 exposure and risk analyses presented in the first draft REA (US EPA, 2012b) support or call into question the adequacy of the public health protection provided by the current O_3 primary standard?**

In considering this question, we first note that the REA is currently in draft form and that the final REA will include additional analyses and information to inform a decision regarding the adequacy of the current O_3 NAAQs. Specifically, we note that future drafts of the REA will include quantitative estimates of O_3-induced lung function decrements, estimates of repeated exposures to O_3 concentrations above health benchmarks, estimates of risks associated with long-term O_3 concentrations, an alternative model-based approach to adjusting air quality to simulate just meeting the current standard, and any additional changes judged appropriate in light of comments and recommendations from CASAC and the public. Therefore, while this section considers the available exposure and risk information within the context of the adequacy of the current O_3 standard, we also acknowledge that additional information will be available in future drafts to more completely inform consideration of this question.

In first considering estimated exposure results within the context of the adequacy of the current standard we note that adjusting air quality concentrations in order to simulate just meeting the current O_3 standard resulted in substantial decreases in the estimated numbers of exposures at or above benchmark concentrations. This was particularly notable for the 80 ppb benchmark concentration, for which estimated exposures were almost eliminated in all four cities. Nonetheless, we note that when simulating just meeting the current O_3 standard, substantial numbers of children and asthmatic children are estimated to experience one or more O_3 concentrations per year above the 60 ppb benchmark, and in some cases above the 70 ppb

benchmark. Exposures at and above these lower benchmark levels have been demonstrated to decrease lung function, increase respiratory symptoms, and increase airway inflammation in healthy adults. Given that children and asthmatics are likely to experience larger respiratory responses than the healthy adults on which the estimates at the benchmark concentrations were based, this analysis indicates that important O_3-related health risks will remain in areas that would meet the current standard.

Further, we note that the potential for serious adverse events (e.g., hospitalizations) following exposures of at-risk individuals to O_3 concentrations above these benchmark concentrations is likely related to the frequency of exposures, in addition to the exposure concentrations. We recognize that the first draft REA does not characterize the occurrence of repeated exposures above benchmark concentrations. To the extent that such information is available in the second draft REA, we will take it into account in reaching conclusions in the second draft PA.

In next considering the risk results for mortality and morbidity within the context of considering the adequacy of the current O_3 standard, we note that while the current standard was estimated to reduce O_3-attributable mortality by up to approximately 20% and O_3-attributable morbidity by up to approximately 30%, depending on the location and time frame simulated, substantial risks were estimated to remain in areas that just met the O_3 standard. This includes estimates of up to hundreds of O_3-attributable deaths per year and thousands of O_3-attributable hospitalizations and emergency department visits per year in some cities. These risk estimates, combined with the exposure results discussed above, suggest the potential for substantial O_3-related health risks that could reasonably be judged to be important from a public health perspective, even in locations that meet the current O_3 standard.

We also recognize that there is a broader array of O_3-related adverse health outcomes for which risk estimates could not be quantified (that are part of a broader ‘‘pyramid of effects’’) and that the scope of the first draft REA was limited to just a sample of urban areas and to some, but not all, at-risk populations, leading to a limited estimation of public health impacts associated with O_3 exposures across the country.

In light of the above considerations, we reach the preliminary conclusion that the available exposure and risk information from the first draft REA supports the available health evidence discussed above (section 4.2.1) and that, at a minimum, exposure and risk results support the appropriateness of considering a range of potential alternative standards that would increase public health protection against respiratory effects and mortality. We acknowledge that these preliminary conclusions are based on a set of draft analyses and that our conclusions in the

final PA with regard to the current standard will be informed by the exposure and risk analyses included in the final REA.

4.2.3 CASAC Advice from Previous Review

In the last review of the O_3 NAAQS, CASAC stated the following in its letter to the Administrator: ‘‘the CASAC unanimously recommends that the current primary ozone standard be revised and that the level that should be considered for the revised standard be from 0.060 to 0.070 ppm’’ [60 to 70 ppb] (Henderson, 2006c, p. 5). This recommendation followed from CASAC’s more general recommendation that the then current standard, with a level of 0.08 ppm (effectively 0.084 ppb), needed to be made substantially more protective of human health, particularly for at-risk subpopulations. In a subsequent letter sent specifically to offer advice to aid the Administrator and Agency staff in developing the O_3 proposal, the CASAC reiterated that the Panel members ‘‘were unanimous in recommending that the level of the current primary ozone standard should be lowered from 0.08 ppm to no greater than 0.070 ppm’’ (Henderson, 2007, p. 2). Further, the CASAC Panel expressed the view that the 2006 Criteria Document and 2007 Staff Paper, together with the information in its earlier letter, provided ‘‘overwhelming scientific evidence for this recommendation’’ (Henderson, 2007, p. 2). In expressing these views and recommendations, the Panel emphasized the Clean Air Act requirement that the primary standard must be set to protect the public health with an adequate margin of safety (Henderson, 2007).

Following the 2008 decision to revise the primary O_3 standard by setting the level at 0.075 ppm (75 ppb), CASAC raised serious questions as to whether the standard met the requirements of the CAA. In April 2008, the members of the CASAC Ozone Review Panel sent a letter to EPA stating “[I]n our most-recent letters to you on this subject—dated October 2006 and March 2007—the CASAC unanimously recommended selection of an 8-hour average Ozone NAAQS within the range of 0.060 to 0.070 parts per million [60 to 70 ppb] for the primary (human health-based) Ozone NAAQS” (Henderson, 2008). The letter continued:

> The CASAC now wishes to convey, by means of this letter, its additional, unsolicited advice with regard to the primary and secondary Ozone NAAQS. In doing so, the participating members of the CASAC Ozone Review Panel are unanimous in strongly urging you or your successor as EPA Administrator to ensure that these recommendations be considered during the next review cycle for the Ozone NAAQS that will begin next year (Henderson, 2008).

Moreover, the CASAC Panel noted that ‘‘numerous medical organizations and public health groups have also expressed their support of these CASAC recommendations’’ (Henderson, 2008). The letter further stated the following strong, unanimous view:

> [The CASAC did] not endorse the new primary ozone standard as being sufficient protective of public health. The CASAC—as the Agency's statutorily-established science advisory committee for advising you on the national ambient air quality standards—unanimously recommended decreasing the primary standard to within the range of 0.060–0.070 ppm [60 to 70 ppb]. It is the Committee's consensus scientific opinion that your decision to set the primary ozone standard above this range fails to satisfy the explicit stipulations of the Clean Air Act that you ensure an adequate margin of safety for all individuals, including sensitive populations (Henderson, 2008).

As discussed above (section 1.2.3), in 2010 the Administrator proposed to reconsider and revise parts of the 2008 final rule. With regard to the primary standard, she proposed to revise the level to within the range of 60 to 70 ppb (FR 75 2938). This proposal was based on the scientific and technical record from the 2008 rulemaking, including public comments and CASAC advice and recommendations. In response to EPA's request for additional advice, CASAC again reaffirmed their conclusion that "the evidence from controlled human and epidemiological studies strongly supports the selection of a new primary ozone standard within the 60 – 70 ppb range for an 8-hour averaging time" (Samet, 2011). As requested by EPA, CASAC's advice and recommendations were based on the scientific and technical record from the 2008 rulemaking. In considering this record for the 2008 rulemaking, CASAC stated the following to summarize the basis for their conclusions (Samet, 2011, pp. ii to iii):

- The evidence available on dose-response for effects of ozone shows associations extending to levels within the range of concentrations currently experienced in the United States.

- There is scientific certainty that 6.6-hour exposures with exercise of young, healthy, non-smoking adult volunteers to concentrations ≥ 80 ppb cause clinically relevant decrements of lung function.

- Some healthy individuals have been shown to have clinically relevant responses, even at 60 ppb.

- Since the majority of clinical studies involve young, healthy adult populations, less is known about health effects in such potentially ozone sensitive populations as the elderly, children and those with cardiopulmonary disease. For these susceptible groups, decrements in lung function may be greater than in healthy volunteers and are likely to have a greater clinical significance.

- Children and adults with asthma are at increased risk of acute exacerbations on or shortly after days when elevated ozone concentrations

occur, even when exposures do not exceed the NAAQS concentration of 75 ppb.

- Large segments of the population fall into what EPA terms a "sensitive population group,'' i.e., those at increased risk because they are more intrinsically susceptible (children, the elderly, and individuals with chronic lung disease) and those who are more vulnerable due to increased exposure because they work outside or live in areas that are more polluted than the mean levels in their communities.

More specifically, with respect to evidence from epidemiologic studies, CASAC stated "[W]hile epidemiological studies are inherently more uncertain as exposures and risk estimates decrease (due to the greater potential for biases to dominate small effect estimates), specific evidence in the literature does not suggest that our confidence on the specific attribution of the estimated effects of ozone on health outcomes differs over the proposed range of 60-70 ppb." (Samet, 2011, p.10).

In reaching staff conclusions in future drafts of the PA, in addition to taking note of this advice provided by CASAC in the last review, which was based on the scientific evidence and exposure/risk information available in the last review, we will consider advice and recommendations from CASAC as part of the current review (e.g., following their review of this first draft PA), which is based on an updated body of scientific evidence and exposure/risk information.

4.2.4 Preliminary Staff Conclusions on the Adequacy of the Current O_3 Standard

In this section, we present staff's preliminary conclusions regarding the adequacy of the public health protection provided by the current 8-hour O_3 primary standard. In discussing these preliminary conclusions, we revisit the following overarching question for this chapter:

- **To what extent does the available scientific evidence and exposure/risk information support or call into question the adequacy of the public health protection afforded by the current O_3 primary standard?**

As discussed above, in addressing this question we have considered the available scientific evidence assessed in the ISA, as discussed above in Chapter 2 and considered in section 4.2.1, the available exposure and risk information assessed in the REA, as discussed above in Chapter 3 and considered in section 4.2.2, and the advice and recommendations received from CASAC during the last review of the O_3 NAAQS, including advice received following the proposal to reconsider the 2008 decision, as discussed above in section 4.2.3.

With regard to the scientific evidence related to short-term O_3 exposures as considered above (section 4.2.1), we reach the preliminary conclusion that the available evidence clearly

calls into question the adequacy of the current standard and provides strong support for considering potential alternative standards to increase public health protection, especially for at-risk groups. This preliminary conclusion places considerable weight on the array of O_3-related respiratory effects that have been reported following short-term exposures to O_3 concentrations below the level of the current standard, including clear evidence from controlled human exposure studies of lung function decrements, respiratory symptoms and pulmonary inflammation, as well as evidence of clearly adverse effects from epidemiologic studies, including respiratory hospital admissions and emergency department visits, and premature mortality. Staff believes that this body of scientific evidence is very robust, recognizing that it includes large numbers of various types of studies, including toxicological studies, controlled human exposure studies, and community epidemiological studies, that provide consistent and coherent evidence of a causal relationship between short-term O_3 exposures and an array of respiratory morbidity and mortality effects, especially for at-risk populations. Moreover, the evidence supports a likely causal relationship between short-term O_3 exposures and non-accidental and cardiopulmonary mortality. In emphasizing such effects, this preliminary conclusion also places considerable weight on the plausibility of the linkages between the body of evidence for respiratory effects and mortality following short-term exposures to O_3 concentrations below those allowed by the current O_3 standard and the broader body of experimental and epidemiologic evidence for O_3-related respiratory effects and mortality reported following exposures to higher concentrations. In reaching this preliminary conclusion, we acknowledge that uncertainties persist in the health evidence; however, in staff's view the broad array of health effects reported following exposures to O_3 concentrations below those allowed by the current standard (i.e., respiratory effects and mortality), combined with the plausible linkages between these effects and the much larger body of epidemiologic and controlled human exposure evidence at higher O_3 concentrations, supports the appropriateness of considering revising the current O_3 standard in order to increase public health protection against adverse health effects from short-term O_3 exposures, particularly for children, older adults, people with asthma, and for other at-risk groups.

With regard to the scientific evidence related to long-term O_3 exposures as discussed above (section 4.2.1), we note that while O_3-related effects have also been reported following long-term exposures, available studies have not been conducted in areas that would likely have met the current 8-hour standard. We also note that epidemiologic associations between long-term ambient O_3 concentrations and respiratory effects have been reported in locations with ambient O_3 concentrations above those allowed by the current short-term O_3 standard, and that in the absence of discernible thresholds in such associations, there is uncertainty in the extent to which such associations would persist at lower O_3 concentrations. Further, we note that respiratory-related effects reported following long-term O_3 exposures in animals have been

reported following repeated exposures to O_3 concentrations well above the level of the current O_3 standard. In light of the above considerations we reach the preliminary conclusion that there is clear support for retaining at least the level of protection against adverse health effects associated with long-term O_3 exposures afforded by the current standard, but that the evidence does not provide clear support for reaching a conclusion regarding the appropriateness of increasing public health protection against health effects related to long-term O_3 exposures beyond that afforded by the current standard.

With regard to the exposure and risk information related to short-term exposures as discussed above (section 4.2.2), we reach the preliminary conclusion that the available exposure and risk information from the first draft REA supports the available health evidence and that, at a minimum, exposure and risk results support the appropriateness of considering a range of potential alternative standards that would increase public health protection against adverse respiratory effects and mortality related to short-term O_3 exposures.

With regard to CASAC advice (section 4.2.3), we note that the CASAC O_3 Panel has repeatedly recommended setting the level of the 8-hour O_3 standard no higher than 70 ppb, within a range of 60 to 70 ppb, which is below the level of the current standard (i.e., 0.075 ppm or 75 ppb). Since this advice was provided, based on evidence available in the last review, the evidence for adverse health effects following short-term exposures to O_3 concentrations below 75 ppb has become even stronger, with the addition of several controlled human exposure and epidemiologic studies conducted at relatively low O_3 concentrations. Given this, we note that, at a minimum, nothing in the recent evidence would contradict CASAC's previous advice and that, in fact, recent evidence provides stronger support for that advice.

In light of all of the above considerations, staff reaches the preliminary conclusion that the body of information now available supports consideration of revising the current 8-hour O_3 primary standard, so as to afford greater public health protection against the adverse health effects of short-term O_3 exposures, especially to at-risk groups, and that it does not support retention of the current standard. In so doing, we also recognize that consideration should be given to the extent which such a revised standard would also provide appropriate protection against the adverse health effects of long-term O_3 exposures.

4.3 ADDITIONAL ANALYSES TO INFORM SECOND DRAFT PA

Given our preliminary conclusion that the body of available evidence and information supports consideration of revising the current 8-hour primary O_3 standard so as to afford greater public health protection from the adverse health effects of short-term O_3 exposures, we next consider the following overarching question:

- **What additional analyses would be appropriate to help inform consideration of potential alternative standards in the second draft of the PA?**

In posing this question, it is *not* our purpose to draw preliminary staff conclusions in this first draft PA about a range of potential alternative standards that would be appropriate for consideration by the Administrator in this review. Such preliminary staff conclusions would clearly be premature at this time prior to completion of the ISA and prior to conducting additional exposure and risk analyses, as well as further analyses of air quality information from epidemiologic studies, so as to translate such information into a basis for considering what potential alternative standards would be appropriate for consideration. Rather, such preliminary staff conclusions will be developed in the second draft PA based on the assessment of scientific information in the final ISA, the results of additional exposure and risk analyses in the second draft Health REA, further analyses of the epidemiologic evidence in the context of the entire body of available evidence on O_3-related health effects, and CASAC advice and public comment.

In addressing this overarching question, we consider more specifically the following two questions:

- **Beyond the exposure and risk analyses of air quality adjusted to simulate just meeting the current standard in the first draft REA, what range of alternative O_3 levels would be appropriate for further exposure and risk analyses in the second draft REA?**

- **What approaches are appropriate to use in translating information from epidemiologic studies into a basis for identifying potential alternative standards for consideration in the second draft PA?**

These questions are addressed below in sections 4.3.1 and 4.3.2, respectively.

4.3.1 Additional Exposure and Risk Analyses

In considering the first question posed above, we are specifically considering alternative air quality scenarios defined in terms of simulations of just meeting short-term standards that would increase public health protection against the effects of short-term O_3 exposures relative to the degree of protection provided by the current primary O_3 standard. In identifying a range of

alternative scenarios that would be appropriate for further exposure and risk analyses, we note that to fully define such alternatives, all the elements of a standard need to be specified, including indicator, averaging time, form, and level. In this review, the newly available evidence provides a basis for considering alternative averaging times and levels, while the evidence continues to support the current O_3 indicator and provides no basis to focus consideration on alternative forms of the primary O_3 standard at this time. We note that consideration may also be given in the second draft REA to assessing the degree of protection that such alternative scenarios may afford against the effects of long-term O_3 exposures.

In identifying a range of alternative scenarios that would be appropriate for quantitative exposure and risk analyses in the second draft of the REA, we recognize that decisions on the specific set of alternatives to be analyzed depends in part on initial results from such analyses that may inform how broad a set of alternatives it may be useful to include. In identifying such alternatives in this first draft document, we are soliciting CASAC advice and public comment on such a range to further inform selection of the specific alternative scenarios that will be analyzed in the second draft REA.

Given the evidence for O_3-related effects following both short-term and long-term O_3 exposures discussed above in chapter 2 and more fully in the ISA (US EPA, 2012a, chapters 6 and 7), section 4.3.1.1 below considers both short- and long-term averaging times. Section 4.3.1.2 considers available evidence and information in identifying a range of levels that may be appropriate to define alternative air quality scenarios that would be appropriate for further exposure and risk analyses in the second draft REA.

4.3.1.1 Averaging time

In considering both short- and long-term averaging times, we first note that because O_3-related effects have been reported following both short-term and long-term O_3 exposures, an important consideration in the current review is the extent to which different O_3 standards would be expected to provide appropriate protection against both short-term and long-term O_3 exposures. In considering the potential appropriateness of short- and long-term averaging times, we consider the available scientific evidence and air quality information.

As discussed above in detail (section 4.2.1), a number of studies have reported O_3-related health effects following short-term exposures to O_3 concentrations below the level of the current 8-hour standard (75 ppb) or to distributions of O_3 concentrations that would be allowed by the current standard, which support the appropriateness of analyzing alternative scenarios that would increase public health protection against short-term O_3 exposures. This includes controlled human exposure studies that have reported respiratory effects in healthy adults following short-

term (hours) exposures to O_3 concentrations as low as 60 ppb; epidemiologic studies reporting associations between short-term (minutes to hours) ambient O_3 concentrations allowed by the current standard and lung function decrements or respiratory symptoms; and epidemiologic studies reporting associations between short-term (8-hour, 24-hour) ambient O_3 concentrations allowed by the current standard and respiratory-related hospital admissions, respiratory-related emergency department visits, and respiratory and total mortality.

In addition, while a number of studies support the appropriateness of an O_3 standard that protects public health against long-term O_3 exposures, the large majority of the cities included in U.S. multi-city studies of long-term O_3-related respiratory effects would likely not have met the current 8-hour O_3 standard during the study periods. Specifically, as discussed in more detail above (section 4.2.1), epidemiologic associations between long-term ambient O_3 concentrations and respiratory effects have been reported in locations with 4th-highest 8-hour daily maximum O_3 concentrations well above the level of the current 8-hour O_3 standard. Also, respiratory-related effects reported following long-term O_3 exposures in animals have been reported following repeated exposures to O_3 concentrations well above the level of the current O_3 standard (section 4.2.1, above).

In light of the above considerations, we reach the preliminary conclusion that, while the available evidence provides strong support for considering the degree of public health protection provided against both short-term and long-term O_3 exposures, the evidence provides little support for the need to increase public health protection beyond that provided by the current 8-hour standard specifically against long-term O_3 exposures. Nonetheless, in light of the possibility that O_3-related health effects following long-term exposures could persist at lower O_3 concentrations than may occur in areas that meet the current standard, we have also considered the extent to which just meeting the current 8-hour standard would be expected to reduce long-term ambient O_3 concentrations in areas other than where the currently available studies were conducted. As noted above in section 4.2.1.2, several long-term exposure studies provide information on O_3 concentrations that have been associated with respiratory effects. These studies may further inform consideration of the relationships between short- and long-term concentrations beyond the considerations presented here. We plan to conduct additional air quality analyses that will help more fully inform this consideration in the second draft PA.

When considering the extent to which available air quality information suggests that meeting the current 8-hour standard could also reduce long-term O_3 concentrations, we note that when ambient O_3 concentrations were adjusted to simulate just meeting the current standard in the 12 cities evaluated in the first draft REA, estimated long-term O_3 concentrations also decreased (Wells et al., 2012, Table 2-6). Specifically, as illustrated in Table 4-4 below, when

air quality was adjusted to simulate just meeting the current O_3 standard, the 4th-highest 8-hour daily maximum O_3 concentrations decreased by approximately 10 to 30% across the 12 urban study locations. Somewhat smaller decreases in long-term O_3 concentrations were also estimated, based on two different long-term O_3 metrics including the seasonal averages of 1-hour and 8-hour daily maximum O_3 concentrations. Although we acknowledge that these initial simulations done in support of the first draft REA are not intended to reflect specific strategies for reducing ambient O_3 concentrations, they suggest that reductions in ambient O_3 implemented to meet an 8-hour O_3 standard would also reduce long-term O_3 concentrations. Further, we note modeling approaches that are planned for use in the second draft REA will provide more relevant analyses to further inform this consideration in the second draft PA.

Table 4-4. Average Estimated Percent Decrease in Maximum and Seasonal O_3 Concentrations with Simulation of Just Meeting the Current Standard (2006-2008) Using Quadratic Rollback[19]

Urban Area	4th-highest 8-hour daily maximum	Seasonal Average 1-hour maximum	Seasonal Average 8-hour maximum
Atlanta	22	17	15
Baltimore	18	15	13
Boston	9	7	7
Cleveland	12	9	8
Denver	13	12	11
Detroit	8	7	6
Houston	17	13	11
Los Angeles	38	32	29
New York	17	13	12
Philadelphia	19	15	13
Sacramento	26	21	19
St. Louis	12	10	9

[19]Averages were calculated from Table 2-6 in Wells et al., 2012.

In light of the above considerations, and based on the available scientific evidence and air quality information, we reach the preliminary conclusion that a standard with a short-term averaging time, specifically the current 8-hour averaging time, can be an appropriate approach to providing adequate protection against both short-term and long-term O_3 exposures. In support of this preliminary conclusion, we note that (1) O_3-related health effects have been reported in a number of studies following short-term O_3 exposures below those allowed by the current standard; (2) while O_3-related health effects have also been reported following long-term exposures, the O_3 concentrations in such studies were above those allowed by the current O_3 standard; and (3) to the extent that O_3-related health effects reported following long-term exposures could persist at O_3 concentrations below those allowed by the current standard, potential alternative 8-hour O_3 standards would be expected to further decrease long-term concentrations, beyond the decreases estimated for the current standard.

4.3.1.2 Alternative Levels

In considering alternative levels that would be appropriate for defining air quality scenarios for further exposure and risk analyses in the second draft REA, we focus on levels in conjunction with the same averaging time (8-hour), form (the 3-year average of the annual 4th-highest daily 8-hour maximum) and indicator (O_3) as the current O_3 standard. In considering the available evidence to help inform identification of such alternative levels, we focus in particular on controlled human exposure studies, which provide the clearest evidence for respiratory effects following exposures to specific O_3 concentrations, and also consider epidemiologic studies reporting associations with O_3 concentrations below those allowed by the current O_3 standard.

As discussed in detail above (section 4.2.1.1), controlled human exposure studies of O_3-induced lung function decrements, respiratory symptoms, and airway inflammation provide strong evidence that exposures to O_3 concentrations below the level of the current O_3 standard can impair respiratory functioning, resulting in respiratory effects that could be clinically significant, particularly for members of at-risk populations (e.g., people with asthma). In particular, with regard to these studies we note the following:

- Controlled human exposure studies have reported consistent decrements in group mean lung function in healthy adults following 6.6-hour exposures to O_3 concentrations ranging from 60 ppb to 120 ppb (US EPA, 2012a, Figure 6-1). Average decrements were approximately 3% following exposures to 60 ppb O_3 and 6% following exposures to 70 ppb O_3, with larger decrements at higher exposure levels. Group mean decrements reported in these studies have generally been statistically significant. Lung function decrements have not been reported to be statistically significant in controlled human exposure studies following exposures to 40 ppb O_3 (US EPA, 2011b, section 6.2.1.1).

- Following 6.6-hour exposures to an average O_3 concentration of 60 ppb, the proportion of healthy adult study subjects with FEV_1 decrements at or above 10% (i.e., a decrement that is potentially adverse for asthmatics (Henderson, 2006)) ranged from 3% to 20% across studies. When the results from such studies were combined, the ISA notes that 10% of subjects exposed to an average O_3 concentration of 60 ppb experienced such FEV_1 decrements (US EPA, 2011b, section 6.2.1.1). In the one study that evaluated the exposure-response relationship (Schelegle et al., 2009), the percentage of subjects experiencing FEV_1 decrements greater than or equal to 10% increased with increasing O_3 exposure concentrations (i.e., 0 for filtered air controls; 16% for 60 ppb; 19% for 70 ppb; 29% for 80 ppb) (section 4,2,1,1 above).
- Controlled human exposure studies have reported increased respiratory symptoms in healthy adults following exposures to O_3 concentrations at or above 60 ppb. Of the studies that evaluated respiratory symptoms following exposures to 60 ppb O_3, two reported trends towards increased symptoms (Adams, 2006; Schelegle et al., 2009). One of these (Adams, 2006) reported that the O_3-induced increase was statistically different from initial symptoms, though not from filtered air controls. An increase in respiratory symptoms has been reported to be statistically different from filtered air controls following exposure to O_3 concentrations at or above 70 ppb (Schelegle et al., 2009).
- The only controlled human exposure study to have evaluated airway inflammation following exposures below the level of the current O_3 standard (Kim et al., 2011) reported a statistically significant increase in neutrophilic inflammation following 6.6 hour exposures to 60 ppb O_3 in healthy adults with intermittent moderate exertion.

In addition, we note that, as discussed in detail above (section 4.2.1.1), epidemiologic studies also provide evidence for O_3-related respiratory effects in analyses limited to O_3 concentrations below the level of the current O_3 standard. In particular, with regard to these studies we note the following:

- Two epidemiologic studies have reported associations with lung function decrements in children in analyses restricted to relatively low O_3 concentrations. Spektor et al. (1988) reported that the association was statistically significant when all hourly O_3 concentrations were below 60 ppb and Brunekreef et al. (1994) reported a positive, but non-significant decrement for analyses restricted to O_3 concentrations (10 minutes to 2.4 hours) below 61 ppb.
- A small number of studies have reported statistically significant associations in outdoor workers, including one study where the highest 8-hour O_3 concentration was 65 ppb (Chan and Wu, 2005) and one study restricted to maximum hourly concentrations below 40 ppb (Brauer et al., 1996).
- An epidemiologic study reported a statistically significant association with respiratory symptoms in asthmatic children in a location with a maximum 1-hour O_3 concentration of 70 ppb (Rabinovitch et al., 2004).

- An epidemiologic study (Mar and Koenig, 2009) reported positive and statistically significant associations with asthma emergency department visits in both children and adults in Seattle. The average (i.e., over the years of the study) O_3 design value for Seattle during the study period was 71 ppb.
- A large multi-city epidemiologic study (Bell et al., 2006) reported that O_3 mortality effect estimates were positive and statistically significant for restricted distributions of O_3 concentrations that would likely have been below those allowed by the current O_3 standard over the study period in most of the cities evaluated. As discussed in section 4.2.1.3 above, the 50th percentiles of the distributions of highest 8-hour daily maximum O_3 concentrations corresponding to these effect estimates were as low as approximately 70 ppb, and 25th percentiles were as low as approximately 64 ppb. In addition, this study reported that O_3-related mortality effect estimates were positive and approached statistical significance for O_3 concentrations that would likely have been well below those allowed by the current O_3 standard over the study period in most of the cities evaluated. The 50th percentile of the distribution of highest 8-hour daily maximum O_3 concentrations corresponding to this effect estimate was approximately 60 ppb, and the 25th percentile was approximately 55 ppb.

Beyond the evidence-based considerations outlined above, we also note, as discussed above in section 4.2.3, that CASAC has repeatedly recommended that EPA consider setting the level of the primary O_3 standard within the range of 60 to70 ppb (Henderson, 2006; Henderson, 2007; Henderson, 2008; Samet, 2011). This advice has been provided based on the evidence that was available in the last review of the O_3 NAAQS.

Based on the above considerations, in staff's view, the newly available evidence in this review provides increased support for conducting further exposure and risk analyses of alternative levels in the range of 60 to 70 ppb. In addition, it is our view that the new evidence, when considered in the context of the evidence available in the last review, provides support for conducting further exposure and risk analyses of air quality scenarios that extend to a level somewhat below 60 ppb. We recognize increasing uncertainty in interpreting the epidemiologic evidence at such lower levels.

As a basis for these views, as outlined above, we particularly note that, following exposures of healthy adults to 60 ppb O_3, controlled human exposure studies have reported statistically significant group mean lung function decrements, a statistically significant increase in airway inflammation, and trends towards increased respiratory symptoms. In addition, we note that when data were combined from available controlled human exposure studies of O_3-induced lung function decrements, 10% of healthy adults exposed to 60 ppb O_3 experienced lung function decrements that could be adverse for asthmatics. Given that these results were reported in healthy adults, we note that they likely underestimate the magnitude and seriousness of such effects for at-risk groups. Therefore, we believe that the reporting of multiple respiratory effects

in healthy adults following exposures to 60 ppb O_3, combined with the possibility that larger effects could be observed in asthmatics and members of other at-risk groups, supports the appropriateness of including in further exposure and risk analyses an alternative scenario at a level somewhat below 60 ppb. In our view, evidence from epidemiologic panel studies reporting associations with lung function decrements in children and outdoor workers in analyses restricted to low O_3 concentrations supports analyses of such a level, although because these studies evaluated a variety of averaging times (i.e., minutes to hours) they do not provide clear support for analyzing any one specific lower level.

Having preliminarily concluded that the health effects evidence provides support for conducting additional exposure and risk analyses for alternative levels somewhat below 60 ppb, we note that depending on how far below 60 ppb one considers, such levels may be close to peak North American background (NAB) concentrations that occur infrequently at some high elevation sites in the western United States or may even approach seasonal mean background concentrations at such sites. As discussed above (section 1.3.4), estimates of summertime NAB concentrations were generally below about 35 ppb in the eastern United States and below 40 ppb in California, areas where large populations reside and where O_3-related health risks are estimated to be highest (US EPA, 2012b). In considering this information, we recognize that EPA's Rule on Treatment of Data Influenced by Exceptional Events grants authority to exclude air quality monitoring data from regulatory determinations if a state adequately demonstrates that an exceptional event has caused an exceedance or violation of a NAAQS, and that section 179B of the CAA provides for treatment of air quality data from international transport when emissions emanating from outside of the United States have caused an exceedance or violation of a NAAQS (section 1.3.4, above).

4.3.2 Approaches to Translating Epidemiologic Evidence

We next consider the second question posed at the beginning of section 4.3:

- **What approaches are appropriate to use in translating information from epidemiologic studies into a basis for identifying potential alternative standards for consideration in the second draft PA?**

As an initial matter, while available epidemiologic studies provide strong support for the conclusion that O_3-related morbidity and mortality associations extend to O_3 concentrations below the level of the current O_3 standard (section 4.2.1), it is a challenge to translate this epidemiologic evidence into the basis for identifying specific alternative standard levels that would be appropriate for consideration in this review. In particular, we note that such studies do not provide evidence for a discernible population threshold, below which it can be concluded with confidence that O_3-related effects do not occur, though confidence in the nature of the

concentration-response relationship decreases at the low end of the distribution of O_3 concentrations (US EPA, 2011b, section 2.5.4.4). As a result, any approach to using these studies to inform decisions about potential alternative standard levels requires judgments about how to weigh confidence in O_3-related effects over the distributions of O_3 concentrations.

To help inform consideration of potential alternative standard levels in the second draft PA, we are soliciting CASAC advice and public comment on approaches that may be appropriate for interpreting and translating epidemiologic evidence into the basis for such considerations. To facilitate such advice and comment, we discuss approaches to using analyses of concentration-response relationships as well as analyses of restricted air quality distributions to inform consideration of potential alternative standard levels. Based on comments and advice received, the second draft of the PA may expand (e.g., to include additional studies that have characterized concentration-response relationships) and/or modify the approach to inform staff's preliminary conclusions regarding the potential alternative standards levels that are appropriate for consideration by the Administrator. In presenting these approaches, we use the information reported in the studies by Silverman and Ito (2010) and the study by Bell et al. (2006) as examples of applying such approaches in single- and multi-city studies, respectively.

We first consider the O_3 air quality in the study location evaluated by Silverman and Ito (2010), which evaluated the concentration-response relationship between average 8-hour O_3 concentrations (i.e., averaged across monitors) and asthma hospital admissions in New York City (US EPA, 2012a, Figure 6-15), as discussed in more detail above (section 4.2.1.2). While we recognize that there is no single air quality concentration that uniquely identifies the portion of the concentration-response function in which it is appropriate to place the greatest confidence, we note that confidence intervals are smallest around average 8-hour O_3 concentrations around 40 ppb (i.e., approximately 30 to 50 ppb), become somewhat wider at O_3 concentrations below about 30 ppb, and become notably wider below about 20 ppb. In light of this, it may be reasonable to conclude that confidence is greatest that a linear concentration-response relationship exists for O_3 and asthma hospital admissions in New York City for average 8-hour daily maximum O_3 concentrations ranging from about 30 to 50 ppb, with somewhat lower confidence in the nature of the concentration-response relationship below 30 ppb, and more notably decreasing at concentrations below approximately 20 ppb.

As discussed above (section 4.2.1.2), the 8-hour O_3 concentrations reported in the analysis by Silverman and Ito (2010) were based on averaging across multiple monitors in the study area while attainment of the current O_3 standard is based on the annual 4th-highest 8-hour daily maximum O_3 concentration measured at the monitor recording the highest such concentration. Therefore, the average 8-hour concentrations reported by Silverman and Ito

(2010) are not directly comparable to the level of the current O_3 standard. To gain insight into the relationship between average 8-hour daily maximum O_3 concentrations (i.e., based on averaging across monitors) and the highest 8-hour daily maximum concentrations (i.e., from the individual monitor recording the highest such concentration),[20] we have considered available air quality information from EPA's AQS for the monitors used in the study by Silverman and Ito (2010) over the time period of the study (Figure 4-2 above, Wells et al., 2012).

In considering the range of average O_3 concentrations for which we have the greatest confidence in the concentration-response relationship, we first note that for the New York City study area over the period of the study, 742 days had average (i.e., averaged across monitors) 8-hour daily maximum O_3 concentrations from 30 to 50 ppb (Wells et al., 2012). On these days, the highest 8-hour daily maximum O_3 concentrations (i.e., from the monitors recording the highest such concentrations) ranged from approximately 55 ppb (i.e., for average concentrations from 30 to 35 ppb) to just below 75 ppb (i.e., 72 ppb for average concentrations from 45 to 50 ppb) (Figure 4-2). In addition, we note that 996 days had average 8-hour daily maximum O_3 concentrations from 20 to 50 ppb (Wells et al., 2012). The highest 8-hour daily maximum O_3 concentrations on these days extended down to approximately 50 ppb (i.e., 49 ppb for average concentrations from 20 to 25 ppb) (Figure 4-2).

In considering these results within the context of the questions to be addressed in the second draft PA regarding potential alternative standards, we note that at ambient O_3 concentrations for which it may be reasonable to conclude that we have the highest confidence in the linear nature of the concentration-response relationship (i.e., 30 to 50 ppb, 8-hour average), the highest 8-hour daily maximum O_3 concentrations (i.e., from the monitors recording the highest such concentrations) ranged from approximately 55 to 75 ppb. In addition, in considering the average 8-hour concentrations just above those where confidence intervals around the concentration-response function become notably wider (i.e., about 20 ppb, 8-hour average), we note that the highest 8-hour daily maximum O_3 concentrations were approximately 50 ppb (section 4.2.1.2, above). As noted above, the 8-hour daily maximum concentrations identified here are maximum values, not 4th-highest 8-hour daily maximum values, such that they do not reflect the form of the current standard and should not be considered as levels that correspond to a standard.

[20] As noted above (section 4.2.1.3), in preliminary analyses to inform consideration of the adequacy of the current O_3 standard, we characterized the relationships between average and highest 8-hour daily maximum concentrations. We recognize that, to the extent these types of analyses are carried forward into the second draft PA for informing consideration of potential alternative standards, we would also consider the relationships between average and 4th-highest 8-hour daily maximum concentrations.

We next consider the O_3 air quality in the study locations evaluated by Bell et al. (2006) which, as discussed in more detail above (section 4.2.1.3), evaluated associations between mortality and average 24-hour O_3 concentrations (i.e., averaged across monitors) in 98 U.S. cities, in a series of analyses where air quality was restricted to concentrations below progressively lower 24-hour average cut points. In considering these restricted analyses, we note that O_3 effect estimates were similar in magnitude for analyses with cut points ranging from 60 ppb down to 15 ppb. In the Bell et al. analyses, associations with cut points down to 30 ppb were statistically significant, associations with a cut point of 25 ppb approached statistical significance, and associations with cut points of 20 and 15 ppb lost statistical significance. Further, statistical precision decreased as cut points decreased, with a notable widening of confidence intervals for the analyses with cut points at and below 20 ppb.[21]

As with the study by Silverman and Ito (2010), it is not appropriate to compare the 24-hour average O_3 concentrations reported by Bell et al. (2006) directly to 8-hour maximum levels or to the level of the current standard. Therefore, as discussed above (section 4.2.1.3), we have used EPA's AQS to relate average 24-hour O_3 concentrations in each of the 98 study cities (i.e., averaged across monitors in cities with multiple monitors) to the highest 8-hour daily maximum concentrations (i.e., from the individual monitors in each city recording the highest such concentrations) (Wells et al., 2012). In considering these analyses, we focused on 24-hour average cut points of 30, 25, and 20 ppb so as to consider the range over which the associations went from being statistically significant to not being significant, and the statistical precision notably decreased. In considering only days with average 24-hour O_3 concentrations at or below the 30 ppb cut point, the 50th percentile of the distribution of highest 8-hour daily maximum O_3 concentrations (i.e., the distribution across cities[22]) was approximately 70 ppb and the 25th percentile of the distribution was approximately 65 ppb (Wells et al., 2012).[23] In considering only days with average 24-hour O_3 concentrations at or below the 25 ppb cut point, the 50th percentile of the distribution of highest 8-hour daily maximum O_3 concentrations (i.e., the distribution across cities) was approximately 60 ppb and the 25th percentile of the distribution was approximately 55 ppb (Wells et al., 2012). Further, in considering only days with average

[21]As discussed above, the decreasing precision in effect estimates as concentrations approach the lower extreme of the air quality distribution, as indicated by notable widening of confidence bounds, is intrinsically related to data density and is not necessarily indicative of an absence of O_3-associated health effects.

[22]Percentiles were identified from the distribution of the study period averages of highest 8-hour daily maximum O_3 concentrations within each city.

[23] As noted above (section 4.2.1.3), 50th and 25th percentiles were identified from the distribution of the study period averages of highest 8-hour daily maximum O_3 concentrations within each city. Identification of the 50th percentile of this distribution across cities reflects consideration of an estimate of the central tendency of the distribution. Identification of the 25th percentile reflects consideration of the lower part of the distribution where the data density is appreciably less.

24-hour O_3 concentrations at or below the 20 ppb cut point, the 50th percentile of the distribution of highest 8-hour daily maximum O_3 concentrations was approximately 50 ppb and the 25th percentile was approximately 45 ppb (Wells et al., 2012).

In considering the above analyses within the context of the questions to be addressed in the second draft PA regarding potential alternative standards, we note the following:

- In the single-city study by Silverman and Ito, at O_3 concentrations for which we have the highest confidence in the linear nature of the concentration-response relationship (i.e., 30 to 50 ppb averaged across monitors), the highest 8-hour daily maximum O_3 concentrations (i.e., from the monitors recording the highest such concentrations) ranged from approximately 55 to 75 ppb. Confidence intervals become notably wider when the highest 8-hour daily maximum concentrations are below about 50 ppb. In our view, judgments regarding the extent to which this type of analysis supports consideration of alternative 8-hour standard levels within or below this range of O_3 concentrations could depend on the weight placed on the concentration-response relationship over different parts of the distribution of O_3 concentrations and more generally on the relevance of this air quality information for informing such judgments.

- In the multi-city study by Bell et al., O_3 effect estimates were similar in magnitude and were relatively statistically precise for distributions of O_3 concentrations characterized by 50th percentile concentrations (of 8-hour daily maximum concentrations across the 98 cities) at or above 60 ppb and 25th percentile concentrations at or above 55 ppb. Effect estimates remained positive but lost statistical significant for distributions of O_3 concentrations characterized by lower 50th and 25th percentile concentrations. In our view, judgments regarding the extent to which this type of analysis supports consideration of alternative 8-hour standard levels at concentrations identified by such percentiles of air quality distributions across cities in multi-city studies could depend on the weight placed on this type of cut point analysis in general and on specific percentiles within such distributions.

As noted above, our purpose in presenting the approaches discussed above is to solicit CASAC advice and public comment on these approaches to translating epidemiologic evidence into the basis for identifying potential alternative standards that would be appropriate for consideration in the second draft PA. Based on such advice and comment, the second draft PA may expand (e.g., to include additional studies that have characterized concentration-response relationships) and/or modify the approaches outlined above to help inform staff's preliminary conclusions regarding the potential alternative standards levels that are appropriate for consideration by the Administrator.

4.4 SUMMARY OF STAFF CONCLUSIONS ON THE PRIMARY O_3 STANDARD

[To be added in the second draft Policy Assessment.]

4.5 KEY AREAS FOR FUTURE RESEARCH AND DATA COLLECTION

[To be added in the second draft Policy Assessment.]

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5. CONSIDERATION OF THE WELFARE EFFECTS EVIDENCE

In this chapter, we pose the following overarching question:

- **To what extent has scientific information become available that alters or substantiates our understanding of the welfare effects that occur following exposures to O_3 and our understanding of the biologically relevant O_3 exposures at which such effects occur?**

To inform our consideration of this issue, we consider the weight-of-evidence conclusions from the ISA (section 5.1); the scientific evidence regarding the mechanisms governing plant responses to O_3 exposures (section 5.2); the scientific evidence linking O_3 exposures to effects on vegetation (section 5.3); the evidence available regarding the biologically relevant aspects of O_3 exposures important in inducing effects on vegetation (section 5.4); the evidence linking O_3-related effects on vegetation to those at the community and whole ecosystem level (section 5.5); the adversity of O_3-related effects on vegetation and ecosystems in the context of public welfare (section 5.6); and the evidence concerning other welfare effects, such as O_3-related effects on climate and ultraviolet (UV-B) radiation (section 5.7).

5.1 WEIGHT-OF-EVIDENCE CHARACTERIZATION IN THE ISA

Since the conclusion of the last review, the Agency has developed a more formal framework for reaching causal inferences from the body of scientific evidence. This framework provides the basis for a robust, consistent, and transparent process for evaluating the scientific evidence, including uncertainties in the evidence, and drawing conclusions and causal judgments regarding air pollution-related welfare effects. The causality framework and the approach to characterizing the weight of evidence are discussed briefly below (section 5.1.1) and are described in more detail in the ISA (US EPA, 2012a, Preamble). The ISA weight-of-evidence conclusions for O_3 are summarized in section 5.1.2.

5.1.1 Approach to Characterizing the Weight of Evidence

Characterization of the weight of evidence in the ISA is based on the evaluation and synthesis of evidence from across scientific disciplines. The relative importance of different types of evidence varies by pollutant or assessment, as does the availability of different types of evidence for causality determination. Evidence on welfare effects may be drawn from a variety of experimental approaches (e.g., greenhouse, laboratory, field) and numerous disciplines (e.g., community ecology, biogeochemistry and paleological/historical reconstructions) (US EPA

2012a, Preamble). Each of these types of studies has strengths and limitations, as discussed briefly below and in more detail in the ISA (US EPA, 2012a, Preamble).

For ecological effects assessment, both laboratory and field studies (including field experiments and observational studies) can provide useful data for causality determination. Because conditions can be controlled in laboratory studies, responses may be less variable and smaller differences easier to detect. However, the control conditions may limit the range of responses (e.g., animals may not be able to seek alternative food sources), so they may not reflect responses that would occur in the natural environment. In addition, larger-scale processes are difficult to reproduce in the laboratory (US EPA, 2012a, Preamble).

Field observational studies measure biological changes in uncontrolled situations and describe an association between a disturbance and an ecological effect. Field data can provide important information for assessments of multiple stressors or where site-specific factors significantly influence exposure. They are also often useful for analyses of larger geographic scales and higher levels of biological organization. However, because conditions are not controlled, variability is expected to be higher and differences harder to detect. Field surveys are most useful for linking stressors with effects when stressor and effect levels are measured concurrently. The presence of confounding factors can make it difficult to attribute observed effects to specific stressors (US EPA, 2012a, Preamble).

Intermediate between laboratory and field are studies that use environmental media collected from the field to examine response in the laboratory and experiments that are performed in the natural environment while controlling for some environmental conditions (i.e., mesocosm studies). This type of study in manipulated natural environments can be considered a hybrid between a field experiment and laboratory study since some aspects are performed under controlled conditions but others are not. They make it possible to observe community and/or ecosystem dynamics and provide strong evidence for causality when combined with findings of studies that have been made under more controlled conditions (US EPA, 2012a, Preamble).

In considering available evidence from each of these types of studies, the O_3 ISA draws conclusions within the context of a causality framework with a five-level hierarchy. This framework is used to classify the overall weight of evidence into one of the following categories: causal relationship, likely to be a causal relationship, suggestive of a causal relationship, inadequate to infer a causal relationship, and not likely to be a causal relationship (US EPA 2012a, Preamble Table 2). In making such judgments regarding causality, the ISA evaluates several aspects of the evidence including the consistency of effects across studies, the coherence

of the evidence across different types of studies, the strength of reported associations,[1] and the biological plausibility of a causal relationship (US EPA, 2012a, Preamble, Table 1). Confidence increases that O_3 exposures cause a given welfare effect as the number of consistently supportive studies increases, as the coherence of the evidence across different types of studies increases, as the strength of the relationship with O_3 increases, and as the support for biological plausibility increases. The ISA also evaluates evidence related to concentration-response and exposure-response relationships in order to inform conclusions on the concentrations at which effects are present. Considerations related to weight-of-evidence conclusions and concentration- and exposure-response relationships are discussed in more detail in the Preamble to the O_3 ISA (US EPA, 2012a).

5.1.2 Weight-of-Evidence Conclusions for O_3

Applying the causality framework to O_3, the ISA draws the following weight-of-evidence conclusions:

- "Evidence is sufficient to conclude that there is a **causal** relationship between ambient O_3 exposure and the occurrence of O_3-induced visible foliar injury on sensitive vegetation across the U.S." (US EPA 2012a, section 9.4.2.2)
- "Evidence is sufficient to conclude that there is a **causa**l relationship between ambient O_3 exposure and reduced growth of native woody and herbaceous vegetation." (US EPA, 2012a, section 9.4.3.2)
  - "Evidence is sufficient to infer that there is **a causal** relationship between O_3 exposure and reduced productivity, and a **likely to be a causal** relationship between O_3 exposure and reduced carbon sequestration in terrestrial ecosystems." (US EPA, 2012a, section 9.4.3.5)
  - "Evidence is sufficient to conclude that there is a **causal** relationship between O_3 exposure and reduced yield and quality of agricultural crops." (US EPA, 2012a, section 9.4.4.3)
  - "Evidence is sufficient to conclude that there is **likely to be a causal** relationship between O_3 exposure and the alteration of ecosystem water cycling." (US EPA, 2012a, section 9.4.5.1)
  - "Evidence is sufficient to infer that there is a **causal** relationship between O_3 exposure and the alteration of below-ground biogeochemical cycles." (US EPA, 2012a, section 9.4.6.6)
  - "Evidence is sufficient to conclude that there is **likely to be a causal** relationship between O_3 exposure and the alteration of community composition of some ecosystems." (US EPA, 2012a, section 9.4.7.).
  - "Evidence supports a **causal** relationship between changes in tropospheric O_3 concentrations and radiative forcing." (US EPA, 2012a, section 10.5)

[1]The strength of the association refers to the magnitude of the association and its statistical precision.

- "Evidence indicates that there is **likely to be a causal** relationship between changes in tropospheric O_3 concentrations and effects on climate." (US EPA, 2012a, section 10.5)

Given the weight-of-evidence conclusions in the ISA, staff's consideration of welfare effects linked to O_3 exposures focuses on those vegetation and ecosystem-level effects where evidence is sufficient to conclude a causal relationship, i.e., visible foliar injury (section 5.3.1), reduced growth and productivity in forest trees and yields of agricultural crops (section 5.3.2), alteration of below-ground biogeochemical cycling (section 5.5.4) and radiative forcing (5.7.1). Other effects where evidence is sufficient to conclude a likely to be causal relationship linked to cumulative O_3 exposures are also discussed below, such as reduced carbon sequestration in terrestrial ecosystems (section 5.5.2), alteration of ecosystem water cycling (section 5.5.3), the alteration of community composition of some ecosystems (section 5.5.5) and O_3 impacts on climate (5.7.1). While not as strongly supported by the evidence, a number of other important welfare effects will be discussed, including O_3 impacts on insects and other wildlife (section 5.5.6) and UVB radiation (5.7.2) (US EPA, 2012a).

Figure 5-1 below (US EPA, 2012a, Figure 9-1) is a simplified illustrative diagram of the major pathway through which O_3 enters plants and the major endpoints O_3 may affect. There is evidence that the effects observed across this continuum are related to one another; effects of O_3 at lower levels of organization, such as the leaf of an individual plant, can result in effects at higher levels. Ozone enters leaves through stomata and can alter stomatal conductance and disrupt CO_2 fixation. These effects can change rates of leaf gas exchange, growth and reproduction at the individual plant level and result in changes in ecosystems, such as productivity, carbon storage, water cycling, nutrient cycling, and community composition (US EPA, 2012a, Section 2.6). This pathway forms the framework for the discussion of O_3-related effects on vegetation and ecosystems, as presented below in sections 5.2 through 5.5.

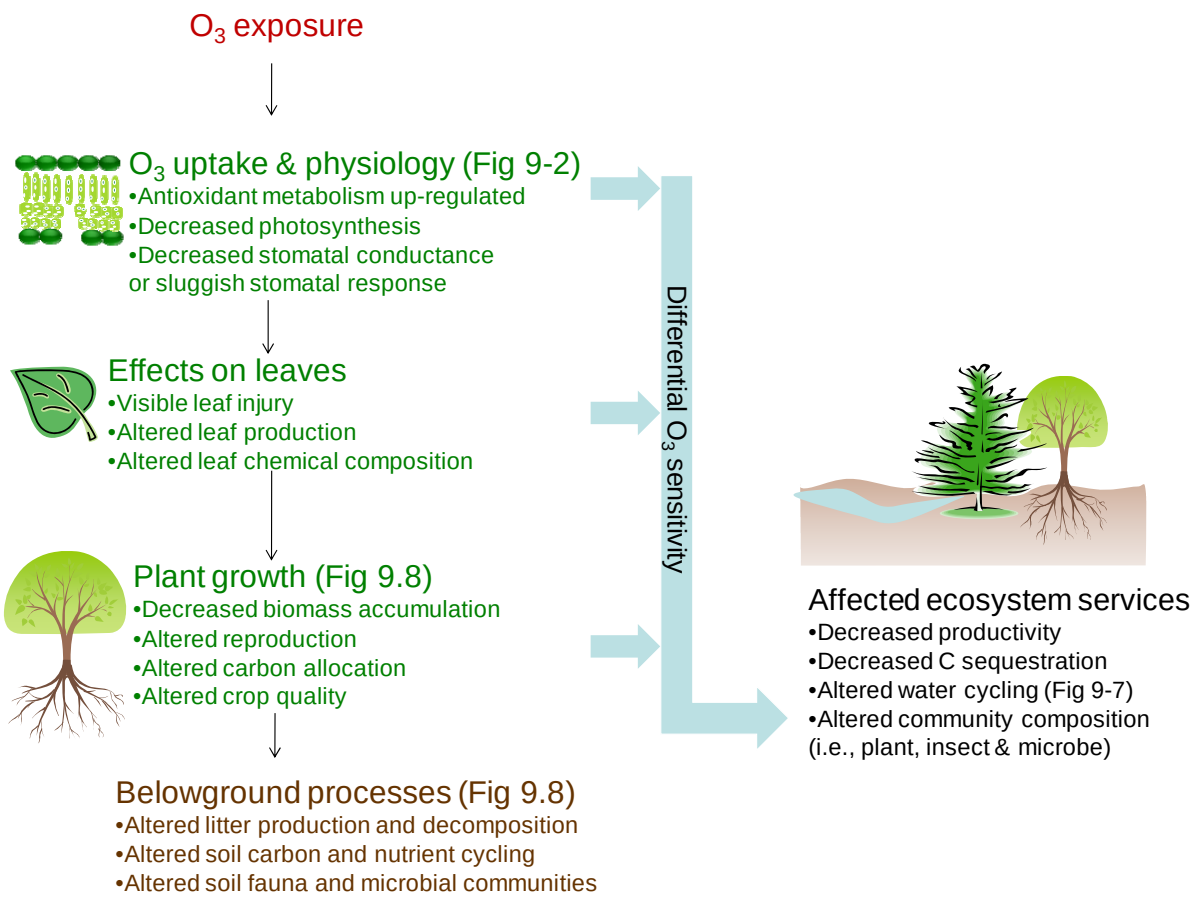

Figure 5-1 An illustrative diagram of the major pathway through which O_3 enters plants and the major endpoints that O_3 may affect in plants and ecosystems. (Figure 9-1 ISA)

5.2 MECHANISMS GOVERNING PLANT RESPONSE TO O_3 EXPOSURES

As seen in Figure 5-1 above, O_3-induced impacts on plants occur first at the molecular, biochemical, and physiological levels. What happens at these levels determines whether these impacts are translated into effects at higher levels of biological organization at the whole leaf, plant, community and ecosystem levels. Thus, while the policy relevance of the scientific understanding regarding the mechanisms governing plant response to O_3 is not as obvious, it adds to the biological plausibility and coherence of the weight-of-evidence for O_3-induced effects at the higher vegetation and ecosystem levels and further informs the interpretation of predictions of risk associated with vegetation response at ambient O_3 exposures. Therefore, a brief discussion of the state of the science regarding the mechanisms of O_3 impacts at the molecular, biochemical, and physiological levels is included here.

While the fundamental conclusions regarding the mechanisms of O_3-induced vegetation response have not changed substantially since the completion of the 2006 AQCD, scientific understanding has continued to expand. Thus, for many of the topics covered under this section, information from the 2006 O_3 AQCD is still valid and has been summarized along with more recent findings. One significant new body of research has provided important new insights on the changes in gene expression in plants exposed to elevated O_3, due in part to the advent of new technologies. However, because these studies often use model organisms or mutants or transgenic plants and exposure conditions that may not reflect ambient field conditions (US EPA, 2012a, section 9.3.1), additional work remains to elucidate whether these plant responses are transferable to other plant species exposed to more realistic ambient conditions (US EPA, 2012a, section 9.3.6). These new findings continue to refine and enhance our understanding of how exposure to and uptake of O_3 can initiate a cascade of responses within the plant, that, upon reaching sufficient magnitude , lead to an array of whole plant effects, including those considered injury and/or damage.

The remainder of this section briefly describes the complex cascade of reactions and processes that link ambient O_3 to injury and/or damage at the whole plant level. While there is some overlap between the different organizational levels due to multiple interactions and feedbacks, the latest science will be discussed in the following sections: uptake of O_3 into the leaf (section 5.2.1); cellular to systemic response (section 5.2.2); detoxification (section 5.2.3) and effects on plant metabolism (section 5.2.4).

5.2.1 Ozone Uptake into the Leaf

Ozone enters the plant through openings in the leaves called stomata. Because O_3 does not typically penetrate the leaf's cuticle, it must reach the stomatal openings in the leaf for absorption to occur. The movement of O_3 and other gases such as CO_2 into and out of leaves is controlled by stomatal guard cells that regulate the size of the stomatal apertures. These guard cells respond to a variety of internal species-specific factors as well as external site specific environmental factors such as light, temperature, humidity, CO_2 concentration, soil fertility, water status, and in some cases, the presence of air pollutants, including O_3. These modifying factors (see also discussion of modifying factors in section 5.3.3) produce stomatal conductances that vary between leaves of the same plant, individuals and genotypes within a species as well as diurnally and seasonally. Environmental conditions which promote high rates of gas exchange will favor the uptake of the pollutant by the leaf, while other factors such as boundary layer resistance and the size of the stomatal aperture may limit uptake (US EPA, 2012a).

Ozone-induced changes in stomatal conductance have been reviewed in detail in previous O_3 AQCDs. The findings summarized in those documents demonstrate that stomatal conductance

is often reduced in plants exposed to O_3. Results from recent studies support this understanding (US EPA, 2012a, section 9.3.2 and 9.3.6). The reduction in stomatal conductance can occur as the result of either direct impacts of O_3 on the stomatal complex which causes closure or from a number of indirect effects of O_3 on cellular functions, including a decrease in carboxylation efficiency that leads to a buildup of CO_2 in the substomatal cavity. Impacts on the stomatal complex is important not only because of its affect on a plant's response to O_3 but because it can also compromise the ability of the stomata to respond to other environmental stimuli, including light, CO_2 concentration and drought. Stomatal sluggishness has been described as a delay in stomatal response to changing environmental conditions in sensitive species exposed to higher concentrations and/or longer-term O_3 exposures (US EPA, 2012a, section, 9.3.2). Such stomatal sluggishness has been suggested as a possible mechanism for O_3-induced changes in plant water use efficiency (see section 5.5.3 below).

5.2.2 Cellular to Systemic Response

After O_3 enters the leaf, it can react with a variety of biochemical compounds, either that are exposed to the air or after it is solubilized into the water lining the cell wall. Experimental evidence suggests that there are likely several different mechanisms by which the plant detects the presence of O_3 or its breakdown products, including a change in the redox state of the plant and the oxidation of sensitive molecules. One known signaling molecule is the reactive oxygen species (ROS) hydrogen peroxide (H_2O_2). The presence of higher-than-normal levels of H_2O_2 within the leaf is a potential trigger for a set of metabolic reactions that include those typical of the well documented "wounding" response or pathogen defense pathway generated by cutting of the leaf or by pathogen/insect attack. Ethylene is another compound produced when plants are subjected to biotic or abiotic stressors (US EPA, 2012a, section 9.3.3). Calcium and protein kinases are likely involved in relaying information about the presence of the stressor to the nucleus and other cellular compartments as a first step in determining whether and how the plant will respond to the stress (US EPA, 2012a, section 9.3.3).

The advent of DNA microarray technology has allowed for the study of gene expression in cells on a large scale, providing a comprehensive picture of simultaneous alterations in gene expression. These studies have provided more insight into the complex interactions between molecules, how those interactions lead to the communication of information in the cell (or between neighboring cells), and which role these interactions play in determining tolerance or sensitivity and how a plant may respond to stresses such as O_3 (US EPA, 2012a. section 9.3.3).

Genes involved in plant defense, signaling and those associated with the synthesis of plant hormones and secondary metabolism were generally upregulated, while those related to photosynthesis and general metabolism were typically downregulated in O_3-treated plants.

Proteome studies support these results by demonstrating concomitant increases or decreases in the proteins encoded by these genes (US EPA, 2012a, section 9.3.6). Gene and protein expression patterns generally differ between O_3-sensitive and tolerant plants, which could result from differential uptake or detoxification of O_3 or from differential regulation of the transcriptome and proteome (US EPA, 2012a. section 9.3.3). Finally, plant hormones, including ethylene (ET), salic acid (SA), and jasmonic acid (JA), can play an important role in determining plant response to O_3, as demonstrated in many studies. More recent studies have supported these conclusions (US EPA, 2012a, section 9.3.3).

While much work remains to be done to better elucidate how plants detect O_3, what determines their sensitivity to the pollutant and how they might respond to it, it is clear that the mechanism for O_3 detection and signal transduction is very complex. Many of the phytohormones and other signaling molecules thought to be involved in these processes are interactive and depend upon a variety of other factors, which could be either internal or external to the plant. This results in a highly dynamic and complex system, capable of resulting in a spectrum of plant sensitivity to oxidative stress and generating a variety of plant responses to that stress (US EPA, 2012a, section 9.3.3). These mechanisms may vary by species or developmental stage of the plant or may co-exist and be activated by different exposure conditions.

5.2.3 Detoxification

Ozone injury will not occur if (1) the rate and amount of O_3 uptake is small enough for the plant to detoxify or metabolize O_3 or its metabolites or (2) the plant is able to repair or compensate for the O_3 impacts. Because plants are exposed to an oxidizing environment on a continual basis, and because many reactions that are part of the basic metabolic processes, such as photosynthesis and respiration, generate ROS, there are extensive and complex mechanisms in place to detoxify these oxidizing radicals, including both enzymes and metabolites, which are located in several locations in the cell and also in the apoplast of the cell (US EPA, 2012a, section 9.3.4).

Antioxidant metabolites and enzymes located in the apoplast, including ascorbate, are thought to form a first line of defense by detoxifying O_3 and/or the ROS that are formed as breakdown products of O_3 (US EPA, 2012a, section 9.3.2). However, the pattern of changes in the amounts of these antioxidants, including ascorbate, varies greatly among different species and conditions, and the redox buffering capacity of the apoplast is far less than that of the cytoplasm, as it lacks the regeneration systems necessary to retain a reduced pool of antioxidants. Thus, it is not only the quantity and types of antioxidant enzymes and metabolites present but also the cellular ability to regenerate those antioxidants efficiently that play a large role in

determining the plant's ability to effectively protect itself from sustained exposure to oxidative stress (US EPA, 2012a, section 9.3.4).

In spite of the new research, however, it is still not clear as to what extent detoxification protects against O_3 injury. It is likely that the role of antioxidants and their interaction with other plant responses to O_3, such as the activation of signal transduction pathways, is far more complex than is currently understood. In addition, it has been hypothesized that alterations in carbon metabolism would be necessary to supply the needed reducing power for antioxidant regeneration (Dizengremel et al., 2008) (US EPA, 2012a, section 9.3.4). Thus, the 2006 AQCD conclusions regarding the need for further investigation on these interactions, including whether generation of these antioxidants in response to O_3-induced stress potentially diverts resources and energy away from other vital uses, remain appropriate.

Once O_3 injury has occurred in leaf tissue, some plants are able to repair or compensate for the impacts. In general, plants have a variety of compensatory mechanisms for low levels of stress including reallocation of resources, changes in root/shoot ratio, production of new tissue, and/or biochemical shifts, such as increased photosynthetic capacity in new foliage and changes in respiration rates, indicating possible repair or replacement of damaged membranes or enzymes. Since these mechanisms are genetically determined, not all plants have the same complement of compensatory mechanisms or degree of tolerance, and these may vary over the life of the plant as not all stages of a plant's development are equally sensitive to O_3. At higher levels or over longer periods of O_3 stress, some of these compensatory mechanisms, such as a reallocation of resources away from storage in the roots in favor of leaves or shoots, could occur at a cost to the overall health of the plant. However, it is not yet clear to what degree or how the use of plant resources for repair or compensatory processes affects the overall carbohydrate budget or subsequent plant response to O_3 or other stresses (US EPA, 1996, US EPA, 2006).

5.2.4 Effects on Plant Metabolism

Ozone inhibits photosynthesis, the process by which plants produce energy rich compounds (e.g., carbohydrates) in the leaves. This impairment can result from direct impact to chloroplast function and/or O_3-induced stomatal closure resulting in reduced uptake of CO_2. The 2012 ISA states that "[t]he 2006 O_3 AQCD described the mechanism by which plant exposure to O_3 reduces the quantity of the central carboxylating enzyme, Rubisco, that plays an important role in the production of carbohydrates within the chloroplast. Recent studies, including those evaluating O_3 induced changes in the transcriptome and proteome of several different species, confirm these findings" (US EPA, 2012a, section 9.3.5). While several measures of the light reactions of photosynthesis are sensitive to exposure to O_3, photosynthetic carbon assimilation is generally considered to be more affected by pollutant exposure, resulting in an overall decline in

photosynthesis. Experimental evidence suggests that both decreases in Rubisco synthesis and enhanced degradation of the protein contribute to the measured reduction in its quantity (US EPA, 2006). As discussed in the 2006 AQCD, several studies have found that O_3 has a greater effect as leaves age, with the greatest impact of O_3 occurring on the oldest leaves. The loss of this key enzyme as a function of increasing O_3 exposure is also linked to an early senescence or a speeding up of normal development leading to senescence (US EPA, 2006).

Due to its central importance, any decrease in Rubisco may have severe consequences for the plant's productivity, including reductions in biomass and yield. Proteomics studies have also confirmed the effects of O_3 on proteins involved in carbon assimilation (US EPA, 2012a, section 9.3.5). If total plant photosynthesis is sufficiently reduced, the plant will respond by reallocating the remaining carbohydrate at the level of the whole organism, typically away from the roots and into above ground vegetative components (US EPA, 2012a, section 9.4.3).

5.3 EFFECTS ON VEGETATION

Ozone injury at the cellular level can accumulate sufficiently to induce effects at the level of a whole leaf or plant. These larger scale effects can include: visible foliar injury and/or premature senescence (section 5.3.1); reduced carbohydrate production, carbohydrate reallocation, reduced growth, reduced reproduction and yield, and reduced plant vigor (section 5.3.2). Section 5.3.3 then describes factors that are known to modify these responses. Much of what is now known about these O_3-related effects, as summarized below, is based on research that was available in the 1997 and 2008 reviews. Studies available in this rulemaking continue to support and expand this knowledge (US EPA, 2012a).

5.3.1 Visible Foliar Injury and Biomonitoring

Cellular injury to leaves due to exposure to O_3 can and often does become visible. While both visible and non-visible injury can be significant to the plant, this section focuses on visible foliar injury for several reasons: it is often associated with additional public welfare impacts such as impaired aesthetics in specially designated protected areas (such as federal Class I areas) and impaired marketability of O_3–sensitive ornamental species; it is easily observed and measured in the field, making some species useful as indicators in biomonitoring networks. Thus, the remainder of this section uses the terms injury or foliar injury to refer to visible foliar injury.

Acute foliar injury usually appears within 24 hours after exposure to O_3 and, depending on species, can occur under a range of exposures and durations, whereas chronic foliar injury may be mild to severe. In some cases, cell death or premature leaf senescence may occur. Because the significance of O_3–induced injury at the leaf and whole plant levels depends on how

much of the total leaf area of the plant has been affected, as well as the plant's age, size, developmental stage, and degree of functional redundancy among the existing leaf area, it is not presently possible to determine, with consistency across species and environments, what degree of injury at the leaf level has significance to the vigor of the whole plant (72 FR 37886/7).

Typical visible injury symptoms on broad-leaved plants include stippling, flecking, surface bleaching, bifacial necrosis, pigmentation (e.g., bronzing), chlorosis, and/or premature senescence. Typical visible injury symptoms for conifers include chlorotic banding, tip burn, flecking, chlorotic mottling, and/or premature senescence of needles. Although common patterns of injury develop within a species, these foliar lesions can vary considerably between and within taxonomic groups. Several pictorial atlases and guides have been published, providing details on diagnosis and identification of O_3-induced visible foliar injury on many plant species throughout North America (Flagler, 1998; NAPAP, 1987) and Europe (Innes et al., 2001; Sánchez et al., 2001) (US EPA, 2012a, section 9.4.2).

The use of sensitive plants as biological indicators to detect phytotoxic levels of O_3 is a longstanding and effective methodology (Chappelka and Samuelson, 1998; Manning and Krupa, 1992). Each bioindicator exhibits typical O_3 injury symptoms when exposed under appropriate conditions. These symptoms are considered diagnostic as they have been verified in exposure-response studies under experimental conditions. Since the 2006 O_3 AQCD, new sensitive plant species have been identified from field surveys and verified in controlled exposure studies and several multiple-year field surveys have also been conducted at National Wildlife Refuges in Maine, Michigan, New Jersey, and South Carolina (US EPA, 2012a, section 9.4.2).

The USDA Forest Service through the Forest Health Monitoring Program (FHM) (1990 - 2001) and currently the Forest Inventory and Analysis (FIA) Program has been collecting data regarding the incidence and severity of visible foliar injury on a variety of O_3-sensitive plant species throughout the U.S. (Coulston et al., 2003; Smith et al., 2003; Campbell et al. 2007). The plots where these data are taken are known as biosites. These biosites are located throughout the country, and analysis of visible foliar injury within these sites follows a set of established protocols. For more details, see http://www.nrs.fs.fed.us/fia/topics/ozone/ (USDA, 2011). The network has provided evidence of O_3 concentrations high enough to induce visible symptoms on sensitive vegetation. From repeated observations and measurements made over a number of years, specific patterns of areas experiencing visible O_3 injury symptoms can be identified (US EPA, 2012a, section 9.4.2).

When considering the use of visible foliar injury information in a policy context, there are two important caveats. First, visible foliar injury occurs only when sensitive plants are exposed to elevated O_3 concentrations in a predisposing environment. A major modifying factor

for O_3-induced visible foliar injury is the amount of soil moisture available to a plant during the year that the visible foliar injury is being assessed. This is because lack of soil moisture generally decreases stomatal conductance of plants and, therefore, limits the amount of O_3 entering the leaf that can cause injury (Matyssek et al., 2006; Panek, 2004; Grulke et al., 2003a; Panek and Goldstein, 2001; Temple et al., 1992; Temple et al., 1988). Consequently, many studies have shown that dry periods in local areas tend to decrease the incidence and severity of O_3-induced visible foliar injury; therefore, the incidence of visible foliar injury is not always higher in years and areas with higher O_3, especially with co-occurring drought (Smith et al., 2003). Other factors such as leaf age influence the severity of symptom expression with older leaves showing greater injury severity as a result of greater seasonal exposure (Zhang et al., 2010) (US EPA, 2012, section 9.4.2). Thus, the degree and extent of visible foliar injury development varies from year to year and site to site (Orendovici-Best et al., 2008; Chappelka et al., 2007; Smith et al., 2003), even among co-members of a population exposed to similar O_3 levels, due to the influence of co-occurring environmental and genetic factors. Second, direct links between O_3-induced visible foliar injury symptoms and other adverse effects are also not always found, so that it is not always a reliable indicator of the potential for other negative plant effects occurring (US EPA, 2012, section 9.4.2), because other effects (e.g., biomass loss) have been reported with and without the presence of visible injury.

As stated above, however, the presence of O_3-induced visible symptoms alone can represent an important adverse impact to the public welfare. Specifically, it can reduce the appearance and market value of ornamentals (such as petunia, geranium, and poinsettia) used in urban landscapes, and affect the aesthetic value of scenic vistas in protected natural areas such as national parks and wilderness areas. Many businesses rely on healthy-looking vegetation for their livelihoods (e.g., horticulturalists, landscapers, Christmas tree growers, farmers of leafy crops), and a variety of ornamental species have been listed as sensitive to O_3 (Abt Associates Inc., 1995). Though not quantified, there is likely some level of economic impact to businesses and homeowners from O_3-related injury on sensitive ornamental species due to the cost associated with more frequent replacement and/or increased maintenance (fertilizer or pesticide application). In addition, because O_3 not only results in discoloration of leaves but can also lead to more rapid senescence (early shedding of leaves) there potentially could be some lost tourism revenue at sites where fall foliage is less available or attractive (72 FR 37887).

In summary, visible foliar injury resulting from exposure to O_3 has been well characterized and documented over several decades of research on many tree, shrub, herbaceous, and crop species (US EPA, 2012a, 2006, 1996, 1984, 1978a). Ozone-induced visible foliar injury symptoms on certain bioindicator plant species are considered diagnostic as they have

been verified experimentally in exposure-response studies, using exposure methodologies such as continuous stirred tank reactors (CSTRs), OTCs, and free-air fumigation. Experimental evidence has clearly established a consistent association of visible injury with O_3 exposure, with greater exposure often resulting in greater and more prevalent injury. Since the 2006 O_3 AQCD, results of several multi-year field surveys of O_3-induced visible foliar injury at National Wildlife Refuges in Maine, Michigan, New Jersey, and South Carolina have been published. New sensitive species showing visible foliar injury continue to be identified from field surveys and verified in controlled exposure studies (US EPA, 2012a, section 9.4.2).

5.3.2 Growth, Productivity and Carbon Storage

Studies published since the 2008 review continue to support the conclusions of previous AQCDs (US EPA, 1996 and 2006) that there is strong and consistent evidence that ambient concentrations of O_3 decrease photosynthesis and growth in numerous plant species across the U.S. (US EPA, 2012a, section 9.4.3; section 5.2.4 above). Regarding photosynthesis, one recent meta-analysis of 55 studies (Wittig et al., 2007) reported that current O_3 concentrations in the northern hemisphere are decreasing stomatal conductance by 13% and photosynthesis by 11% across tree species, and that decreases in photosynthesis are consistent with the cumulative uptake of O_3 into the leaf (US EPA, 2012a, section 9.4.3). As discussed in section 5.2.4 above and in the ISA (US EPA, 2012a, section 9.3.5), there are numerous mechanisms that provide the biological plausibility for O_3 leading to decreases in photosynthesis.

As expected, reductions in photosynthesis are often followed by observed reductions in growth. In a recent study, McLaughlin et al., (2007a) investigated the effects of ambient O_3 on tree growth at forest sites in the southern Appalachian Mountains. The authors reported that the cumulative effects of ambient levels of O_3 decreased seasonal stem growth by 30-50% for most tree species in a high O_3 year, compared to a low O_3 year. Another field- based gradient study documented O_3-induced growth effects on eastern cottonwood. This study placed eastern cottonwood (*Populus deltoides*) saplings at sites along a continuum of ambient O_3 exposures that gradually increased from urban to rural areas in the New York City area (Gregg et al., 2003). Eastern cottonwood is a fast growing O_3-sensitive tree species that is important ecologically along streams and commercially for pulpwood, furniture manufacturing, and as a possible new source for energy biomass (Burns and Hankola, 1990). Gregg et al. (2003) found that the cottonwood saplings grown in urban New York City grew faster than saplings grown in downwind rural areas. Because these saplings were grown in pots with carefully controlled soil nutrient and moisture levels, the authors were able to control for most of the differences between sites. After carefully considering these and other factors, the authors concluded the primary explanation for the difference in growth was the gradient of cumulative O_3 exposures that

increased as one moved downwind from urban to less urban and more rural sites. It was determined that the lower O_3 exposure within the city center was due to NO_x titration reactions which removed O_3 from the ambient air. This study found results of a similar magnitude as those previously seen in OTC studies but without the use of chambers or other fumigation methods (Gregg et al., 2003). The authors were able to reproduce the growth responses observed in the field in a companion OTC experiment, confirming O_3 as the stressor inducing the growth loss response (US EPA, 2006).

A set of field-based studies published since the 2006 AQCD employed the modified Free Air CO_2 Enrichment (FACE) methodology to expose vegetation in a forest in Wisconsin to elevated O_3 without the use of chambers. This exposure method more closely replicates conditions in the field than do OTCs. Over the first seven years of stand development at the Aspen FACE site, Kubiske et al. (2006) observed that elevated O_3 decreased tree heights, diameters, and main stem volumes in the aspen community by 11, 16, and 20%, respectively. In addition, Kubiske et al. (2007) reported that elevated O_3 may change intra- and inter-species competition. For example, O_3 treatments increased the rate of conversion from a mixed aspen-birch community to a birch dominated community.

In previous AQCDs, the majority of evidence of O_3 growth effects on trees and other vegetation and yield loss in crops came from open-top-chamber (OTC) studies such as those conducted at the NHEERL-WED research site in Corvallis, Oregon and those conducted through the National Crop Loss Assessment Network (NCLAN) program, respectively. Despite the robustness of the concentration-response (C-R) functions developed using OTC, the debate over their applicability in the field has persisted.

To further evaluate this issue, EPA staff identified two FACE projects which had sufficient data that could support an examination of the predictive capability of C-R functions generated in OTCs when applied under field exposure conditions. Specifically, the AspenFACE and SoyFACE projects were conducted over multiple years and the hourly O_3 data were available. There are necessary differences in the modeling of exposure-response in annual plants such as soybean, and in perennial plants such as aspen trees, when exposure takes place over multiple years. These differences and the needed adjustments to the comparative analyses are taken into account in the analyses and discussed in the ISA (US EPA, 2012a, section 9.6.3). The EPA staff first conducted a comparison between yield of soybean as predicted by the composite function three-step process (ISA, section 9.6.2) using NCLAN data, and observations of yield in SoyFACE. The median composite function for relative yield was derived for the NCLAN soybean Weibull functions for non-droughted studies, and comparisons between the predictions of the median composite and SoyFACE observations were conducted. For the years 2007 and

2008, SoyFACE yield data were available for 7 and 6 genotypes, respectively. Those data were used to compare the relative change in yield observed in SoyFACE in a given year between ambient O_3 and elevated O_3, versus the relative change in yield predicted by the NCLAN-based median composite function between those same two values of O_3 exposure. Since comparisons of absolute values were thought to also be of interest, the predictive functions were also scaled to the observed data.

As discussed in section 9.6.3.2 of the ISA (US EPA, 2012a), the agreement between predictions based on NCLAN data and SoyFACE observations was notably close in single-year comparisons. Together with the very high agreement between median composite models for NCLAN and SoyFACE, it provides very strong mutual confirmation of those two projects' results with respect to the response of yield of soybeans to O_3 exposure. It is readily apparent from these results that the methodology described in Section 9.6.2 of the ISA for obtaining predictions of yield or yield loss from NCLAN data is strongly validated by SoyFACE results. As described in section 9.2 of the ISA, the exposure technologies used in the two projects were in sharp contrast, specifically with respect to the balance each achieved between control of potential interacting factors or confounders, and fidelity to natural conditions. The comparisons that EPA conducted therefore demonstrate that the methodology used in developing the composite functions is resistant to the influence of nuisance variables and that predictions are reliable. They may also suggest that the aspects in which the two exposure technologies differ have less influence on exposure-response than initially supposed. These results are also in agreement with comparative studies reviewed in section 9.2.6 of the ISA (US EPA, 2012a)

In a second analysis, EPA staff compared relative and absolute above-ground biomass loss at ambient and elevated exposures observed in AspenFACE for aspen with the NHEERL/WED-OTC C-R function derived predictions. EPA found that effects on biomass accumulation in aspen during the first seven years closely agreed with the exposure-response function based on data from earlier OTC experiments (US EPA, 2012a, section 9.6.3). As in the comparisons between NCLAN and SoyFACE, the agreement between predictions based on NHEERL/WED data and Aspen FACE observations was very close. The results of the two projects strongly reinforce each other with respect to the response of aspen biomass to O_3 exposure. The methodology used for obtaining the median composite function is shown to be capable of deriving a predictive model despite potential confounders, and despite the added measurement error that is expected from calculating biomass using allometric equations. In addition, the function based on one year of growth was shown to be applicable to subsequent years (US EPA, 2012a, section 9.6.3.2).

As discussed in section 9.6.3.2 of the ISA (US EPA, 2012a), the results of experiments that used different exposure methodologies, different genotypes, locations, and durations converged to the same values of response to O_3 exposure for each of two very dissimilar plant species, and predictions based on the earlier experiments were validated by the data from current ones. However, in these comparisons, the process used in establishing predictive functions involved aggregating data over variables such as time, locations, and genotypes, and the use of a robust statistic (quartiles) for that aggregation. The validating data, from SoyFACE and Aspen FACE, were in turn aggregated over the same variables. The accuracy of predictions is not expected to be conserved for individual values of those variables over which aggregation occurred. For example, the predicted values for soybean, based on data for five genotypes, are not expected to be valid for each genotype separately. As shown in the validation, however, aggregation that occurred over different values of the same variable did not affect accuracy: composite functions based on one set of genotypes were predictive for another set, as long as medians were used for both sets.

Further support for the coherence of O_3 growth effects across numerous studies and species that used a variety of experimental techniques comes from a recent meta-analysis of peer reviewed studies from the last 40 years (Wittig et al., 2009). This meta-analysis found that current ambient O_3 concentrations as reported in those studies (with an average of 40 ppb) significantly decreased annual total biomass growth (7%) across 263 studies (US EPA, 2012a, section 9.4.3). The decreased growth effect was reported to be greater (11 to 17%) in elevated O_3 exposures (with an average 97 ppb) (Wittig et al., 2009) (US EPA, 2012a, section 9.4.3).

Thus, on the basis of the combined evidence from the SoyFACE and AspenFACE/OTC comparisons and the results of the field-based studies discussed above, the ISA concludes that additional compelling and important support is provided for the continued use of the C-R functions derived using OTC from the NCLAN and NHEERL-WED studies to estimate risk to crops and tree seedlings under ambient field exposure conditions. These results strengthen our understanding of O_3 effects on studied crop and forest species and make a significant contribution to the coherence of the weight of evidence available in this review. They also further demonstrate the relevance of the knowledge gained from trees grown in OTC and provide additional evidence that O_3-induced effects observed in chambers can be anticipated to occur in unmanaged systems in the field.

In addition to reduced growth, some plants adapt to O_3-induced reduction in photosynthesis by reallocating the remaining carbohydrate at the level of the whole organism. Many studies have demonstrated that O_3 reduces C allocation to roots (US EPA, 2012a, section

9.4.3). For example, in one meta-analysis, Grantz et al. (2006) estimated the effect of O_3 on the root:shoot allometric coefficient (k), the ratio between the relative growth rate of the root and shoot. The results showed that O_3 reduced the root:shoot allometric coefficient by 5.6%, and the largest decline of the root:shoot allometric coefficient was observed in slow-growing plants. Further, Vollsnes et al. (2010) studied the in vivo root development of subterranean clover (*Trifolium subterraneum*) before, during and after short-term O_3 exposure. It was found that O_3 reduced root tip formation, root elongation, the total root length, and the ratios between below- and above-ground growth within one week after exposure. Those effects persisted for up to three weeks; however, biomass and biomass ratios were not significantly altered at the harvest five weeks after exposure.

When fewer carbohydrates are present in the roots, less energy is available for root-related functions such as acquisition of water and nutrients. Thus, by inhibiting photosynthesis and the amount of carbohydrates available for transfer to the roots, O_3 can impact below ground processes. These below-ground changes could signal a shift in nutrient cycling with significance at the ecosystem level (Young and Sanzone, 2002) (see discussion in section 5.5.4 below). These below ground effects have been documented in the field. Data from a long-studied pollution gradient in the San Bernardino Mountains of southern California suggest that O_3 substantially reduces root growth in natural stands of ponderosa pine (*Pinus ponderosa*). Root growth in mature trees was decreased at least 87 percent in a high-pollution site as compared to a low-pollution site (Grulke et al., 1998), and a similar pattern was found in a separate study with whole-tree harvest along this gradient (Grulke and Balduman, 1999). Though effects on other ecosystem components were not examined, a reduction of root growth of this magnitude could have significant implications for the below-ground communities at those sites. Therefore, studies that examine only above-ground vegetative components may miss important O_3-induced changes below ground.

Trees and other perennials, in addition to cumulating the effects of O_3 exposures over the annual growing season, can also cumulate effects across multiple years. It has been reported that effects can "carry over" from one year to another (US EPA, 2006). Growth affected by a reduction in carbohydrate storage in one year may result in the limitation of growth in the following year (Andersen, et al., 1997) (US EPA, 2012a, section 9.4.8). Carry-over effects have been documented in the growth of some tree seedlings and in roots. More recent studies at the Aspen FACE site have also reported effects on paper birch and aspen that likely have implications for the subsequent growing season. Specifically, scientists found that elevated O_3 decreased birch seed weight, germination, and bud starch levels as well as aspen bud size. The effects on birch seeds could lead to a negative impact on species regeneration, while the bud

effects may have been related to the observed delay in spring leaf development and have the potential to alter carbon metabolism of overwintering buds, which may have carry-over effects in the following year (US EPA, 2012a, section 9.4.3). However, because most studies on the effects of O_3 on growth do not take into account the possibility of carry-over effects on growth in subsequent years, the true implication of these annual biomass losses may be missed. It is likely that under ambient exposure conditions, some sensitive trees and perennial plants could experience compounded impacts that result from multiple year exposures.

The detrimental effect of O_3 on crop production has been recognized since the 1960s, and a large body of research has subsequently stemmed from those initial findings. Previous O_3 AQCDs have extensively reviewed this body of literature (US EPA, 2006). Current O_3 concentrations across the U.S. are high enough to cause yield loss for a variety of agricultural crops including, but not limited to, soybean, wheat, potato, watermelon, beans, turnip, onion, lettuce, and tomato (US EPA, 2012a, section 9.4.4).

New research is beginning to consider the mechanism of damage caused by prolonged, lower O_3 concentrations (so-called chronic exposure) compared to short, very high O_3 concentration (so-called acute exposure). Both types of O_3 exposure cause damage to agricultural crops, but through very different mechanisms. Historically, most research on the mechanism of O_3 damage used acute exposure studies. During the last decade, it has become clear that the cellular and biochemical processes involved in the response to acute O_3 exposure are not involved in response to chronic O_3 exposure, even though both cause yield loss in agriculturally important crops (US EPA, 2012a, section 9.4.4). In addition, recent research has highlighted the effects of O_3 on crop quality. Increasing O_3 concentration decreases nutritive quality of grasses, decreases macro- and micro-nutrient concentrations in fruits and vegetable crops, and decreases cotton fiber quality. These areas of research require further investigation to determine mechanisms and exposure-response relationships (US EPA, 2012a, section 9.4.4).

5.3.3 Factors that Modify Plant Response to O_3

A plant's response to O_3 is influenced by the many ambient biotic and abiotic factors in its milieu, such as insects, pathogens, root microbes and fungi, temperature, water and nutrient availability, and other air pollutants, as well as elevated CO_2. These factors, when present, can potentially exacerbate or mitigate the effects of O_3. Thus, observed plant response to O_3 in the field represents an integration of the plant's response to all the biotic and abiotic factors to which it is exposed. Because these interactions are species specific and dependent on the particular circumstances of the interaction(s), it is impossible to incorporate the nearly infinite number of possible combinations in any quantitative way into an assessment of vegetation risk. As will be discussed in section 5.4 below, it is also not possible to fully account for these interactions in an

exposure index. However, in interpreting the range of risks experienced by vegetation across the country, it is helpful to understand how plant response to O_3 can be modified by other biotic and abiotic factors and how plant response to other factors can be altered by exposure to O_3. Therefore, some of the most important modifying factors are summarized here.

Regarding biotic factors, the most influential is actually within the plant itself: genes. Plant response to O_3 is determined by the set of genes that are directly related to oxidant stress and to an unknown number of genes that are not specifically related to oxidants, but instead control leaf and cell wall thickness, stomatal conductance, and the internal architecture of the air spaces (US EPA, 2012a, section 9.4.8). The genetic makeup of each plant therefore confers an inherent sensitivity or tolerance to O_3 exposure.

Plant response to O_3 can also be influenced by the presence and type of a disease outbreak or insect infestation. Conversely, a plant's response to O_3 can also alter the degree or severity of the disease or pest attack. Ozone can also directly affect the disease or pest species, and the interaction between O_3, a plant, and a pest or pathogen, may influence the response of the target host species to O_3 (US EPA, 2012a, section 9.4.8; see also discussion in section 5.5.6 below).

In contrast, there are also mutually beneficial relationships or symbioses involving higher plants and bacteria or fungi. These include (1) the nitrogen-fixing species *Rhizobium* and *Frankia* that nodulate the roots of legumes and alder and (2) the mycorrhizae that infect the roots of many crop and tree species, all of which may be affected by exposure of the host plants to O_3. In some cases, these interactions may offer some protection to the host plant from other stresses. In addition, O_3 has also been shown to alter soil fauna communities (US EPA, 2012a, section 9.4.8; see also discussion in section 5.5.4 below).

Intra- and inter-specific competition are also important factors in determining vegetation response to O_3. Plant competition involves the ability of individual plants to acquire the environmental resources needed for growth and development: light, water, nutrients, and space. Intra-specific competition involves individuals of the same species, typically in monoculture crop situations, while inter-specific competition refers to the interference exerted by individuals of different species on each other when they are in a mixed culture (US EPA, 2012a, section 9.4.8).

Physical or abiotic factors also play a large role in influencing plant response to O_3. These can include temperature, light, relative humidity, soil moisture conditions and the presence of other pollutants. However, the nature of these interactions appears to be complicated, largely species-specific and depends to some extent upon the sequence in which the stressors occur and

how closely a plant is to its optimal growing conditions when the change or stress occurs. Most studies of stressor interactions have just included O_3 and one other stressor at a time (US EPA, 2012a, section 9.4.8). However, it should be realized that there are situations or scenarios in which multiple biotic and abiotic conditions change together. For example, under climate change, shifts in temperature, precipitation, CO_2, O_3 and insects and/or disease incidence are expected to be interrelated. Additional research into multiple interactions would help our understanding of how plants integrate these stressors.

5.4 BIOLOGICALLY RELEVANT EXPOSURE INDICES

The CAA requires that national ambient air quality standards be based on air quality criteria, which "shall 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 such pollutant in the ambient air, in varying quantities." It further states that the criteria "… shall include information on (A) those variable factors (including atmospheric conditions) which of themselves or in combination with other factors, may alter the effects on public health or welfare…." Thus, in order to ensure that national ambient air quality standards provide the requisite degree of public health and welfare protection, it is important that the standard that is set by EPA would control the aspects of pollutant exposure that are known, based on available information, to induce the adverse health and/or welfare response. This is done by reviewing the most recent available science that elucidates the aspects of pollutant exposures that are important in inducing an adverse response. This section summarizes the vegetation exposure and effects science that forms the basis for our understanding of the variable aspects of ambient O_3 exposures that have biological relevance (section 5.4.1), exposure indices or metrics that have been designed to reflect or incorporate this science, making them biologically relevant (5.4.2), and past and current conclusions based on the exposure and effects science, as well as policy considerations, regarding appropriate indices to consider in the context of national standards in past and current reviews (5.4.3).

5.4.1 Exposure Factors that Influence Plant Response

There is an extensive body of vegetation effects research from which various factors with known or suspected bearing on the exposure-response relationship have been identified. These factors include concentration, time of day, respite time, frequency of peak occurrence, plant phenology, predisposition, among others (US EPA, 2012a, section 9.5.2). Much of the work identifying the aspects of exposure important for plant response had been done by the mid-1990s and was summarized in the 1996 Criteria Document. In particular, the importance of the duration of the exposure (5.4.1.1) and the relatively greater importance of higher concentrations

over lower (5.4.1.2) in determining plant response to O_3 have been well documented. These conclusions have been reiterated in the current ISA which states that "[t]he attributes of exposure indices that are most relevant to plant damage are the weighting of O_3 concentrations and the daily and seasonal time-periods" (US EPA, 2012a, section 9.5.1).

5.4.1.1 Relevant exposure periods: diurnal and seasonal

With respect to the importance of exposure duration in explaining plant response, the 1996 AQCD stated, "when O_3 effects are the primary cause of variation in plant response, plants from replicate studies of varying duration showed greater reductions in yield or growth when exposed for the longer duration" and "the mean exposure index of unspecified duration could not account for the year-to-year variation in response" (US EPA, 1996, pg. 5-96). Further, "because the mean exposure index treats all concentrations equally and does not specifically include an exposure duration component, the use of a mean exposure index for characterizing plant exposures appears inappropriate for relating exposure with vegetation effects" (US EPA, 1996, pg. 5-88). As discussed below, there is both a diurnal and seasonal component to biologically relevant exposures.

Diurnal. The conditions for uptake of O_3 into the plant occur mainly during the daytime hours. In general, plants have the highest stomatal conductance during the daytime and in many areas atmospheric turbulent mixing is greatest during the day as well (Uddling et al., 2010; US EPA, 2006). This is because the high-temperature and high-light conditions that typically promote the formation of tropospheric O_3 also promote physiological activity in vegetation (US EPA, 2012a, section 9.5.3).

In addition to daytime uptake, several studies have also reported O_3 uptake at night. As a result, EPA has considered the appropriateness of including nighttime hours in an exposure index, both in the context of the last and current reviews. However, typically, the rate of stomatal conductance at night is much lower than during the day (Caird et al., 2007). Atmospheric turbulence at night is also often low, which results in stable boundary layers and unfavorable conditions for O_3 uptake into vegetation (Finkelstein et al., 2000). Notable exceptions to maximum daytime conductance are cacti and other plants with crassulacean acid metabolism (CAM photosynthesis) which only open their stomata at night. Due to a paucity of information on exposure-response relationships in species with CAM photosynthesis, this section will focus on plants with C3 and C4 photosynthesis, which generally have maximum stomatal conductance during the daytime (US EPA, 2012a, section 9.5.3).

For significant nocturnal stomatal flux and O_3 effects to occur, the right combination of specific conditions must exist. In particular, a susceptible plant with nocturnal stomatal

conductance and low defenses must be growing in an area with relatively high night-time O_3 concentrations and appreciable nocturnal atmospheric turbulence. It is unclear how many areas there are in the U.S. where these conditions occur. It may be possible that these conditions exist in mountainous areas of southern California, front-range of Colorado (Turnipseed et al., 2009) and the Great Smoky Mountains of North Carolina and Tennessee. More information is needed in locations with high night-time O_3 to assess the local O_3 patterns, micrometeorology and responses of potentially vulnerable plant species. Work by Mereu et al. (2009) in Italy on Mediterranean species indicated that nocturnal uptake was from 10 to 18% of total daily uptake during a weak drought and up to 24% as the drought became more pronounced. The proportion of night-time uptake was greater during the drought due to decreases in daytime stomatal conductance (Mereu et al., 2009). These studies show that effects can be seen with night-time exposures to O_3, but when atmospheric conditions are stable at night, it is uncertain how these exposures may affect plants and trees with complex canopies in the field (US EPA, 2012a, section 9.5.3). Therefore, due to the substantial uncertainties that remain regarding the extent and importance of nocturnal exposures, EPA continues to focus on exposures occurring during daytime/daylight hours.

Seasonal. Vegetation across the U.S. has widely varying periods of physiological activity during the year due to variability in climate and phenology. In order for a particular plant to be vulnerable to O_3 pollution, it must have foliage and be physiologically active at the time of exposure. Annual crops are typically grown for periods of two to three months. In contrast, perennial species may be photosynthetically active longer (up to 12 months each year for some species) depending on the species and where it is grown. In general, the period of maximum physiological activity and thus, potential O_3 uptake for vegetation coincides with some or all of the intra-annual period defined as the O_3 season, which varies on a state-by-state basis (US EPA, 2012a, Figure 3-24). This is because the high-temperature and high-light conditions that typically promote the formation of tropospheric O_3 also promote physiological activity in vegetation. There are very limited exceptions to this pattern where O_3 can form in the winter in areas in the western U.S. with intense natural gas exploration (Pinto, 2009), but this is typically when plants are dormant and there is little chance of O_3 uptake. The selection of any single window of time for a national standard to consider hourly O_3 concentrations represents a compromise, given the significant variability in growth patterns and lengths of growing season among the wide range of vegetation species that may experience adverse effects associated with O_3 exposure (US EPA, 2012a, section 9.5.3).

Various intra-annual averaging and accumulation time periods have been considered for the protection of vegetation. The 2007 proposal for the secondary O_3 standard (72 FR 37899)

proposed to use the maximum consecutive 3-month period within the O_3 season. Alternatively, the U.S. Forest Service and federal land managers have used a 24-h W126 accumulated for 6 months from April through September (FLAG, 2000). However, some monitors in the U.S. are operational for as little as four months and would not have enough data for a 6-month seasonal window. The exposure period in the vast majority of O_3 exposure studies conducted in the U.S. has been much shorter than 6 months. Most of the crop studies done through NCLAN had exposures less than three months with an average of 77 days. Open-top chamber studies of tree seedlings, compiled by the EPA, had an average exposure of just over three months or 99 days. In more recent FACE experiments, SoyFACE exposed soybeans for an average of approximately 120 days per year, and the Aspen FACE experiment exposed trees to an average of approximately 145 days per year of elevated O_3, which included the entire growing season at those particular sites. Despite the possibility that plants may be exposed to ambient O_3 longer than 3 months in some locations, there is a lack of exposure experiments conducted for longer than 3 months (US EPA, 2012a, section 9.5.3).

In an analysis conducted by ORD/NCEA to test the importance of going beyond the previously recommended 3 month period to capture cumulative O_3 exposures over a longer growing season, the 3- and 6-month maximum W126 values were calculated for over 1,200 AQS and CASTNET EPA monitoring sites for the years 2008-2009. This analysis found that these two accumulation periods resulted in highly correlated metrics (US EPA, 2012a, section 9.5.2, Figure 9-13). The two accumulation periods were centered on the yearly maximum for each monitoring site, and it is possible that this correlation would be weaker if the two periods were not temporally aligned. In the U.S., W126 cumulated over 3 months and W126 cumulated over 6 months are proxies of one another, as long as the period in which daily W126 is accumulated corresponds to the seasonal maximum. Therefore, it is expected that either statistic will predict vegetation response equally well. In other words, the strength of the correlation between maximum 3-month W126 and maximum 6-month W126 is such that there is no material difference in their predictive value for vegetation response. (US EPA, 2012a, section 9.5.3)

5.4.1.2 Relevant exposure concentrations: differential weighting

It has been clearly shown in the scientific literature that, all else being equal, plants respond more to higher concentrations, though there continues to be no evidence of an exposure threshold for vegetation effects (US EPA, 2012a, section 9.5.3). Regarding the relative importance of higher concentrations than lower in determining plant response, the 1996 Criteria Document concluded that “the ultimate impact of long-term exposures to O_3 on crops and seedling biomass response depends on the integration of repeated peak concentrations during the growth of the plant” and further that, “at this time, exposure indices that weight the hourly O_3

concentrations differentially appear to be the best candidates for relating exposure with predicted plant response" (US EPA, 1996, pgs. 5-136). While the significant role of peak O_3 concentrations was established based on several experimental studies previously described in the 1996 AQCD, several more recent studies (Oksanen and Holopainen, 2001; Yun and Laurence, 1999; Nussbaum et al., 1995) have added further support for the important role that peak concentrations, as well as the pattern of occurrence, plays in plant response to O_3 (US EPA, 2012a, section 9.5.3). For example, Oksanen and Holopainen (2001) found that the peak concentrations and the shape of the O_3 exposure (i.e., duration of the event) were important determinants of foliar injury in European white birch saplings, though growth reductions were found to be more related to total cumulative exposure (US EPA, 2012a, section 9.5.3).

5.4.2. Biologically Relevant Exposure Metrics

In conjunction with the extensive body of vegetation effects research on plant response to O_3, "mathematical approaches for summarizing ambient air quality information in biologically meaningful forms for O_3 vegetation effects assessment purposes have been explored for more than 80 years" (US EPA, 2012a, section 9.5.2). A large set of indices have been developed that use a variety of functions to weight factors that have been shown to influence vegetation exposure-response relationships (US EPA, 2012a, section 9.5.2). As with any summary statistic, exposure indices retain information on some, but not all, characteristics of the original observations. As discussed in the ISA, several indices have been developed to attempt to incorporate some of the biological, environmental, and exposure factors that influence the magnitude of the biological response and contribute to observed variability (US EPA, 2012a, section 9.5.2). The resulting indices were evaluated by ranking them according to the goodness-of-fit of a regression model of growth or yield response (Lee et al., 1989). For example, in an analysis using the National Crop Loss Assessment Network (NCLAN) data, Lee et al. (1988) found several indices which cumulated and weighted higher concentrations (e.g., W126, SUM06, SUM08, and AOT40) performed very well. Among this group of indices, no one index had consistently better fits than the other indices across all studies and species (Heagle et al., 1994b; Lefohn et al., 1988; Musselman et al., 1988). Lee et al. (1988) also found that adding phenology weighting to the index somewhat improved the performance of the indices. However, because it required data on species and site conditions, it was not considered appropriate for general use. Based on the above science, the attributes of exposure indices that are most relevant to plant damage are the cumulation and weighting of hourly O_3 concentrations and the diurnal and seasonal time-periods (US EPA, 2012a, section 9.5.2).

In past reviews, EPA staff has compared the appropriateness of using different cumulative, peak weighted metrics in the context of selecting a form for a secondary national

ambient air quality standard for O_3. In particular, the 1996 Staff Paper compared three of these forms, the SUM06, AOT06, and W126 exposure metrics (US EPA, 1996, pp. 223-227). Below are the definitions of the three cumulative index forms previously evaluated in the NAAQS context:

- **SUM06:** Sum of all hourly O_3 concentrations greater than or equal to 0.06 ppm observed during a specified daily and seasonal time window.
- **AOT06:** Sum of the differences between hourly O_3 concentrations greater than the specified threshold of 0.06 ppm during a specified daily and seasonal time window.
- **W126:** Sigmoidally weighted sum of all hourly O_3 concentrations observed during a specified daily and seasonal time window (Lefohn et al., 1988; Lefohn and Runeckles, 1987).

Following completion of the Staff Paper, a consensus workshop was convened to consider the science supporting a range of topics, including biologically relevant indices. In comparing the SUM06 to the W126 form, there was a consensus that the cumulative concentration-weighted indices being considered were equally capable of predicting plant response (Heck and Cowling, 1997).

Based on both its own staff analysis and the workshop consensus statement, the EPA proposed as one alternative in the 1997 review to use the SUM06 form of the secondary NAAQS for O_3 to protect vegetation from damage (72 FR 37818). In the subsequent 2008 review, the EPA staff decided to revisit its selection of the SUM06 form by again comparing the different relevant features of the SUM06 form to the W126 form (U.S. EPA, 2007b, pp. 8-21/22). On the basis of that comparison which took into account both science and policy considerations relevant in that review, the EPA proposed to use the W126 form as the most appropriate to use in that context.

In its discussion of biologically relevant exposure indices, the current ISA continues this comparison and further elaborates by stating, "[i]t should be noted that there are some important differences between the SUM06 and W126. When considering the response of vegetation to O_3 exposures represented by the threshold (e.g., SUM06) and non-threshold (e.g., W126) indices, the W126 metric does not have a cut-off in the weighting scheme as does SUM06 and thus it includes consideration of potentially damaging exposures below 60 ppb. The W126 metric also adds increasing weight to hourly concentrations from about 40 ppb to about 100 ppb (Lefohn et al., 1988; Lefohn and Runeckles, 1987)." This is unlike cut-off metrics such as the SUM06 where all concentrations below 0.06 ppm are given a weight of zero and concentrations at or

above 0.06 ppm are treated equally and given a weight of 1.0. This is an important feature of the W126 since as hourly concentrations become higher, they become increasingly likely to overwhelm plant defenses and are known to be more detrimental to vegetation (US EPA, 2012a, section 9.5.3).

Given the above, EPA staff concludes that it is appropriate to continue to focus on the W126 form in this review. The equation for the W126 (75 FR 2999 and US EPA, 2012a, section 9.5.2, equation 9-1) is provided here. This daily ozone index is defined as follows:

$$daily\ W126 = \sum_{i=8am}^{i<8pm} w_{c_i} C_i \text{ , where } C_i = \text{hourly } O_3 \text{ at hour } i\text{, and } w_c = \frac{1}{1+4403e^{-126C}} .$$

The daily index values are then summed over each month within the O_3 season, and the annual highest consecutive three month sum is determined.

In addition to the development of exposure metrics, research has and continues to be conducted on the development of flux-based models. These models attempt to calculate the O_3 concentration from the atmosphere that enters the leaf (i.e., flux or deposition). Interest has been increasing in recent years, particularly in Europe, in using mathematically tractable flux models for O_3 assessments at the regional, national, and European scale (Matyssek et al., 2008; Paoletti and Manning, 2007; Emberson et al., 2000b; Emberson et al., 2000a) (US EPA, 2012a, section 9.5.5). Clearly, from a theoretical perspective, a measure of plant O_3 uptake or dose from ambient air (either rate of uptake or cumulative seasonal uptake) might seem more desirable as a better predictor of O_3 damage to plants than an exposure index and therefore more useful in improving risk assessment. This is because an uptake estimate would have to integrate all those environmental factors that influence stomatal conductance, including but not limited to temperature, humidity, and soil water status (see discussion in section 5.3.3 above).

However, there are still important limitations with this approach that make it inappropriate to consider in the context of a national standard for the U.S. First, while some efforts have been made in the U.S. to calculate O_3 flux into leaves and canopies (Turnipseed et al., 2009; Uddling et al., 2009; Bergweiler et al., 2008; Hogg et al., 2007; Grulke et al., 2004; Grantz et al., 1997; Grantz et al., 1995), little information has been published relating these fluxes to effects on vegetation. At this time, dose-response relationships have not been developed for these flux calculations for plants growing in the U.S., and large amounts of data on the physiology of each plant species and the local growing conditions for the growing range of each plant species, including climate patterns, would be required for flux calculations. The

models have to also distinguish between stomatal and non-stomatal components of O_3 deposition to adequately estimate actual concentration reaching the target tissue of a plant to elicit a response (Uddling et al., 2009) (US EPA, 2012a, section 9.5.4).

The lack of data in the U.S. and the lack of understanding of detoxification processes have made this technique less viable for vulnerability and risk assessments in the U.S. Thus, EPA staff recognizes that the selection of an appropriate form of exposure index that can be nationally applied will necessarily represent a simplification of the multiple factors that can potentially affect specific plant response across the wide variety of species and ecosystems/conditions that occur within the U.S.

5.4.3 Conclusions

The 2012 ISA (US EPA, 2012a, section 9.5.5) states that the main conclusions from the 1996 and 2006 O_3 AQCDs regarding a biologically relevant O_3 exposure index are still valid. These key conclusions can be restated as follows:

- O_3 effects in plants are cumulative;
- higher O_3 concentrations appear to be more important than lower concentrations in eliciting a response;
- plant sensitivity to O_3 varies with time of day and plant development stage; and
- quantifying exposure with indices that accumulate the O_3 hourly concentrations and preferentially weight the higher concentrations improves the explanatory power of exposure/response models for growth and yield, over using indices based on mean and peak exposure values.

5.5 ECOSYSTEM-LEVEL IMPACTS

Ecosystems are comprised of complex assemblages of organisms and the physical environment with which they interact. Each level of organization within an ecosystem has functional and structural characteristics. At the ecosystem level, functional characteristics include, but are not limited to, energy flow; nutrient, hydrologic, and biogeochemical cycling; and maintenance of food chains. The sum of the functions carried out by ecosystem components provides many benefits to humankind, as in the case of forest ecosystems (Smith, 1992). Some of these benefits, also termed “ecosystem goods and services,” include food, fiber production, aesthetics, genetic diversity, maintenance of water quality, air quality, and climate, and energy exchange. A conceptual framework for discussing the effects of stressors, including air pollutants such as O_3, on ecosystems was developed by the EPA Science Advisory Board (Young and Sanzone, 2002). In this report, the authors identify six essential ecological attributes (EEAs) of ecosystems including landscape condition, biotic condition, chemical/physical condition, ecological processes, hydrology/geomorphology, and natural disturbance regime. Each EEA is

depicted as one of six triangles that together build a hexagon. On the outside of each triangle is a list of stressors that can act on the EEA. Tropospheric O_3 is listed as a stressor of both biotic condition and the chemical/physical condition of ecosystems. As each EEA is linked to all the others, it is clearly envisioned in this framework that O_3 could either directly or indirectly impact all of the EEAs associated with an ecosystem that is being stressed by O_3.

Vegetation often plays an influential role in defining the structure and function of an ecosystem, as evidenced by the use of dominant vegetation forms to classify many types of natural ecosystems, e.g., tundra, wetland, deciduous forest, and conifer forest. Plants simultaneously inhabit both above- and below-ground environments, integrating and influencing key ecosystem cycles of energy, water, and nutrients. When a sufficient number of individual plants within a community have been affected, O_3-related effects can be propagated up to ecosystem-level effects. Thus, through its impact on vegetation, O_3 can be an important ecosystem stressor.

5.5.1 Overview: Ecosystem Scale, Structure, Function, and Services

For this assessment, "ecosystem" is defined as the interactive system formed from all living organisms and their abiotic (physical and chemical) environment within a given area (IPCC, 2007a). The boundaries of what could be called an ecosystem are somewhat arbitrary, depending on the focus of interest or study. Thus, the extent of an ecosystem may range from very small spatial scales or levels of biological organization to, ultimately, the entire Earth (IPCC, 2007a). All ecosystems, regardless of size or complexity, have interactions and physical exchanges between biota and abiotic factors: this includes both structural (e.g., soil type and food web trophic levels) and functional (e.g., energy flow, decomposition, nitrification) attributes (US EPA, 2012a, section 9.4.1).

Ecosystems can be described, in part, by their structure, i.e., the number and type of species present. Structure may refer to a variety of measurements including the species richness, abundance, community composition and biodiversity as well as landscape attributes. Competition among and within species and their tolerance to environmental stressors are key elements of survivorship. When environmental conditions are shifted, for example, by the presence of anthropogenic air pollution, these competitive relationships may change, and tolerance to stress may be exceeded. Ecosystems may also be defined on a functional basis. "Function" refers to the suite of processes and interactions among the ecosystem components and their environment that involve nutrient and energy flow as well as other attributes including water dynamics and the flux of trace gases. Plants, via such processes as photosynthesis, respiration, C allocation, nutrient uptake and evaporation, affect energy flow, C, nutrient cycling and water cycling. The energy accumulated and stored by vegetation (via photosynthetic C

capture) is available to other organisms. Energy moves from one organism to another through food webs, until it is ultimately released as heat. Nutrients and water can be recycled. Air pollution alters the function of ecosystems when elemental cycles or the energy flow are altered. This alteration can also be manifested in changes in the biotic composition of ecosystems (US EPA, 2012a, 9.4.1).

There are at least three levels of ecosystem response to pollutants: (1) the individual organism and its environment; (2) the population and its environment; and (3) the biological community composed of many species and their environment (Billings, 1978). Individual organisms within a population vary in their ability to withstand the stress of environmental change. The response of individual organisms within a population is based on their genetic constitution, stage of growth at time of exposure to stress, and the microhabitat in which they are growing (Levine and Pinto, 1998). The stress range within which organisms can exist and function determines the ability of the population to survive (US EPA, 2012a, 9.4.1).

Ecosystem structure and function may be translated into ecosystem services. Ecosystem services are the benefits people obtain from ecosystems (UNEP, 2003). Ecosystems provide many goods and services that are of vital importance for the functioning of the biosphere and provide the basis for the delivery of tangible benefits to human society. Hassan et al. (2005) define these benefits to include supporting, provisioning, regulating, and cultural services (US EPA, 2012a, 9.4.1).

Supporting services are necessary for the production of all other ecosystem services. Some examples include biomass production, production of atmospheric O_2, soil formation and retention, nutrient cycling, water cycling, and provisioning of habitat. Biodiversity is a supporting service that is increasingly recognized to sustain many of the goods and services that humans enjoy from ecosystems. These provide a basis for three higher-level categories of services. Provisioning services may include products (Gitay et al., 2001), i.e., food (including game, roots, seeds, nuts and other fruit, spices, fodder), water, fiber (including wood, textiles), and medicinal and cosmetic products (such as aromatic plants, pigments). Regulating services that are of paramount importance for human society may include (1) C sequestration, (2) climate and water regulation, (3) protection from natural hazards such as floods, avalanches, or rock-fall, (4) water and air purification, and (5) disease and pest regulation. Cultural services satisfy human spiritual and aesthetic appreciation of ecosystems and their components, including recreational and other nonmaterial benefits (US EPA, 2012a, 9.4.1).

Collectively these examples suggest that O_3 is an important stressor in natural ecosystems, but ecosystem changes, including those for which O_3 was a contributor, are difficult to evaluate in natural settings, due to the complexity of interactions, the number of potential

confounders, and the large spatial and temporal scales. In most ecosystem level studies, only a few ecosystem components are examined and characterized for O_3 effects. Thus, the full extent of ecosystem changes in these ecosystems is not fully understood. Clearly, there is a need for highly integrated ecosystem studies that specifically investigate the effect of O_3 on ecosystem structure and function in order to fully understand the extent to which O_3 is affecting ecosystem services.

In the sections that follow, available information on the ecosystem-level effects of O_3 on productivity and C sequestration (5.5.2), water cycling (5.5.3), below-ground processes (5.5.4), community composition (5.5.5), and insects and wildlife (5.5.6) are considered and, where appropriate, put in the context of ecosystem services (US EPA, 2012a, 9.4.1).

5.5.2 Productivity and Carbon Sequestration

During the last NAAQS review, there were limited studies that investigated the effect of O_3 exposure on ecosystem productivity and C sequestration. Both experimental and modeling studies have provided new information on effects of O_3 exposure at the stand or site level, i.e., at the local scale (US EPA, 2012a, section 9.4.3).

Recent field-based studies from long-term FACE experiments, such as Aspen FACE, SoyFACE and the Kranzberg Forest (Germany), provide more evidence of the association of O_3 exposure and reduced productivity at the ecosystem level of organization. Studies at the leaf and plant scales show that O_3 decreased photosynthesis and plant growth, which provides coherence and biological plausibility for the decrease in ecosystem productivity (US EPA, 2012a, section 9.4.3).

For example, the above- and below-ground biomass and net primary production (NPP) were measured at the Aspen FACE site after 7 years of O_3 exposure. Elevated O_3 caused 23, 13 and 14% reductions in total biomass relative to the control in the aspen, aspen–birch and aspen–maple communities, respectively (King et al., 2005). At the Kranzberg Forest FACE experiment in Germany, O_3 reduced annual volume growth by 9.5 m^3/ha in a mixed mature stand of Norway spruce and European beech (Pretzsch et al., 2010). At the grassland FACE experiment at Alp Flix, Switzerland, O_3 reduced the seasonal mean rates of ecosystem respiration and total carbon gain (GPP) by 8% but had no significant impacts on aboveground dry matter productivity or growing season net ecosystem production (NEP) (Volk et al., 2011). Ozone also altered C accumulation and turnover in soil, as discussed in Section 9.4.6 (US EPA, 2012a, section 9.4.3).

Changes in forest stand productivity under elevated O_3 were assessed by several model studies. TREGRO (Table 9-2) has been widely used to simulate the effects of O_3 on the growth of several species in different regions in the U.S. Hogsett et al. (2008) used TREGRO to

evaluate the effectiveness of various forms and levels of air quality standards for protecting tree growth in the San Bernardino Mountains of California. They found that O_3 exposures at the Crestline site resulted in a mean 20.9% biomass reduction from 1980 to 1985 and 10.3% biomass reduction from 1995 to 2000, compared to the ‘‘background’’ O_3 concentrations (O_3 concentration in Crook County, Oregon). The level of vegetation protection projected was different depending on the air quality scenarios under consideration (US EPA, 2012a, section 9.4.3).

The model ZELIG is a forest succession gap model which has been used to evaluate the dynamics of natural stand succession. Combining TREGRO with ZELIG, Weinstein et al. (2005) simulated the effects of different O_3 levels (0.5, 1.5, 1.75, and 2 times [×] ambient) on the growth and competitive interactions of white fir and ponderosa pine at three sites in California: Lassen National Park, Yosemite National Park, and Crestline. Their results suggested that O_3 had little impact on white fir but greatly reduced the growth of ponderosa pine (US EPA, 2012a, section 9.4.3). To evaluate the influence of interspecies competition on O_3 effects, the linked TREGRO and ZELIG modeling system was used to predict the effects of O_3 over 100 years on the basal area of species in a *Liriodendron tulipifera*-dominated forest in the Great Smoky Mountains National Park (Weinstein et al., 2001). Ambient O_3 was predicted to decrease individual tree C budget by 28% and reduce the basal area of *L. tulipifera* by 10%, whereas a 1.5×-ambient exposure was predicted to cause a 42% decrease in the individual tree C budget and a 30% reduction in basal area. Individual tree C balance for *Acer rubrum* decreased 14% and 23% under ambient and 1.5×-ambient exposure, respectively. *Prunus serotina* was predicted to have less than a 2% decrease in tree C balance in all scenarios, but its basal area was greatly altered by the O_3 effects on the other tree species. Basal area of *A. rubrum* and *P. serotina* was predicted to increase for some years but then decrease by up to 30%, depending on the scenario (US EPA, 2012a, section 9.4.3).

The effects of O_3 on stand productivity and dynamics were also studied by other tree growth or stand models, such as ECOPHYS, INTRASTAND and LINKAGES. ECOPHYS is a functional-structural tree growth model. The model used the linear relationship between the maximum capacity of carboxylation and O_3 dose to predict the relative effect of O_3 on leaf photosynthesis (Martin et al., 2001). Simulations with ECOPHYS found that O_3 decreased stem dry matter production, stem diameter and leaf dry matter production, induced earlier leaf abscission, and inhibited root growth (Martin et al., 2001). INTRASTAND is an hourly time step model for forest stand carbon and water budgets. LINKAGES is a monthly time step model simulating forest growth and community dynamics. Linking INTRASTAND with LINKAGES, Hanson et al. (2005) found that a simulated increase in O_3 concentration in 2100 (a mean 20-ppb

increase over the current O_3 concentration) yields a 35% loss of net ecosystem C exchange (NEE) with respect to the current conditions (174 g C/m2/year) (US EPA, 2012a, section 9.4.3).

Since the publication of the 2006 O_3 AQCD, there is additional evidence suggesting that O_3 exposure alters ecosystem productivity and biogeochemical cycling at the regional scale, i.e., at scales ranging from watershed to subcontinental divisions and at continental and global scales. Most of those studies were conducted by using process-based ecosystem models. In one example, Ollinger et al. (1997a) simulated the effect of O_3 on hardwood forest productivity of 64 hardwood sites in the northeastern U.S. with PnET-iI. Their simulations indicated that O_3 caused a 3-16% reduction in NPP from 1987 to 1992 (US EPA, 2012a, section 9.4.3).

Felzer et al. (2004) developed TEM 4.3 (US EPA, 2012a, Table 9-2) to simulate the effects of O_3 on plant growth and estimated effects of O_3 on NPP and C sequestration of deciduous trees, conifers and crops in the conterminous U.S. The results indicated that O_3 reduced NPP and C sequestration in the U.S. with the largest decreases (over 13% in some locations) in NPP occurring in the Midwest agricultural lands during the mid-summer. DLEM was developed to simulate the detrimental effect of O_3 on ecosystems and has been used to examine the O_3 damage on NPP and C sequestration in Great Smoky Mountains National Park (Zhang et al., 2007), grassland ecosystems and terrestrial ecosystems in China (Ren et al., 2007b; Ren et al., 2007a) (US EPA, 2012a, section 9.4.3).

Instead of using AOT40 as their O_3 exposure metric as PnET, TEM and DLEM did, Sitch et al. (2007) incorporated a different O_3 metric named CUOt (cumulative stomatal uptake of O_3), derived from Pleijel et al. (2004a), into the MOSES-TRIFFID coupled model (Table 9-2). In the model, reduced ecosystem C uptake due to O_3 damage results in additional CO_2 accumulation in the atmosphere and an indirect radiative forcing of climate change. Their simulations indicated that the indirect radiative forcing caused by O_3 (0.62-1.09 W/m2) could have even greater impact on global warming than the direct radiative forcing of O_3 (0.89 W/m2) (Sitch et al., 2007) (US EPA, 2012a, section 9.4.3).

Results from the various model studies are difficult to compare because of the various spatial and temporal scales used. However, all the studies showed that O_3 exposure decreased ecosystem productivity and C sequestration. These results are consistent and coherent with experimental results obtained from studies at the leaf, plant and ecosystem scales (Sitch et al., 2007; Felzer et al., 2005). Many of the models use the same underlying function to simulate the effect of O_3 exposure to C uptake. Therefore, it is not surprising that the results are similar. While these models can be improved and more evaluation with experimental data can be done, these models represent the state of the science for estimating the effect of O_3 exposure on productivity and C sequestration (US EPA, 2012a, section 9.4.3).

Although O_3 generally causes negative effects on plant growth, the magnitude of the response varies among plant communities. For example, O_3 had little impact on white fir but greatly reduced growth of ponderosa pine in southern California (Weinstein et al., 2005). Ozone decreased net primary production (NPP) of most forest types in the Mid-Atlantic region but had small impacts on spruce-fir forest (Pan et al., 2009) (US EPA, 2012a, section 9.4.3).

In addition to plant growth, other indicators that are typically estimated by model studies include net ecosystem CO_2 exchange (NEE), C sequestration, and crop yield. Model simulations consistently found that O_3 exposure caused negative impacts on these indicators, but the severity of these impacts was influenced by multiple interactions of biological and environmental factors such as N deposition, elevated CO_2 and land use history. Model simulations suggested that O_3 partially offset the growth stimulation caused by elevated CO_2 and N deposition in both Northeast- and Mid-Atlantic-region forest ecosystems of the U.S. (Pan et al., 2009; Ollinger et al., 2002) (US EPA, 2012a, section 9.4.3).

Results across different ecosystem models, such as TREGRO, PnET, TEM and DLEM, are consistent with the FACE experimental evidence, which show that O_3 reduced productivity of various ecosystems. Productivity is measured by various metrics such as GPP, NPP, NEP, NCE, NEE and individual tree biomass gain. All these metrics indicate a decrease in CO_2 fixation by the systems that were studied (US EPA, 2012a, section 9.4.3).

5.5.3 Water Cycling

Ozone can affect water use in plants and ecosystems through several mechanisms including damage to stomatal functioning and loss of leaf area. However, there is not a clear consensus on the nature of leaf-level stomatal conductance response to O_3 exposure. When measured under steady-state high light conditions, leaf-level stomatal conductance is often found to be reduced when plants are exposed to O_3. In contrast, measurements of stomatal conductance under dynamic light and VPD conditions, which are more typical in the field indicate sluggish responses under elevated O_3 exposure, which could potentially lead to increased water loss from vegetation in some situations (US EPA, 2012a, section 9.4.5).

Field studies by (McLaughlin et al., 2007a; 2007b) provided valuable insight into the possible consequences of stomatal sluggishness for ecosystem water cycling. McLaughlin et al. (2007a,b) indicated that O_3 increased water use in a mixed deciduous forest in eastern Tennessee. McLaughlin et al. (2007a,b) found that O_3, with daily maximum levels ranging from 69.2 to 82.9 ppb, reduced stem growth by 30-50% in the high-O_3 year 2002. The decrease in growth rate was caused in part by amplification of diurnal cycles of water loss and recovery. Peak hourly O_3 exposure increased the rate of water loss through transpiration as indicated by the increased stem

sap flow. The authors suggested that a potential mechanism for the increased sap flow could be altered stomatal regulation from O_3 exposure, but this was inferred through sap flow measurements and was not directly measured. The increased canopy water loss resulted in higher water uptake by the trees as reflected in the reduced soil moisture in the rooting zone. The change in tree water use led to further impacts on the hydrological cycle at the landscape level. Increased water use under high O_3 exposure was reported to reduce late-season modeled streamflow in three forested watersheds in eastern Tennessee (McLaughlin et al., 2007b).

In addition to the impacts on stomatal performance, O_3-induced physiological changes, such as reduced leaf area index and accelerated leaf senescence could alter water use efficiency. Elevated O_3 could also affect evapotranspiration by altering tree crown interception of precipitation. Although evidence was limited (based on a few field and modeling studies), findings showed an association between O_3 exposure and alteration of water use and cycling in vegetation and at the watershed level (US EPA, 2012a, section 9.4.5).

5.5.4 Below-ground Processes

Since the 2006 O_3 AQCD, more evidence has shown that although the responses are often site specific, O_3 altered the quality and quantity of litter input to soil, microbial community composition, and C and nutrient cycling. Biogeochemical cycling of below-ground processes is fueled by C input from plants. Studies at the leaf and plant level have provided biologically plausible mechanisms, such as reduced photosynthetic rates, increased metabolic cost, and reduced root C allocation for the association of O_3 exposure and the alteration of below-ground processes (US EPA, 2012a, section 9.4.6).

Results from Aspen FACE and other experimental studies consistently found that O_3 reduced litter production and altered C chemistry, such as soluble sugars, soluble phenolics, condensed tannins, lignin, and macro/micro nutrient concentration in litter (Parsons et al., 2008; Kasurinen et al., 2006; Liu et al., 2005). Under elevated O_3, the changes in substrate quality and quantity could alter microbial metabolism and therefore soil C and nutrient cycling. Several studies indicated that O_3 suppressed soil enzyme activities (Pritsch et al., 2009; Chung et al., 2006). However, the impact of O_3 on litter decomposition was inconsistent and varied among species, sites and exposure length. Similarly, O_3 had inconsistent impacts on dynamics of micro and macro nutrients (US EPA, 2012a, section 9.4.6).

Studies from the Aspen FACE experiment suggested that the response of below-ground C cycle to O_3 exposure, such as litter decomposition, soil respiration and soil C content, changed over time. For example, in the early part of the experiment (1998-2003), O_3 had no impact on soil respiration but reduced the formation rates of total soil C under elevated CO_2. However,

after 10-11 years of exposure, O_3 was found to increase soil respiration but have no significant impact on soil C formation under elevated CO_2 (US EPA, 2012a, section 9.4.6).

5.5.5 Community Composition

In the 2006 O_3 AQCD, the impact of O_3 exposure on species competition and community composition was assessed. Ozone was found to cause a significant decline in ponderosa and Jeffrey pine in the San Bernardino Mountains in southern California. Ozone exposure also tended to shift the grass-legume mixtures in favor of grass species (US EPA, 2006). Since the 2006 O3 AQCD, more evidence has shown that O_3 exposure changed the competitive interactions and could lead to loss of O_3-sensitive species or genotypes. Studies at plant level found that the severity of O_3 damage on growth, reproduction and foliar injury varied among species, which provided the biological plausibility for the alteration of community composition. Additionally, research since the last review has shown that O_3 can alter community composition and diversity of soil microbial communities (US EPA, 2012a, section 9.4.7).

The decline of conifer forests under O_3 exposure was continually observed in several regions. Ozone damage was believed to be an important causal factor in the dramatic decline of sacred fir in the valley of Mexico (de Lourdes de Bauer and Hernandez-Tejeda, 2007), as well as cembran pine in southern France and the Carpathian Mountains (Wieser et al., 2006). Results from the Aspen FACE site indicated that O_3 could alter community composition of broadleaf forests as well. At the Aspen FACE site, O_3 reduced growth and increased mortality of a sensitive aspen clone, while the O_3-tolerant clone emerged as the dominant clone in the pure aspen community. In the mixed aspen-birch and aspen-maple communities, O_3 reduced the competitive capacity of aspen compared to birch and maple (Kubiske et al., 2007) (US EPA, 2012a, section 9.4.7).

The tendency for O_3 exposure to shift the biomass of grass-legume mixtures in favor of grass species was reported in the 2006 O_3 AQCD and has been generally confirmed by recent studies. However, in a high elevation mature/species-rich grass-legume pasture, O_3 fumigation showed no significant impact on community composition (Bassin et al., 2007b) (US EPA, 2012a, section 9.4.7).

Ozone exposure altered the community composition of not only plant species, but also microorganisms. The shift in community composition of bacteria and fungi has been observed in both natural and agricultural ecosystems, although no general patterns could be identified (Kanerva et al., 2008; Morsky et al., 2008; Kasurinen et al., 2005) (US EPA, 2012a, section 9.4.7).

5.5.6 Insects and Other Wildlife

Recent information on O_3 effects on insects and other wildlife is limited to a few species, and there is no consensus on how these organisms respond to elevated O_3. Studies published since the last review show impacts of elevated O_3 on both species-level responses (reproduction, growth, feeding behavior) and community and ecosystem-level responses (population growth, abundance, shift in community structure) in some insects and soil fauna. Changes in ecologically important behaviors such as feeding and thermoregulation have recently been observed with O_3 exposure in amphibians and reptiles, however, these responses occur at concentrations of O_3 much higher than ambient levels.

Recent information available since the last review considers the effects of O_3 on chemical signaling in insect and wildlife interactions. Specifically, studies on O_3 effects on pollination and seed dispersal, defenses against herbivory and predator-prey interactions all consider the ability of O_3 to alter the chemical signature of VOCs emitted during these pheromone-mediated events. The effects of O_3 on chemical signaling between plants, herbivores and pollinators as well as interactions between multiple trophic levels comprise an emerging area of study that may result in further elucidation of O_3 effects at the species, community and ecosystem levels (US EPA, 2012a, section 9.4.9).

5.6 CONSIDERATIONS REGARDING ADVERSITY IN PUBLIC WELFARE CONTEXT

The 2008 final rule recognized that the statute requires that a secondary standard be protective against only those known or anticipated O_3 effects that are "adverse" to the public welfare, not all identifiable O_3-induced effects. Unlike the use of the terms adverse, injury or damage in the scientific literature, in the NAAQS policy context, these terms have been interpreted in a particular way. Specifically, O_3-induced "injury" to vegetation has been defined as encompassing all plant reactions, including reversible changes or changes in plant metabolism (e.g., altered photosynthetic rate), altered plant quality or reduced growth that does not impair the intended use or value of the plant. In contrast, "damage" has been defined to include only those injury effects that reach sufficient magnitude as to also reduce or impair the intended use or value of the plant to the public and thus potentially become adverse to the public welfare. Examples of vegetation effects that have been classified as damage include reductions in aesthetic values (e.g., foliar injury in ornamental species) as well as losses in terms of weight, number, or size of harvestable plant parts. For example, biomass loss in tree species can be considered damage or adverse to the public welfare if it includes slower growth in species harvested for timber or other fiber uses. In the context of evaluating effects on single plants or

species grown in monocultures such as managed forests, this construct continues to remain useful (73 FR 16492/96).

However, given the increasing scientific literature linking O_3 effects on plants or species to effects at the community or ecosystem level, as discussed above in section 5.5, a more expansive construct or paradigm of what constitutes O_3 "damage" beyond that of the individual or species level is appropriate. A number of broader paradigms have been discussed in the literature (72 FR 37890), and in the 2008 review, the Administrator expressed support for using such a broader paradigm (73 FR 16492/96).

Since the 2008 O_3 review, EPA's approach to assessing adversity to the public welfare has continued to evolve. In particular, the concept of ecosystem services has been incorporated into this broader paradigm. An extensive look at the range of services than can be provided by ecosystems is described in the Millennium Ecosystem Assessment (MEA, 2005) (see discussion in section 5.5 above). Ecosystem services can be generally defined as the benefits that individuals and organizations obtain from ecosystems. EPA has defined ecological goods and services as the "outputs of ecological functions or processes that directly or indirectly contribute to social welfare or have the potential to do so in the future. Some outputs may be bought and sold, but most are not marketed" (77 FR 20232). The most recent secondary NAAQS reviews have recognized that changes in ecosystem services may be used to aid in characterizing a known or anticipated adverse effect to public welfare and that an evaluation of adversity to the public welfare might consider the likelihood, type, magnitude, and spatial scale of the effect, as well as the potential for recovery and any uncertainties relating to these conditions (US EPA, 2009, Appendix 8; 77 FR 20231). In the context of this review, ecosystem services are being evaluated and assessed in the REA to determine the possible benefits received from ecosystem resources and how those benefits might be expected to change under different air quality scenarios (US EPA, 2012c, chapter 6).

In addition, to the above considerations regarding adversity, in the last review the Administrator also recognized that the public welfare significance of O_3-induced effects on sensitive vegetation growing within the U.S. can vary, depending on the nature of the effect, the intended use of the sensitive plants or ecosystems, and the types of environments in which the sensitive vegetation and ecosystems are located. Any given O_3-related effect on vegetation and ecosystems (e.g., biomass loss, foliar injury), therefore, may be judged to have a different degree of impact on the public depending, for example, on whether that effect occurs in a Class I area, a city park, or commercial cropland. In the 2008 review, the Administrator judged it appropriate that this variation in the significance of O_3-related vegetation effects should be taken into

consideration in judging the level of ambient O_3 that is requisite to protect the public welfare from any known or anticipated adverse effects (73 FR 16496).

5.7 CONSIDERATIONS REGARDING OTHER WELFARE EFFECTS

5.7.1 Ozone Effects on Climate Change

Tropospheric O_3 is a major greenhouse gas, third in importance after CO_2 and CH_4. While the developed world has successfully reduced emissions of O_3 precursors in recent decades, many developing countries have experienced large increases in precursor emissions and these trends are expected to continue, at least in the near term. Projections of radiative forcing due to changing O_3 over the 21st century show wide variation, due in large part to the uncertainty of future emissions of source gases. In the near-term (2000-2030), projections of O_3 radiative forcing range from near zero to +0.3 W/m^2, depending on the emissions scenario (Stevenson et al., 2006). Reduction of tropospheric O_3 concentrations could therefore provide an important means to slow climate change in addition to the added benefit of improving surface air quality (US EPA, 2012a, section 10.5).

It is clear that increases in tropospheric O_3 lead to warming. However the precursors of O_3 also have competing effects on the greenhouse gas CH_4, complicating emissions reduction strategies. A decrease in CO or VOC emissions would enhance OH concentrations, shortening the lifetime of CH_4, while a decrease in NO_X emissions could depress OH concentrations in certain regions and lengthen the CH_4 lifetime (US EPA, 2012a, section 10.5).

Abatement of CH_4 emissions would likely provide the most straightforward means to address climate change since CH_4 is itself an important precursor of background O_3 (West et al., 2007; West et al., 2006; Fiore et al., 2002). A reduction of CH_4 emissions would also improve air quality in its own right. A set of global abatement measures identified by West and Fiore (2005) could reduce CH_4 emissions by 10% at a cost savings, decrease background O_3 by about 1 ppb in the Northern Hemisphere summer, and lead to a global net cooling of 0.12 W/m^2. West et al. (2007) explored further the benefits of CH_4 abatement, finding that a 20% reduction in global CH_4 emissions would lead to greater cooling per unit reduction in surface O_3, compared to 20% reductions in VOCs or CO (US EPA, 2012a, section 10.5).

Important uncertainties remain regarding the effect of tropospheric O_3 on future climate change. To address these uncertainties, further research is needed to: (1) improve knowledge of the natural atmosphere; (2) interpret observed trends of O_3 in the free troposphere and remote regions; (3) improve understanding of the CH_4 budget, especially emissions from wetlands and agricultural sources, (4) understand the relationship between regional O_3 radiative forcing and

regional climate change; and (5) determine the optimal mix of emissions reductions that would act to limit future climate change (US EPA, 2012a, section 10.5).

The IPCC has estimated the effect of the tropospheric O_3 change since preindustrial times on climate has been estimated to be about 25-40% of the anthropogenic CO_2 effect and about 75% of the anthropogenic CH_4 effect. There are large uncertainties in the radiative forcing estimate attributed to tropospheric O_3, making the effect of tropospheric O_3 on climate more uncertain than the effect of the long-lived greenhouse gases (US EPA, 2012a, section 10.5).

Radiative forcing does not take into account the climate feedbacks that could amplify or dampen the actual surface temperature response. Quantifying the change in surface temperature requires a complex climate simulation in which all important feedbacks and interactions are accounted for. As these processes are not well understood or easily modeled, the surface temperature response to a given radiative forcing is highly uncertain and can vary greatly among models and from region to region within the same model (US EPA, 2012a, section 10.5).

5.7.2. UV-B Radiation Effects on Ecosystems and Materials

UV radiation emitted from the Sun contains sufficient energy when it reaches the Earth to break (photolyze) chemical bonds in molecules, thereby leading to damaging effects on living organisms and materials. Atmospheric O_3 plays a crucial role in reducing exposure to solar UV radiation at the Earth's surface. Ozone in the stratosphere is responsible for the majority of this shielding effect, as approximately 90% of total atmospheric O_3 is located there over mid-latitudes. Ozone in the troposphere provides supplemental shielding of radiation in the wavelength band from 280-315 nm, referred to as UV-B radiation (US EPA, 2012a, section 10.4.1). UV-B radiation has important effects on ecosystems and is associated with materials damage. There is a lack of published studies that critically examine the incremental welfare effects (adverse or beneficial) attributable specifically t3o changes in UV-B exposure resulting from perturbations in tropospheric O_3 concentrations. While the effects are expected to be small, they cannot yet be critically assessed within reasonable uncertainty (US EPA, 2012a, section 10.4.4, 10.5).

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6. CONSIDERATION OF EXPOSURE AND RISK ASSESSMENTS

In order to put O_3-related vegetation and ecosystems effects information discussed in the ISA into the context of welfare risks at the national scale, the first draft Welfare REA has performed analyses to estimate O_3 exposures to vegetation and ecosystems and O_3-associated risks related to these welfare effects across the United States, including impacts in federal Class I case study areas (US EPA, 2012b). The first draft REA has estimated the O_3 exposures and welfare risks that are associated with recent air quality and with air quality adjusted to simulate just meeting the current O_3 standard (US EPA, 2012b). The second draft and final REA will also include estimates of O_3 exposures and risks associated with air quality adjusted to simulate just meeting potential alternative O_3 standards.[1]

The first draft REA has identified the following goals for the exposure and risk assessments: (1) to provide estimates of the ecological effects of O_3 exposure across a range of environments; (2) to provide estimates of ecological effects within selected case study areas; (3) to provide estimates of the effects of O_3 exposure on specific urban and non-urban ecosystem services based on the causal ecological effects; and (4) to develop a better understanding of the response of ecological systems and ecosystem services to changing levels of O_3 exposure to inform the PA regarding alternative standards that might be considered. This quantitative exposure and risk assessment builds on the approach used and lessons learned in the last O_3 risk assessment and focuses on improving the characterization of the overall confidence in the risk estimates, including related uncertainties, by incorporating a number of enhancements, in terms of both the methods and data used in the analyses. This assessment considers a variety of welfare endpoints for which, in staff's judgment, there is adequate information to develop quantitative risk estimates that can meaningfully inform the review of the secondary O_3 NAAQS (US EPA, 2012c, section 1.2).

Air quality inputs to the exposure and risk assessments include (1) ambient monitoring data for all Air Quality Systems (AQS) monitors in the U.S. for several relevant metrics for 2006-2010; (2) a CMAQ model results for 2007; and (3) a national-scale spatial surface generated by fusing 2006-2008 measured ambient O_3 data for all AQS monitors in the U.S. with the 2007 CMAQ model simulation for the three-year period of 2006-2008 and for each individual year within that period. The generated national-scale spatial surface provides estimates of W126 concentrations throughout the U.S. for 2006-2008 and of scenarios of just

[1]Air quality simulations are meant to provide perspective on the O_3-associated exposures and welfare risks under different air quality scenarios. These simulations do not reflect any consideration of specific control programs or strategies designed to achieve the reductions in emissions required to meet the specified standards. Further, these simulations do not represent predictions of when, whether, or how areas might meet the specified standards.

meeting the current O_3 standard of 0.075 ppm. The 2006-2008 W126 national-scale "fused" spatial surface reflects changes in the distribution of O_3 air quality estimated to occur when an area just meets the current O_3 NAAQS.

Simulation of just meeting the current O_3 standard is accomplished in the first draft REA using a quadratic rollback method, similar to that used in the previous risk and exposure analysis for the 2008 O_3 NAAQS review (U.S. EPA, 2007a,b,c). In evaluating just meeting the current standard, the first draft REA focuses on air quality changes that are likely to occur as the U.S. puts in place programs to meet the standard. As such, the REA uses U.S. background concentrations as a floor for the quadratic rollback. The first draft REA also explores alternative simulation approaches based on modeled sensitivities of O_3 to U.S. emissions. These alternative approaches, which will be evaluated more fully in the second draft REA,[2] will remove the need for imposing a specific floor to prevent adjustments beyond those likely to occur due to U.S. emissions reductions.

In selecting welfare effects endpoints on which to base estimates of O_3-related impacts, the first draft REA considers the weight-of-evidence conclusions from the ISA. Specifically, the first draft REA notes the ISA conclusions that there is a causal relationship between O_3 exposure and visible foliar injury, reduced growth and productivity and alteration of below-ground biogeochemical cycles and likely to be a causal relationship between O_3 exposure and reduced carbon sequestration, alteration of terrestrial ecosystem water cycling, and community composition. In light of these conclusions, the first draft REA estimates vegetation effects in terms of relative biomass loss following cumulative, seasonal O_3 exposures, and provides preliminary estimates of the impacts of relative biomass loss on several ecosystem services associated with forest ecosystems. The first draft REA also provides information on the geographic extent of vegetation species that are sensitive to visible foliar injury, although estimates of the magnitude of that injury under recent ozone conditions and after just meeting the current standard will not be available until the second draft REA. The remainder of this chapter discusses the assessment of O_3 exposures (section 6.1) and preliminary O_3-associated vegetation risks (section 6.2) for recent O_3 air quality concentrations and for O_3 air quality adjusted to simulate just meeting the current 8-hour O_3 standard.

[2]In the second draft, the REA will evaluate approaches for simulating attainment of current and alternative standards that are based on modeling the response of O_3 concentrations to reductions in anthropogenic NOx and VOC emissions, using the Higher-order Decoupled Direct Method (HDDM) capabilities in the Community Multi-scale Air Quality (CMAQ) model. This modeling incorporates all known emissions, including emissions from non-anthropogenic sources and anthropogenic emissions from sources in and outside of the U.S. As a result, the need to specify values for U.S. background is not necessary, as it is incorporated in the modeling directly. The evaluation of this new approach is presented in Chapter 4 of the draft REA (US EPA, 2012b) and in Simon et al. (2012).

Two additional analyses have also been conducted. These assessments include (1) a simulation of changes in urban forest structure, functions and values using the i-Tree version 4.0 (i.e., i-Tree Eco, previously known as UFORE. The Urban Forest Effects (UFORE) which contains protocols to measure and monitor urban forests as well as estimate ecosystem functions and values and (2) a simulation of market outcomes under alternative O_3 concentrations using the Forest and Agricultural Sector Optimization Model with Greenhouse Gases (FASOMGHG). [3] These results, along with assessments of visible foliar injury and newly incorporated additional federal Class 1 case study and critical habitat area assessments in the second draft REA will be fully considered in the second draft PA.

6.1 EXPOSURE

6.1.1 Monitoring and Air Quality

State and local monitoring agencies operate O_3 monitoring sites at various locations, depending on the size of the area and typical peak O_3 concentrations (US EPA, 2012a, sections 3.5.6.1, 3.7.4). In 2010, there were 1,250 State and local O_3 monitors reporting concentrations to EPA (US EPA, 2012a, Figures 3-21 and 3-22). Ozone monitors are only required in Metropolitan Statistical Areas (MSAs) with populations over 350,000.[4] Since O_3 concentrations decrease significantly in the colder parts of the year in many areas, O_3 is required to be monitored only during the "O_3 season," which varies by state (US EPA, 2012a, section 3.5.6 and Figure 3-20).[5] In 2010, there were approximately 112 monitoring sites being operated in rural areas. These sites included 15 National Core (NCore) monitors, 80 Clean Air Status and Trends Network (CASTNET) monitors, and 17 Portable O_3 Monitoring Systems (POMS) network monitors operated by the National Park Service (NPS). The locations of these monitors are shown in Figure 6-1 (US EPA, 2012c, figure 4-2).

As discussed in chapter 1 above and in chapter 3 of the ISA, rural monitoring sites tend to be less directly affected by anthropogenic pollution sources than urban sites, although rural sites can be affected by transport of O_3 or O_3 precursors from upwind urban areas and by local anthropogenic sources such as motor vehicles, power generation, biomass combustion, or oil and gas operations (US EPA, 2012a, section 3.6.2). In addition, O_3 tends to persist longer in rural

[3]These analyses are included in a revised version of chapter 6 of the Welfare REA and its associated appendices that is being released in parallel with this first draft Policy Assessment.

[4]The current monitor and probe siting requirements have an urban focus and do not address siting in non-urban, rural areas. States may operate O_3 monitors in non-urban or rural areas to meet other objectives (e.g., support for research studies of atmospheric chemistry or ecosystem impacts).

[5]Some States and Territories operate O_3 monitors year-round, including Arizona, California, Hawaii, Louisiana, Nevada, New Mexico, Puerto Rico, Texas, American Samoa, Guam and the Virgin Islands.

than in urban areas due to lower rates of chemical scavenging in non-urban environments. At higher elevations, increased O_3 concentrations can also result from stratospheric intrusions (US EPA, 2012a, sections 3.4, 3.6.2). As a result, O_3 concentrations measured in some rural sites can be higher than those measured in nearby urban areas (US EPA, 2012a, section 3.6.2) and the ISA concludes that cumulative exposures for humans and vegetation in rural areas can be substantial, and they are often higher than cumulative exposures in urban areas (US EPA, 2012a, section 3.7.5).

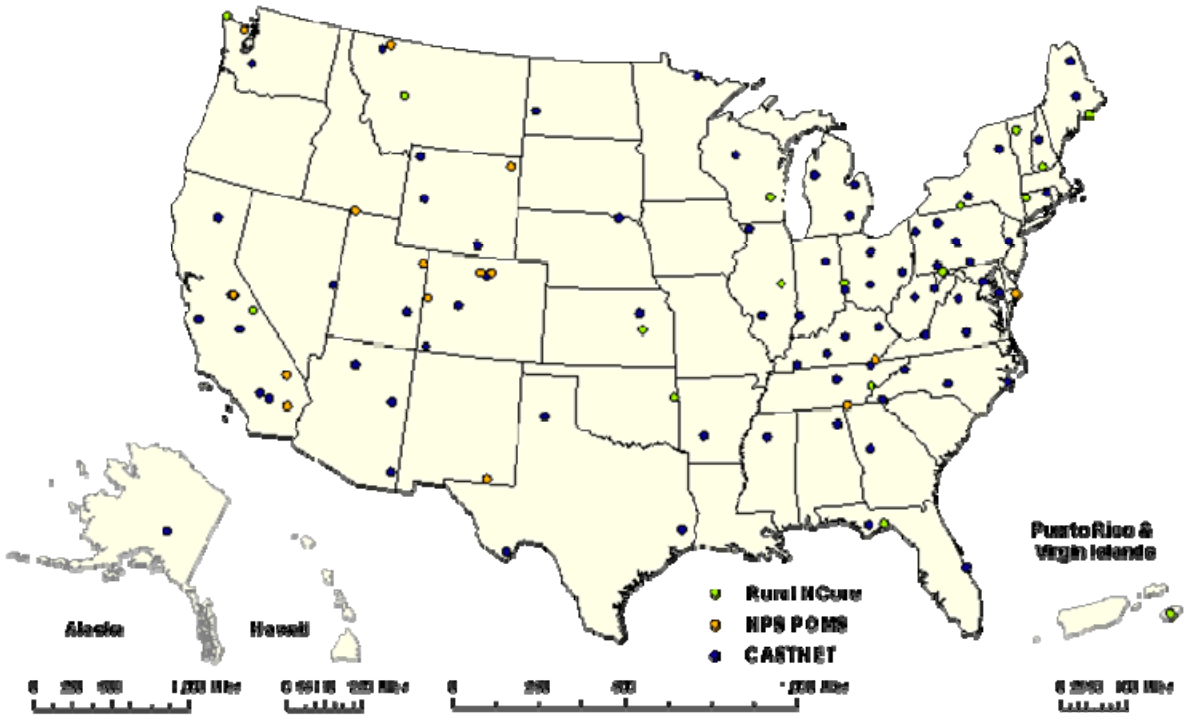

Figure 6-1 U.S. Rural NCore, CASTNET and NPS POMS sites in 2010 (U.S. EPA, 2012a, Figure 3-22)

6.1.2 Approach to Estimating Exposures

Recent O_3 air quality information from both monitored and modeled sources is used to assess current exposures, as well as to estimate the relative change in exposure resulting from adjusting O_3 concentrations to simulate just meeting the current O_3 standard. The air quality monitoring data used to inform the first draft O_3 Risk and Exposure Assessments are hourly O_3 concentrations collected between 1/1/2006 and 12/31/2010 from all US monitors meeting EPA's

siting, method, and quality assurance criteria and extracted from EPA's AQS database[6]. These exposures are assessed both in terms of the current secondary 8-hour average form and in terms of the cumulative concentration weighted W126 exposure metric as it was proposed in 2007 and 2010 and which EPA staff continues to conclude is appropriate for consideration in this review (Chapter 5 above).

In addition to the selection of a the W126 metric, which uses a logistic weighting function to place less emphasis on exposure to low concentrations and more emphasis on exposure to high concentrations (Lefohn et al, 1988), as the form of the standard (US EPA, 2012a, section 9.5.2, equation 9-1), EPA staff has again revisited the appropriateness of the diurnal and seasonal exposure periods (averaging times) defined in previous reviews. As discussed above in chapter 5, staff has again concluded that a 12 hour diurnal (defined as 8:00 am to 8:00 pm local time) and maximum consecutive 3month seasonal exposure period remain appropriate.

6.1.3 Exposure Surface Generation

Due to the fact that the O_3 monitoring network is limited in some parts of the country, especially in rural areas, there was a need to generate a national O_3 exposure surface. The welfare risk and exposure assessment therefore analyzed a national-scale spatial surface of W126 for the three-year period of 2006-2008 and for each individual year: 2006, 2007 and 2008. This analysis employed a data fusion approach to take advantage of the accuracy of monitor observations and the comprehensive spatial information of the CMAQ modeling system to create a national-scale "fused" spatial surface of seasonal average O_3. The spatial surface is created by fusing 2006-2008 measured ambient O_3 data for all AQS monitors in the U.S. with the 2007 CMAQ model simulation run for a 12 km gridded domain, using the EPA's Model Attainment Test Software (MATS; Abt Associates, 2010), which employs the enhanced Voronoi Neighbor Averaging (eVNA) technique (Timin et al., 2010) enhanced with information on the spatial gradient of O_3 provided by CMAQ results. The generated national-scale spatial surface provides estimates of W126 concentrations throughout the U.S. for 2006-2008 and for scenarios of just meeting the current O_3 standard of 0.075 ppm. The ambient 2006-2008 W126 national-scale "fused" spatial surface is shown in Figure 6-2. More detail on the ambient measurements and the 2007 CMAQ model simulation, as well as the spatial fusion technique, can be found in Wells et al. (2012).

[6]EPA's AQS database is a state-of-the-art repository for many types of air quality and related monitoring data. AQS contains monitoring data for the six criteria pollutants dating back to the 1970's, as well as more recent additions such as air toxics, meteorology, and quality assurance data. At present, AQS receives O_3 monitoring data collected hourly from over 1,300 monitors, and quality assured by one of over 100 state, local, or tribal air quality monitoring agencies.

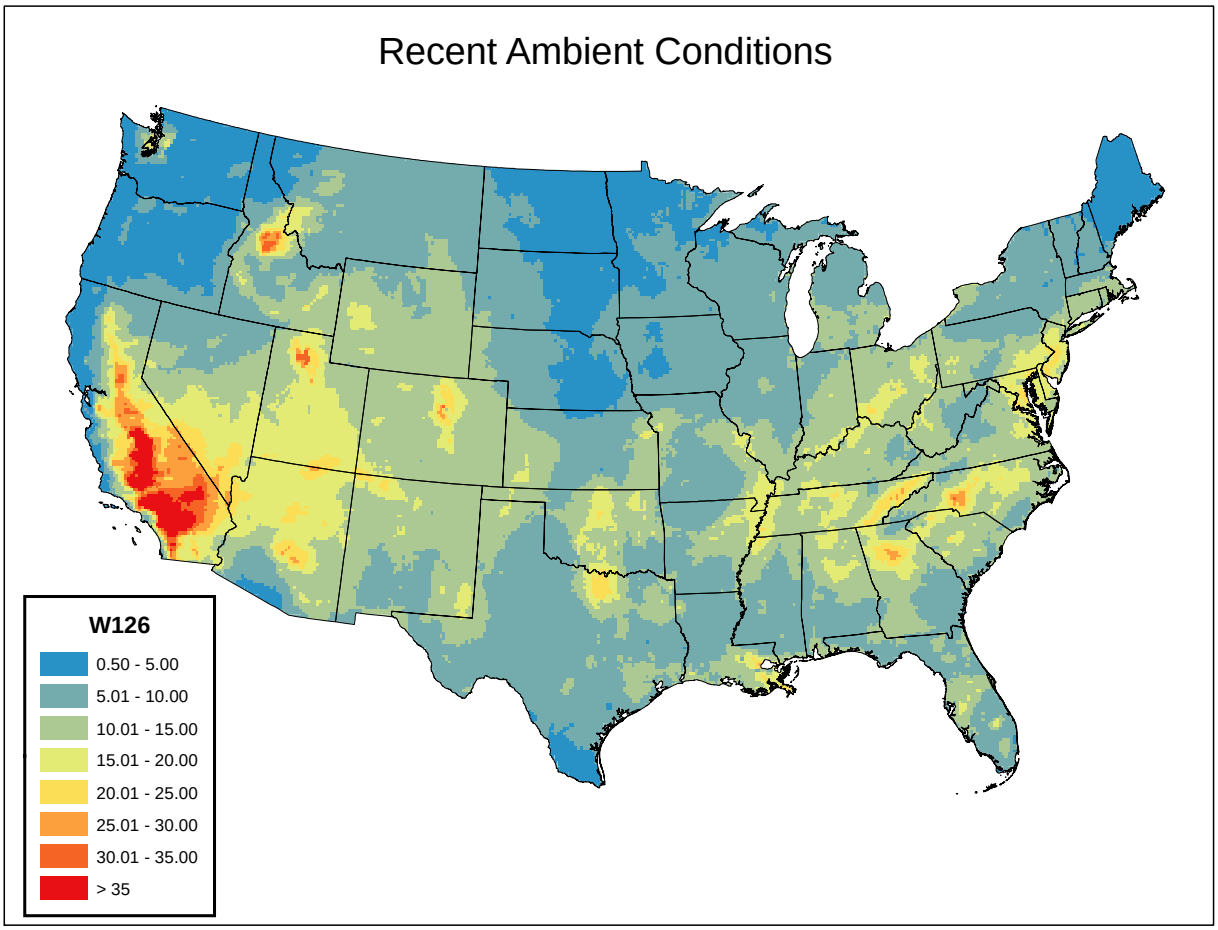

Figure 6-2. National Ozone Exposure Surface of Recent (2006 – 2008) Ambient W126

To generate a national-scale spatial surface that represents 2006-2008 W126 concentrations after simulating just meeting the current NAAQS, the spatial surface for 2006-2008 air quality was adjusted to reflect the rolled-back W126 monitor concentrations at non-attaining monitors in urban areas. To do this, the rolled-back W126 monitor values were inserted into the spatial surface at the monitor locations and the W126 surface was smoothed using the Voronoi Neighbor Averaging (VNA) spatial averaging technique to minimize any sharp gradients between the national-scale spatial surface that represents 2006-2008 W126 concentrations and the rolled-back W126 monitor concentrations.

Figure 6-3 shows the national-scale 2006-2008 W126 surface that reflects simulation of just meeting the current standard of 0.075 ppm. The state of California was most affected by the rollback, with average changes in W126 of around 20 ppm-hours. Other areas with notable changes include the areas around Atlanta, Charlotte, Denver, Phoenix, and Salt Lake City and the

area between Washington, D.C., and Boston (all areas that had relatively high 8-hour O_3 concentrations above the current standard).

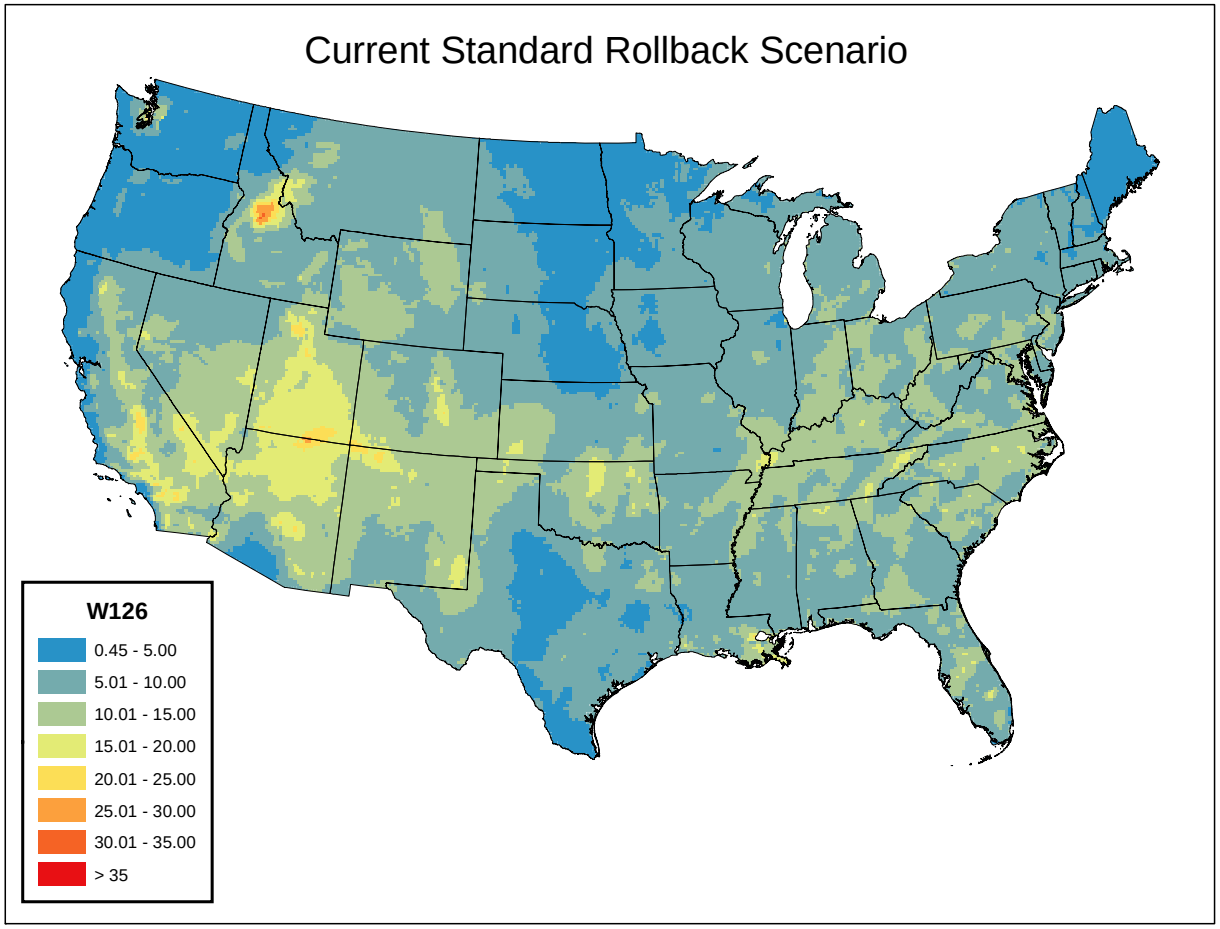

Figure 6-3. National Ozone Exposure Surface Simulating Just Meeting the Current Standard

6.2 CONSIDERATION OF O_3 RISK ESTIMATES

6.2.1 Approaches to Assessing Risks

In the previous review of the secondary standards, the focus of the ecological risk assessment was on estimation of changes in tree seedling biomass and agricultural crop yields and resulting impacts on forest and agricultural production as well as qualitative consideration of effects on ecosystem services. As mentioned above, in this review, we are focusing on those effects determined to have a causal or likely to be a causal relationship to O_3 exposure.

Therefore, we are continuing to focus on the quantitative assessment of O_3 impacts to trees, including individual tree species relative biomass loss, visible foliar injury, aggregated and scaled relative biomass loss, modeled impacts to trees in urban settings, and ecosystem case studies. We have placed less focus on impacts to agricultural ecosystems given the highly managed nature of those systems; however, in assessing impacts of O_3 on ecosystem services related to changes in forest yields, we include the impacts of O_3 on both forest and agricultural production in order to properly model the interactions between the two production systems in determining land use decisions. In addition, we are expanding the discussion of ecosystem services to include a broader array of impacts, both quantitative and qualitative, resulting from known or anticipated effects of O_3 on ecosystem functions. EPA has begun using an ecosystem services framework to help inform determinations of the adversity to public welfare associated with changes in ecosystem functions (Rea et al., 2012).

These services may be characterized as supporting services that are necessary for all other services (e.g., primary production); cultural services including existence and bequest values, aesthetic values, and recreation values, among others; provisioning services (e.g., food and timber); and regulating services such as climate regulation or hydrologic cycle (MEA, 2005). The REA identifies those ecosystem services that are associated with the ecological effects caused or likely to be caused by O_3 exposure. For the first draft REA, ecosystem services potentially impacted by O_3 were able to be quantified for two classes of ecosystem services including those associated with commercial forestry and those associated with urban trees. These cover only a small portion of the total ecosystem services that might be impacted by O_3, and the REA provides contextual information regarding the nature and magnitude of additional ecosystem services that may be impacted by O_3 exposures, noting that the specific magnitude of the impact of O_3 on those ecosystem services is unknown.

6.2.2 Risk of Biomass Loss in Individual Sensitive Tree Species

The previous O_3 AQCDs (US EPA, 1996, 2006) and current third draft ISA (US EPA, 2012a) conclude that there is strong and consistent evidence that ambient concentrations of O_3 decrease photosynthesis and growth in numerous plant species across the U.S. The quantitative exposure-response relationships described in the 2006 O_3 AQCD have not changed in the current draft ISA, with the exception of the addition of eastern cottonwood, and their continued usefulness and relevance has been further confirmed by the EPA staff analyses comparing the performance and predictive capability of OTC-derived C-R functions using data from FACE studies (US EPA, 2012a, section 9.6.3). Therefore, EPA staff concludes that these response functions provide an adequate basis for quantifying biomass loss damages in the risk assessment.

The exposure-response functions summarized in the third draft ISA were computed using the W126 metric and cumulated over 90 days. The median response functions for relative biomass loss (RBL) for each of the 11 tree species used in the risk assessment are shown in Figure 6-4. Understanding the differences in the shapes of these curves can aid in understanding the results of analyses presented later in this chapter. From this figure it is clear that there is significant variability in O_3 sensitivity across studied species. Some species are extremely sensitive (eastern cottonwood and black cherry), even at very low levels of W126, while others appear to be relatively insensitive (Douglas fir and Virginia pine). Several species have response functions with gradual and consistent slopes, resulting in a more or less constant rate of change in RBL over a range of O_3 exposure consistent with ambient exposure levels. In contrast, other species have response functions that indicate large changes in RBL over a small range of O_3 concentrations and relatively small changes in RBL over other O_3 concentration ranges.

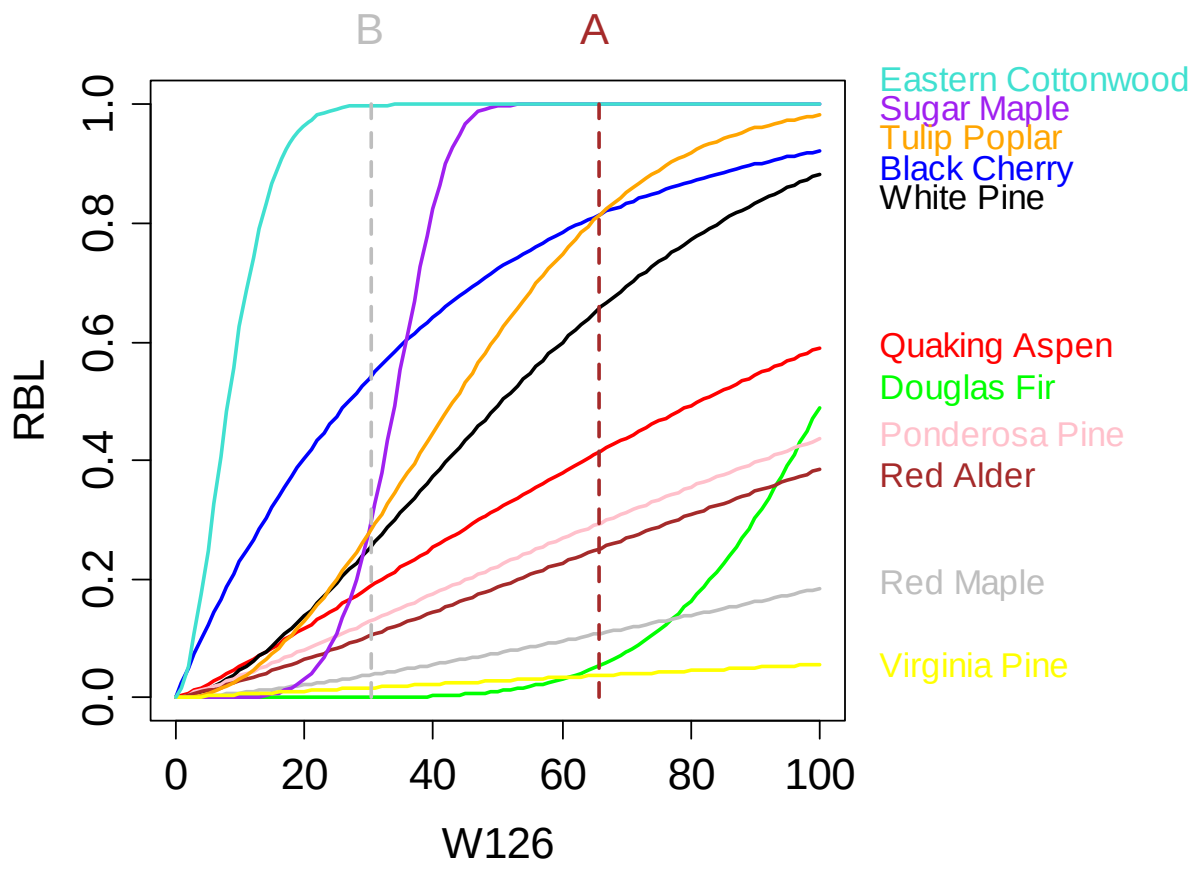

Figure 6-4. Relative Biomass Loss Concentration-Response Functions for 11 Tree species. The vertical dashed lines represent the maximum W126 values for (A) recent (2006 to 2008) conditions, and (B) just meeting the current standard.

The vertical dashed lines in Figure 6-4 represent the maximum W126 observed across the U.S. for the recent ambient exposure surface (brown dashed line) and simulated for the just meeting the current standard scenario (gray dashed line). The RBL value at the point where the response curve for each species intersects these lines represents the maximum potential RBL value for that species under the two O_3 exposure scenarios.

Figure 6-5 zooms in on the portion of Figure 6-4 that includes W126 values from zero up to a W126 of 30, which is close to the maximum W126 value after simulating just meeting the current standard. This figure is important in showing the predicted levels of RBL loss upon just meeting the current secondary standard. After simulating just meeting the current standard, maximum potential RBL exceeds 20 percent for a number of ecologically and economically important species, including sugar maple, black cherry, tulip poplar, and white pine.

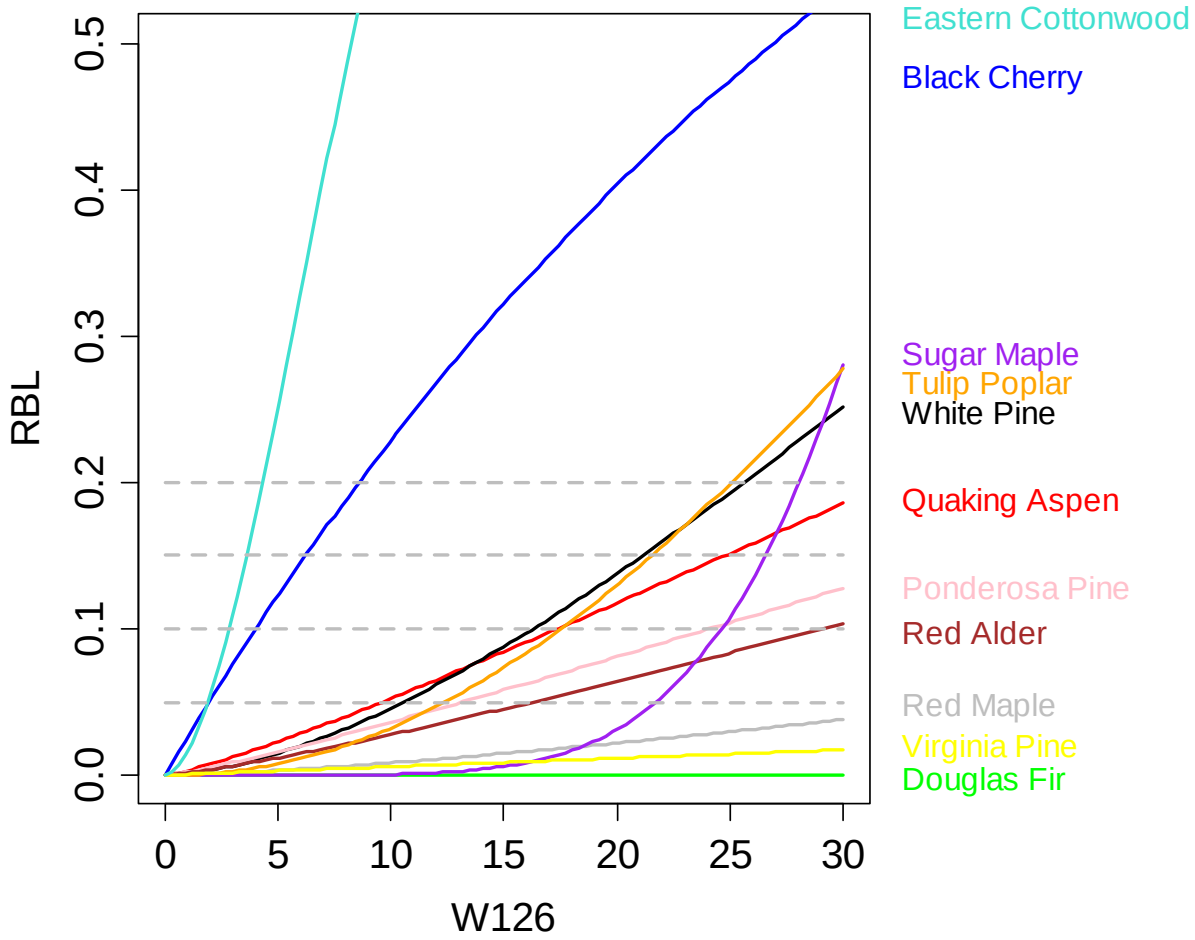

Figure 6-5. "Blow Up" View of Relative Biomass Loss Concentration-Response Functions for 11 Tree species. Gray Horizontal Lines show RBL Levels of 5%, 10%, 15%, and 20%.

Using the functions shown in Figure 6-4 with the air quality surfaces presented in Figures 6-2 and 6-3, staff generated median and maximum RBL values across the grid cells within each species range. Table 6-1 summarizes the results of the analyses for individual tree species under ambient conditions and simulated to meet the current standard. It is important to note that under the scenario of just meeting the current standard, taking into account O_3 exposures within the geographic range of each species, maximum RBL values for five species exceed10%, and for two species (eastern cottonwood and black cherry) exceed 40%.

Table 6-1. Summary of Tree Species Biomass Loss Analyses

Species	Median RBL (Ambient)	Maximum RBL (Ambient)	Median RBL (Current Standard)	Maximum RBL (Current Standard)
Eastern Cottonwood (*Populus deltoides*)	0.564	0.999	0.464	0.990
Black Cherry (*Prunus serotina*)	0.225	0.547	0.194	0.420
Quaking Aspen (*Populus tremuloides*)	0.039	0.377	0.035	0.189
Eastern White Pine (*Pinus strobus*)	0.034	0.226	0.028	0.150
Tulip Poplar (*Liriodendron tulipifera*)	0.045	0.291	0.030	0.138
Ponderosa Pine (*Pinus ponderosa*)	0.038	0.294	0.032	0.130
Red Alder (*Alnus rubra*)	0.005	0.118	0.005	0.106
Sugar Maple (*Acer saccharum*)	0.000	0.206	0.000	0.042
Red Maple (*Acer rubrum*)	0.009	0.039	0.007	0.028
Virginia Pine (*Pinus virginiana*)	0.008	0.018	0.006	0.011
Douglas Fir (Pseudotsuga menzeiesii)	0.000	0.0012	0.000	0.0006

The first draft REA also expanded on the analysis from the previous review by including metrics that weight the RBL for individual species by their relative abundance within forest ecosystems. These metrics provide one measure of the potential importance of species level O_3 impacts for overall forest ecosystem health. However, these importance weighted RBL metrics are most useful as relative indicators of changes in risk, and not as useful as absolute measures of ecosystem risk because 1) the units are not straightforward to interpret (as compared to RBL which is simply a percent of potential biomass), and 2) because we only have C-R functions for 11 different tree species, which represents a very small subset of the total plant species in most forest ecosystems, the aggregate O_3 impacts on most forest ecosystems are not well characterized. However, the proportional change in the importance weighted RBL values between just meeting the current standard and meeting potential alternative standards will be useful in evaluating the impacts of moving from the current 8-hour form to the W126 form, as well as evaluating potential alternative levels of the W126 standard. The importance weighted metrics are also useful in allowing us to focus on potential impacts on RBL and associated ecosystem services in geographic areas of interest, including selected federal Class I areas and

critical habitats. Analyses of alternative standard levels using these importance weighted RBL metrics will be included in the second draft REA, and will be evaluated in the second draft PA.

6.2.3 Risk of Foliar Injury Incidence

Visible foliar injury resulting from exposure to O_3 has been well characterized and documented over several decades for many tree, shrub, herbaceous, and crop species (US EPA, 2012a, 2006, 1996, 1984, 1978). Visible foliar injury symptoms are considered diagnostic as they have been verified experimentally in exposure-response studies using exposure methodologies such as open top chambers and free-air fumigation (see section 9.2 of the ISA for more detail on exposure methodologies). Although the majority of O_3-induced visible foliar injury occurrence has been observed on seedlings and small plants, many studies have reported visible injury to mature coniferous trees, primarily in the western U.S. (Arbaugh et al., 1998) and to mature deciduous trees in eastern North America (Schaub et al., 2005; Vollenweider et al., 2003; Chappelka et al., 1999a; Chappelka et al., 1999b; Somers et al., 1998; Hildebrand et al., 1996).

The first draft REA includes a limited screening analysis of risk of visible foliar injury based on an updating of a 2007 analysis done for the National Park Service (Kohut et al, 2007). This screening analysis focused on indicators of foliar risk including two O_3 exposure indices, a measure of soil moisture, and an indicator of the presence of O_3 sensitive species within a park. While this screening analysis provides some limited information regarding parks that may be likely to experience O_3 related foliar damages, it does not quantify the specific extent of visible foliar injury. The REA for the previous review included additional information regarding visible foliar damage based on the Forest Health Monitoring Program. We plan to update this assessment in the second draft REA based on data we expect to receive from the U.S. Forest Service, and will consider the results of that updated analysis in the second draft PA.

6.3 ECOSYSTEM SERVICES

As mentioned above, a number of analyses pertaining to the O_3 impacts on ecosystem services, i.e. those based on the i-Tree and FASOMGHG models, are being released in parallel with the first draft REA. The FASOMGHG analyses include estimates of impacts of O_3 on yields of O_3 sensitive commercial timber species and the resulting impact on the overall value of forest products, as well as providing estimates of the impacts on carbon storage in commercial forest ecosystems. The i-Tree analyses include estimates of the impacts of O_3 on carbon storage by urban trees, and the impacts of O_3 on air pollution removals by urban trees. While chapter 6 of the first draft REA provides important background discussion and limited preliminary results regarding risk to ecosystem services from O_3 exposures, EPA staff feels it is premature to bring

that discussion forward into this first draft PA. The second draft of the PA will include consideration of the results of the quantitative ecosystem risk analyses, as well as additional qualitative analyses including additional Class I area case study analyses, which are planned for incorporation into the second draft REA..

6.4 UNCERTAINTIES IN RISK ASSESSMENTS

In order to better interpret the results of the exposure and risk assessments described in the REA, and to help inform the Administrator regarding the appropriate weight to put on the results, a full and indepth discussion of the uncertainties associated with the REA analyses is important. Because of the preliminary nature of the results presented in this first draft, and because it is unclear at this time how the methodology for adjusting air quality to just attain the current and various alternative standards may change and what analyses will be most relevant to informing the range of options presented for the Administrator's consideration, this first draft PA does not include a discussion of uncertainties. This will be added in the second draft REA and PA.

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7. PRELIMINARY STAFF CONCLUSIONS REGARDING THE SECONDARY O_3 NAAQS

The purpose of this chapter is to present staff's preliminary considerations and conclusions regarding the adequacy and appropriateness of the current secondary O_3 standard and additional analyses that would be appropriate to inform consideration of potential alternative standards in the second draft PA, including additional exposure and risk analyses in the second draft Welfare REA. Our preliminary conclusions in this first draft chapter are based on the assessments and integrative synthesis of information presented in the third draft O_3 ISA, the exposure and risk analyses presented in the first draft Welfare REA, and the information presented above in chapters 5 and 6. In the final PA, this chapter will present staff's final considerations and conclusions for the Administrator to consider regarding the adequacy and appropriateness of the current secondary O_3 NAAQS and, if appropriate, staff's considerations and conclusions regarding the range of potential alternative standards that could be supported by the scientific evidence and exposure/risk information available in this review.

In this first draft PA, we consider the following overarching questions:

- **To what extent do the available scientific evidence and exposure/risk information support or call into question the adequacy and appropriateness of the public welfare protection afforded by the current secondary O_3 standard?**

- **What additional analyses would be appropriate to help inform consideration of potential alternative standards in the second draft of the PA?**

In considering our approach to developing preliminary conclusions regarding the adequacy and appropriateness of the secondary O_3 standard, we first note that the CAA charges the Administrator with setting secondary NAAQS that are "requisite" (i.e., neither more nor less stringent than necessary) to protect public welfare from any "known or anticipated adverse effects." In light of this requirement, we note that a decision on the adequacy of the public welfare protection provided by the current O_3 standard, and by potential alternative standards, will be a public welfare policy judgment in which the Administrator weighs the available evidence, exposure/risk information, and the uncertainties and limitations inherent in that evidence and information. Therefore, in developing preliminary conclusions in this first draft PA, we are mindful that the Administrator's ultimate judgments on the current and potential alternative standards will most appropriately reflect an interpretation of the available scientific evidence and exposure/risk information that neither overstates nor understates the strengths and limitations of that evidence and information.

Section 7.1 discusses the approach to reviewing the O_3 NAAQS in the last review and provides a general overview of the approach being taken in this review. Section 7.2 presents staff's preliminary considerations and conclusions regarding the adequacy and appropriateness of the current 8-hour O_3 secondary standard. Section 7.3 presents staff's preliminary considerations and conclusions regarding alternative secondary O_3 standards appropriate for further analyses in the second draft REA. In the second draft PA, section 7.4 will present a summary of staff's conclusions on the current standard and, if appropriate, on alternative standards for the Administrator's consideration. Section 7.5 will be added to outline key areas for future research and data collection to address key uncertainties identified in this review.

7.1 APPROACH TO REVIEWING THE SECONDARY O_3 NAAQS

Welfare effects, as defined in section 302(h) (42 U.S.C. 7602(h)) of the CAA, include, but are not limited to, "effects on soils, water, crops, vegetation, manmade 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." As in the last review, this review focuses on effects on O_3-sensitive vegetation, including especially natural vegetation as well as crops, since effects on these public welfare categories are well-studied and currently known to be of most concern at O_3 concentrations typically occurring in the U.S. Further, by adversely affecting natural vegetation, O_3 can adversely affect natural ecosystems and their components (e.g., soils, water, animals, and wildlife) as well as the services that such ecosystems provide. As discussed above in chapter 5, for other welfare effects categories, insufficient new information was available to inform consideration of the adequacy of the current secondary O_3 standard, and they are not discussed further, except in terms of research needs to be added in the next draft of this chapter.

This section discusses the approach taken to consider these O_3-related welfare effects in reviewing the secondary O_3 standard in the review completed in 2008 (section 7.1.1) and the approach being taken in the current review (section 7.1.2).

7.1.1 Approach Taken in 2008 Review

In the last review of the O_3 NAAQS, the Administrator revised the level of the 8-hour O_3 secondary standard to 0.075 ppm, making it identical to the revised primary standard. The Administrator's final decision on the secondary standard involved making a choice between the two fundamentally different options that had been proposed in 2007. In the 2007 proposal, the Administrator agreed with the conclusions drawn in the 2006 Criteria Document, the 2007 Staff Paper and by CASAC that the scientific evidence available in the 2008 review continued to demonstrate the cumulative nature of O_3-induced plant effects and the need to give greater

weight to higher concentrations. Thus, the Administrator proposed that a cumulative exposure index that differentially weights O_3 concentrations could represent a reasonable policy choice for a seasonal secondary standard to protect against the effects of O_3 on vegetation. The Administrator further agreed with both the 2007 Staff Paper and CASAC that the most appropriate cumulative, concentration-weighted form to consider in the 2008 review was the sigmoidally weighted W126 form, due to the recognition that there is no evidence in the literature for an exposure threshold that would be appropriate across all O_3-sensitive vegetation and that this form is unlikely to be significantly influenced by O_3 air quality within the range of PRB levels identified in the 2008 review. Thus, the Administrator proposed as one option to replace the 1997 8-hour average secondary standard form with the cumulative, seasonal W126 form**.** The Administrator also proposed a second option to revise the 1997 secondary standard by making it identical to the 8-hour primary standard proposed in 2007, which was proposed to be within the range of 0.070 to 0.075 ppm. In putting forward such a proposal, as discussed below, the Administrator focused on the decision made in the 1997 review, and the rationale for that decision that made the revised secondary standard identical to the revised primary standard.

The 2008 final rule reported that within the Administration at that time there had been a robust discussion of the strengths and weaknesses associated with each option that had been proposed in 2007. The process by which the Administrator reached his final conclusion is described in the 2008 final rule (73 FR 16497). The rationale for the decision presented in the 2008 final rule (73 FR 16499-16500) is described below.

In considering the appropriateness of establishing a new standard defined in terms of a cumulative, seasonal form, or revising the 1997 secondary standard by making it identical to the revised primary standard, the Administrator took into account the approach used by the Agency in the 1997 review, the conclusions of the 2007 Staff Paper, CASAC advice, and the views of public commenters. In giving consideration to the approach taken in the 1997 review, the Administrator first considered the 2007 Staff Paper analysis of the projected degree of overlap between counties with air quality expected to meet the revised 8-hour primary standard, set at a level of 0.075 ppm, and alternative levels of a W126 standard based on currently monitored air quality data. This analysis showed significant overlap between the revised 8-hour primary standard and selected levels of the W126 standard form being considered, with the degree of overlap between these alternative standards depending greatly on the W126 level selected and the distribution of hourly O_3 concentrations within the annual and/or 3-year average period.[1] On this basis, as an initial matter, the Administrator concluded that a secondary standard set identical

[1] Prior to publication of the 2008 final rule, EPA did further analysis of the degree of overlap to extend the 2007 Staff Paper analyses, and that analysis was available in the docket.

to the proposed primary standard would provide a significant degree of additional protection for vegetation as compared to that provided by the then-current 0.084 ppm secondary standard. In further considering the significant uncertainties that remain in the available body of evidence of O_3-related vegetation effects and in the exposure and risk analyses conducted for the 2008 rulemaking, and the difficulty in determining at what point various types of vegetation effects become adverse for sensitive vegetation and ecosystems, the Administrator focused his consideration on a level for an alternative W126 standard at the upper end of the proposed range (i.e., 21 ppm-hours). The 2007 Staff Paper analysis showed that at that W126 standard level, there would be essentially no counties with air quality that would be expected both to exceed such an alternative W126 standard and to meet the revised 8-hour primary standard – that is, based on this analysis of currently monitored counties, a W126 standard would be unlikely to provide additional protection in any monitored areas beyond that likely to be provided by the revised primary standard.

The Administrator also recognized that the general lack of rural monitoring data made uncertain the degree to which the revised 8-hour standard or an alternative W126 standard would be protective in those areas, and that there would be the potential for not providing the appropriate degree of protection for vegetation in areas with air quality distributions that result in a high cumulative, seasonal exposure but do not result in high 8-hour average exposures. While this potential for under-protection using an 8-hour standard was clear, the number and size of areas at issue and the degree of risk was hard to determine. However, the Administrator concluded at that time that an 8-hour standard would also tend to avoid the potential for providing more protection than is necessary, a risk that he concluded would arise from moving to a new form for the secondary standard despite significant uncertainty in determining the degree of risk for any exposure level and the appropriate level of protection, as well as uncertainty in predicting exposure and risk patterns.

The Administrator also considered the views and recommendations of CASAC and agreed that a cumulative, seasonal standard was the most biologically relevant way to relate exposure to plant growth response. However, as reflected in some public comments, he also judged that there remained significant uncertainties in determining or quantifying the degree of risk attributable to varying levels of O_3 exposure, the degree of protection that any specific cumulative, seasonal standard would produce, and the associated potential for error in determining the standard that will provide a requisite degree of protection -- i.e., sufficient but not more than what is necessary. Given these significant uncertainties, the Administrator concluded at that time that establishing a new secondary standard with a cumulative, seasonal

form would result in uncertain benefits beyond those afforded by the revised primary standard and therefore may be more than necessary to provide the requisite degree of protection.

Based on his consideration of the views discussed above, the Administrator judged in the 2008 rulemaking that the appropriate balance to be drawn was to revise the secondary standard to be identical in every way to the revised primary standard. Specifically, the Administrator revised the then-current 8-hour average 0.084 ppm secondary standard by making it identical to the revised 8-hour primary standard set at a level of 0.075 ppm. The Administrator believed that such a standard would be sufficient to protect public welfare from known or anticipated adverse effects and did not believe that an alternative cumulative, seasonal standard was needed to provide this degree of protection. The Administrator believed that this judgment appropriately considered the requirement for a standard that is neither more nor less stringent than necessary for this purpose.

7.1.2 Approach in the Current Review

In this review our approach to considering the adequacy and appropriateness of the current secondary O_3 standard, and to identifying a range of potential alternative secondary standards for consideration, draws from the approaches used in previous reviews. As discussed above, past approaches have been based most fundamentally on using information from O_3 vegetation effects studies and exposure and risk assessments to inform the selection of O_3 standards that, in the Administrator's judgment, protect the public welfare from any known or anticipated adverse effects. These fundamental considerations again are the basis for our approach in this review. Past approaches have also considered air quality analyses, based on monitored air quality data, of the projected degree of overlap between counties with air quality expected to meet the a secondary standard made identical to the primary standard and counties with air quality expected to meet alternative levels of a standard defined in terms of a biologically relevant, cumulative seasonal exposure index. In this review, we consider the implications of such analyses as a basis for reaching conclusions about the adequacy and appropriateness of the current secondary O_3 standard.

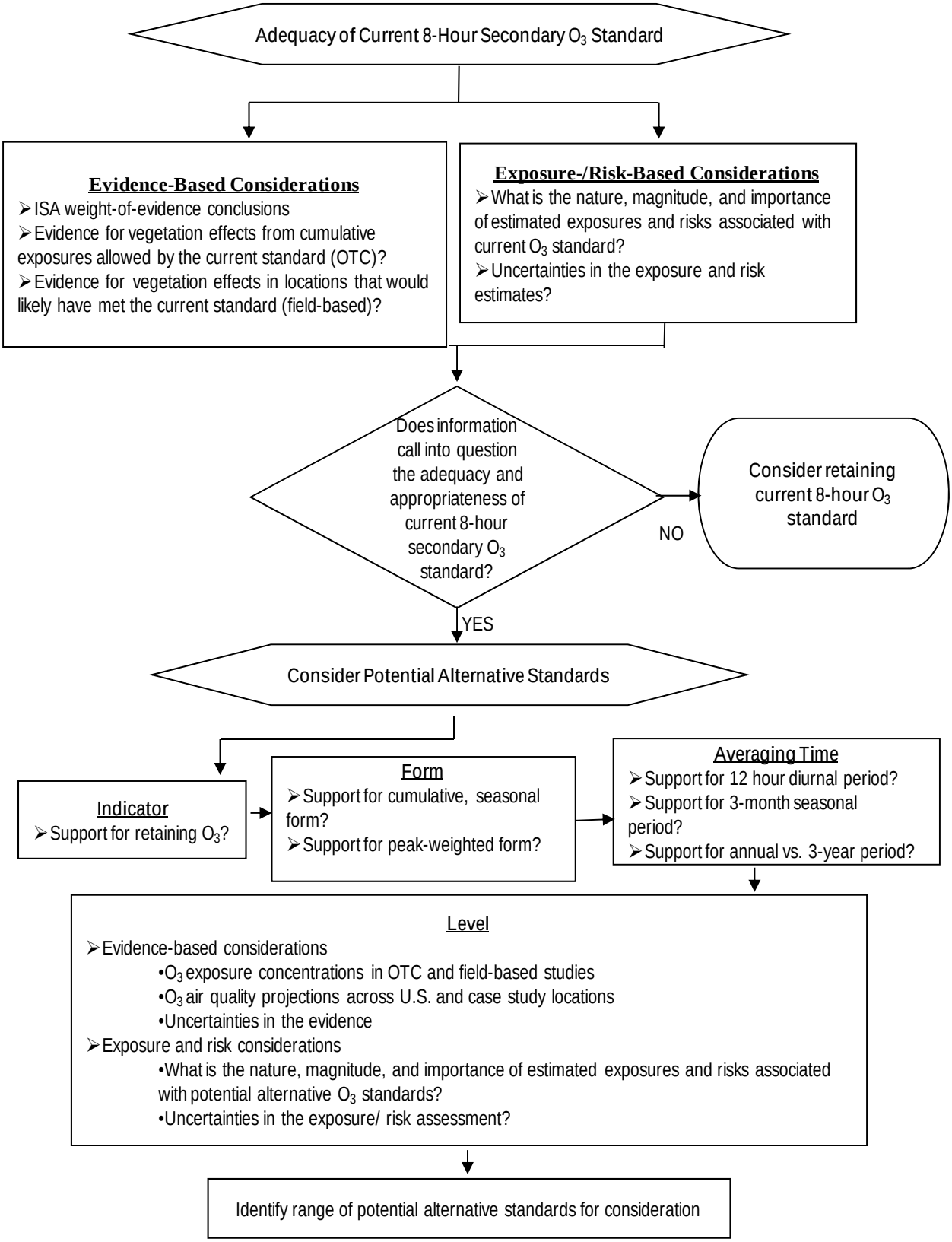
In evaluating whether the current secondary standard is adequate or whether consideration of revisions is appropriate, we are taking a weight-of-evidence approach that considers information across the variety of vegetation-related research areas evaluated in the ISA (e.g., visible foliar injury, tree growth and productivity, and ecosystem effects, including productivity and carbon storage, below ground processes, water cycling, and community composition). We are also considering assessments of air quality, exposures, and qualitative and quantitative risks associated with alternative air quality scenarios, which in the first draft REA includes recent air quality and air quality simulated to just meet the current secondary O_3

standard. With respect to vegetation effects information, we have considered the conclusions drawn at the end of the last review based on evidence from chamber, free air, gradient, model and field-based observation studies for a variety of vegetation effects endpoints in light of more recent evidence. We place greater weight on U.S. studies due to the often species-, site-, and climate-specific nature of O_3-related vegetation response. With respect to quantitative exposure- and risk-based considerations, we consider the initial new, updated assessments as described above in chapter 6 as well as assessments conducted in the last review.

We note that using scientific and technical information to inform decisions on the secondary O_3 standard is complicated by the recognition that no vegetation effects threshold that would apply to all sensitive U.S. vegetation, below which it can be concluded with confidence that O_3-related effects do not occur, can be discerned from the available evidence (US EPA, 2012a, 73 FR 16486). A further complication includes the uncertainties associated with determining at what point the known or anticipated effects become adverse to the public welfare. As a result, any approach to reaching conclusions on the adequacy of the current standard or what alternative standards could be supported by the available scientific evidence and exposure/risk information requires judgments about how to consider that evidence and information, including consideration of how to weigh associated uncertainties. Such an approach to considering the available scientific and technical information is consistent with setting standards that are neither more nor less stringent than necessary, recognizing that a zero-risk standard is not required by the CAA.

Our approach to reviewing the O_3 secondary standard is outlined in Figure 7-1 below, which takes into account the four basic elements of the NAAQS (i.e., indicator, averaging time, form, and level).

Figure 7-1. Overview of Approach to Reviewing the Secondary O_3 NAAQS



7.2 PRELIMINARY STAFF CONCLUSIONS REGARDING THE ADEQUACY OF THE CURRENT SECONDARY O_3 NAAQS

As discussed throughout the third draft ISA, the new evidence available in this review generally continues to support and strengthen key conclusions drawn from the previous reviews (US EPA, 2012a). Thus, in considering the adequacy of the current secondary O_3 standard, we take into account assessments that supported the last review as well as information and assessments in the third draft ISA and the first draft REA prepared for this review.

In particular, we focus primarily on assessments of O_3-related vegetation effects that have been well characterized based on extensive research and for which the ISA has concluded that there is a causal relationship (section 7.2.1). Such effects include visible foliar injury and reduced growth and productivity, especially in sensitive vegetation and in natural terrestrial ecosystems. We also focus on exposure indices that have been considered in past reviews with regard to their appropriateness for use in defining a standard that can provide appropriate protection against such effects (section 7.2.2). In addition, we consider CASAC advice and recommendations from the last review and in conjunction with EPA's 2010 proposed reconsideration of the 2008 O_3 NAAQS (section 7.2.3). Based on these considerations, preliminary staff conclusions are presented in section 7.2.4.

7.2.1 Vegetation Evidence-, Exposure-, and Risk-based Considerations

7.2.1.1 Visible foliar injury

The ISA (chapter 2, section 2.6.1) concludes that visible foliar injury resulting from exposure to O_3 has been well characterized and documented over several decades of many species of trees and other types of vegetation. The ISA concludes that experimental evidence has clearly shown a consistent association of visible injury with O_3 exposure, with greater exposure often resulting in greater and more prevalent injury. As discussed above in chapter 5, new evidence evaluated in the ISA includes several multiple-year field surveys at several National Wildlife Refuges in the U.S., controlled exposure studies that have verified such effects, and a multi-year study that estimated the risk of O_3-induced visible foliar injury in 244 national parks across the country showing high risk of injury in 27% of the parks (US EPA, 2012a; p. 2-40).

While new assessments of visible foliar injury are underway in the first draft REA, as noted above in chapter 6, more complete results will be available for consideration in the next draft of this document. To inform our preliminary consideration of the adequacy of the current standard, we look to the visible foliar injury assessment done in the last review. As described in the 2007 Staff Paper, an assessment combining U.S. Forest Service Forest Inventory and Analysis (FIA) biomonitoring site data with the county level air quality data for those counties

containing the FIA biomonitoring sites was conducted That assessment showed that incidence of visible foliar injury ranged from 21 to 39% during the four-year period (2001-2004) across all counties with air quality levels at or below that of the then-current 8-hour standard of 84 ppb, and from 11 to 30% across all counties with air quality at or below an alternative 8-hour standard of 74 ppb, which is just below the level of the current 75 ppb standard. The magnitude of these percentages suggests that phytotoxic exposures sufficient to induce visible foliar injury would still occur in many areas upon meeting the current secondary O_3 standard. Additionally, the analysis showed that visible foliar injury occurrence is geographically widespread and is occurring on a variety of plant species in forested and other natural systems (see 2007 Staff Paper, Figure 7-19 in section 7.6.3.2).

As discussed above in chapter 5, although visible foliar injury is a valuable indicator of the presence of phytotoxic concentrations of O_3, it is not always a reliable indicator of other negative effects on vegetation In some cases, however, visible foliar injury symptoms have been correlated with decreased vegetative growth and impaired reproductive function. Conversely, the lack of visible foliar injury does not always indicate a lack of other adverse vegetative effects. Nonetheless, EPA has determined in past reviews that the presence of visible foliar injury in and of itself can adversely impact the public welfare. For example, visible foliar injury in national parks and wilderness areas can impact the aesthetic experience for both outdoor enthusiasts and the occasional park visitor. In addition, because these areas are afforded a higher degree of protection, the presence of O_3-induced vegetation effects, including visible foliar injury, can take on increased significance. Specifically, federal land managers (FLMs) "…have determined that given the high ecological, aesthetic, and intrinsic value of federal lands, all native species are significant and warrant protection" (NPS, 2000). As a result, FLMs have identified visible foliar injury, along with other O_3-induced vegetation effects, as air quality related values (AQRV) of concern (NPS, 2000). Numerous O_3-sensitive species are found on Class I federal lands (2007 Staff Paper, Appendix 7J). In addition, the presence of visible foliar injury also has the potential to economically impact those who rely on healthy looking vegetation for their livelihood (e.g., horticulturalists, farmers of leafy crops, landscapers, Christmas tree growers). Many ornamental species have been listed as sensitive to O_3 (Abt, 1993). Similarly, early senescence of fall foliage could also diminish the time available for viewing fall foliage, important in some regions of the country in drawing tourists. Although data are not available to allow the quantification of these impacts, they are nonetheless important to consider qualitatively.

7.2.1.2 Reduced growth and productivity effects

The ISA (chapter 2, section 2.6.2) concludes that ambient O_3 concentrations have long been known to cause decreases in photosynthesis rates and plant growth, and that O_3-induced damage at the plant scale may translate to damage at the stand and ecosystem scales, causing changes in productivity and carbon storage. With regard to natural ecosystems, newly available studies continue to support this conclusion from the last review and strengthen our understanding of O_3 effects in forested ecosystems. Also, with regard to exposure-response relationships, the ISA concludes that the newly available information in this review on effects of O_3 on vegetation has strengthen the assessment of quantitative exposure-response relationships for growth and productivity effects that was presented in the 2006 AQCD (ISA, chapter 2, section 2.6.6.2).

To help inform consideration of these effects, the first draft REA presents a preliminary exposure assessment using updated air quality monitoring data (2006-2010) and new modeling approaches to characterize recent O_3 air quality as well as air quality simulated to just meet the current O_3 standard, as summarized above in chapter 6. To inform our preliminary conclusions on the adequacy of the current standard, we first consider the national O_3 exposure surface generated in terms of the W126 exposure index from the simulation of just meeting the current standard (chapter 6, Figure 6-3) relative to the range of W126 values that was the focus of EPA and CASAC in the last review and in the 2010 proposed reconsideration of secondary O_3 standard set in 2008. In particular, a range of 7 to 21 ppm-hours was proposed in the last review, and a range of 7 to 15 ppm-hours has been repeatedly recommended by CASAC both during and subsequent to the last review and was proposed by EPA in the 2010 reconsideration notice. As discussed in the 2007 and 2010 proposal notices and in various CASAC letters to the past and present EPA Administrators, these ranges are based on consideration of the full array of O_3-related effects on vegetation, as summarized above in chapter 5, with particular emphasis on reduced growth and productivity effects in sensitive vegetation and in terrestrial ecosystems.

In examining the W126 exposure surface depicted in Figure 6-3, based on a preliminary simulation of just meeting the current standard, we observe that a number of relatively small areas in the east and several somewhat larger areas in the west are estimated to have O_3 concentrations in the range of 15 to 20 ppm-hour, which is above the range proposed by EPA in 2010 and recommended by CASAC and in the upper part of the range proposed by EPA in 2007. Even higher concentrations, in the range of 20 to 30 ppm-hours, are estimated to occur primarily in two areas in the mountain west[2]. To the extent that effects judged to be adverse to public welfare in this review are associated with W126 levels within the previously considered range, it

[2] In at least one of these areas, high episodic peak O_3 concentrations have been associated with the occurrence of wild fires.

is also appropriate to consider areas estimated to have O_3 concentrations within this range upon just meeting the current standard. In so doing, we observe that very broad areas across the eastern and western regions of the U.S. are estimated to have O_3 concentrations within the range of 10 to 15 ppm-hours, which includes the mid- to upper part of the ranges previously proposed by EPA and recommended by CASAC. Even broader areas, encompassing most of the rest of the eastern and western regions, are estimated to have O_3 concentrations in the range of 5 to 10 ppm-hours, which includes the lower part of the EPA and CASAC ranges. Thus, this analysis indicates that many areas are estimated to have O_3 concentrations above the ranges of W126 values that were the focus of EPA and CASAC in the last review and in the proposed reconsideration, and that much broader geographic areas are estimated to have concentrations in the upper part of the previously considered range. Based in part on these observations, we reach the preliminary conclusion that O_3 concentrations that have been or could be reasonably anticipated to cause adverse effects in sensitive vegetation and natural terrestrial ecosystems are likely to remain in substantial geographical areas across the country upon just meeting the current standard everywhere.[3]

The first draft REA also presents estimates of O_3-related annual relative biomass loss (RBL) for eleven sensitive tree species, based on the estimated exposure surface simulating just meeting the current standard and on biomass loss concentration-response functions drawn from the ISA based on the W126 metric. These RBL estimates are shown above in chapter 6, Table 6-1. This analysis also reflects consideration of the actual growing ranges of these tree species in that it only estimates RBL in each modeled grid cell that is part of each species' growing range. Results presented include median and maximum RBL estimates from the distribution of RBL estimates for all the modeled grid cells within the species' range. In considering these results, we note that seven of the eleven tree species included in this analysis have maximum annual RBL estimates greater than 10%, with maximum estimates for five of these species (quaking aspen, eastern white pine, tulip poplar, ponderosa pine, and red alder) within the range of approximately 10 to 20% and with much higher estimates for the two most sensitive species (black cherry and eastern cottonwood). Median estimates for these seven species were approximately 3% for four of the species, 19% and 46% for the two most sensitive species, and less than 1% for the other species (red alder).

In the last two O_3 NAAQS reviews, to help inform consideration of what magnitude of annual biomass loss could reasonably by considered to be important from a public welfare

[3] As noted above in chapter 6, alternative modeling approaches to simulating just meeting the current and alternative standards will be applied in the second draft REA. In the second draft PA we will revisit these observations based on refined analyses in the second draft REA.

perspective, EPA considered the consensus views of a group of experts who convened in 1996 to provide input and advice to the Agency in its review of the O_3 NAAQS that was ongoing at that time. At the 1996 Consensus Workshop, these experts expressed views with regard to considering a 2% annual biomass loss as significant within the context of multi-year compounding of effects over the life of the tree. More generally, consensus views were reached on ranges of O_3 concentrations that would be expected to be protective for growth and productivity effects, including a range equivalent to a W126 range of 7 to 13 ppm-hours for tree seedlings in natural forest stands, which was an important consideration in the standard level ranges proposed in the last two reviews (Heck and Cowling, 1997).

Based on the above considerations, these analyses provide support for our preliminary conclusion that O_3 concentrations that can reasonably be anticipated to cause detrimental growth and productivity effects in sensitive vegetation and natural terrestrial ecosystems are likely to remain upon just meeting the current standard for a number of tree species that are important in natural terrestrial ecosystems. We recognize that additional exposure and risk assessments are ongoing and will be presented in the second draft REA, which we will consider, together with CASAC advice and comments, in reaching conclusions on the adequacy of the current standard in the second draft PA.

7.2.2 Biologically Relevant Exposure Indices

In considering the adequacy of the current secondary O_3 standard, the exposure index used to define the standard necessarily is a critical element to consider. The ISA (chapter 2, section 2.6.6.1) states that no information newly available in this review alters the basic conclusions with regard to biologically relevant exposure indices in the 2006 and 1996 AQCDs. Once again, based on the current state of knowledge and the best available data assessed in this review, the ISA concludes that exposure indices that cumulate and differentially weight the higher hourly average concentrations over a season and also include the mid-level values continue to offer the most defensible approach for use in developing response functions and in defining indices for vegetation protection (ISA, chapter 2, section 2.6.6.1).

In considering the adequacy of the current 8-hour average secondary O_3 standard, we note that in the last two O_3 NAAQS reviews, EPA has recognized that the risk to vegetation comes from cumulative seasonal exposures. Thus, it is clear that the purpose of the secondary O_3 standard should be to provide an appropriate degree of protection against cumulative, seasonal exposures to O_3 that are known or anticipated to harm sensitive vegetation or ecosystems. Further, it is also clear that a cumulative, seasonal form has a distinct advantage over an 8-hour average form in protecting against such exposures. Such a form is specifically designed to measure directly the kind of O_3 exposures that can cause harm to vegetation during

the growing season. In contrast, an 8-hour standard does not measure cumulative, seasonal exposures directly and can only indirectly afford some degree of protection against such exposures.

To the extent that clear relationships were to exist between 8-hour daily peak O_3 concentrations and cumulative, seasonal exposures, the 8-hour form and averaging time would have the potential to be effective as an indirect surrogate. However, as discussed in the 2007 proposed rule and the 2008 final rule, the evidence shows that there are known types of O_3 air quality patterns that can lead to high levels of cumulative, seasonal O_3 exposures without the occurrence of high daily 8-hour peak O_3 concentrations, such as in rural, high elevation areas. The lack of any clear consistent relationship between 8-hour daily peak O_3 concentrations and cumulative, seasonal exposures was shown in the last review (2007 Staff Paper, chapter 7, section 7.5; Figure 7-1 and Appendix 7B). Based on 3-year average values, it was shown that for sites with a maximum 8-hour average concentration (fourth-highest maximum value) at the level of the current standard, W126 values varied from approximately less than 5 ppm-hours to over 20 ppm-hours, a range that goes from below the lower end of CASAC's recommended range to above the upper end of the recommended range. Thus, an 8-hour standard form cannot be expected to provide a reasonably consistent degree of protection from known or anticipated adverse effects on vegetation associated with cumulative, seasonal O_3 exposures in all areas across the country. Clearly an 8-hour form and averaging time is a very indirect way to characterize biologically relevant exposure patterns, is poorly correlated with such exposure patterns, and therefore is far less likely to identify and protect against the kind of cumulative, seasonal exposure patterns that have been determined to be harmful than would a standard defined in terms of a cumulative, seasonal exposure index.

Past reasons for not moving to a cumulative, seasonal form in the last two reviews have not been based on disagreement over the biological relevance of the cumulative, seasonal form or the recognized disadvantages of an 8-hour average standard form in measuring and identifying a specified cumulative, seasonal exposure pattern. Rather, the reasons for not moving to such a form have been based on concerns over whether there is an adequate scientific basis to identify the nature and magnitude of cumulative, seasonal exposure patterns that the standard should be designed to protect against in light of various uncertainties in the evidence and the lack of rural monitoring data. This reasoning is built on the implicit presumption that there is less uncertainty associated with specifying an appropriate degree of protection based on an 8-hour average standard than there is in specifying an appropriate degree of protection based on a standard defined in terms of a cumulative, seasonal exposure index. In considering this presumption in this review, EPA staff finds strong support in the available scientific and technical information

for the contrasting view that there is appreciably less uncertainty associated with specifying an appropriate degree of protection based on a cumulative, seasonal standard than on an 8-hour standard, recognizing that the standard is intended to provide protection against effects on vegetation that are inherently related to cumulative, seasonal O_3 exposures.

As discussed below, using a standard with a form based on maximum daily 8-hour O_3 levels as an indirect surrogate to provide the desired degree of protection from cumulative, seasonal O_3 exposures is likely directionally to have a greater risk of under-protection in some areas and a greater risk of over-protection in some other areas, compared to using a W126 cumulative seasonal form. Specifying an appropriate degree of protection for sensitive vegetation in terms of a standard form that is defined based on the scientific evidence relating short-term O_3 exposures to respiratory-related effects in human populations is not warranted based on the scientific evidence.

As discussed above in section 7.1.1, the reasoning that has led to past decisions to set the secondary O_3 standard identical to the primary O_3 standard in both form and level has most explicitly been based on analyses of the projected degree of overlap between counties with air quality expected to meet the selected short-term primary standard and alternative levels of a cumulative, seasonal standard based on then-current monitored air quality data. Such an analysis in the last review showed essentially complete overlap between the revised 8-hour, 75 ppb primary standard and the W126 standard level at the upper end of the proposed range, 21 ppm-hours. That analysis was interpreted as showing that the revised 8-hour primary standard would provide a significant degree of additional protection for vegetation as compared to that provided by the then-current 84 ppb secondary standard. Further, the conclusion was reached that a W126 standard set at 21 ppm-hours would be unlikely to provide additional protection in any monitored areas beyond that likely to be provided by the revised primary standard. However, this line of reasoning is based entirely on available monitoring data and thus does not reflect consideration of areas for which monitoring data are not available, importantly including rural, high elevation areas with natural forested ecosystems. As noted above, it is reasonable to anticipate that such areas may well have relatively high cumulative, seasonal O_3 air quality patterns even as peak 8-hour average O_3 concentrations may be relatively low.

Based on these considerations in the last review, the Administrator concluded that the potential for under-protection from anticipated O_3-related effects in such areas was clear, while noting that the number and size of such areas and the degree of risk of under-protection is hard to determine (73 FR 16500). Nonetheless, it was reasoned that making the secondary standard identical to the primary standard would "tend to avoid the potential for providing more protection than is necessary, a risk that would arise from moving to a new form for the secondary

standard despite significant uncertainty in determining the degree of risk for any exposure level and the appropriate level of protection, as well as uncertainty in predicting exposure and risk patterns" (73 FR 16500).

In this review, it is the staff's view that for any given cumulative, seasonal level that is being considered as providing an appropriate degree of protection, one would expect less risk of under-protection or overprotection with a standard based on a cumulative, seasonal form as compared to determining an 8-hour standard that would indirectly provide the desired degree of cumulative, seasonal protection. As observed above, based on the available scientific and technical information, it is more reasonable to conclude that there would be appreciably less uncertainty associated with specifying an appropriate degree of protection against effects on vegetation that are inherently related to cumulative, seasonal O_3 exposures by using a standard form that is explicitly cumulative and seasonal in nature.

7.2.3 CASAC Views on the Adequacy of the Current Standard

During the last review of the O_3 NAAQS, CASAC stated the following in its letter to the Administrator:

> An important difference between the effects of acute exposures to ozone on human health and the effects of ozone exposures on welfare is that vegetation effects are more dependent on the cumulative exposure to, and uptake of, ozone over the course of the entire growing season (defined to be a minimum of at least three months). Therefore, there is a clear need for a secondary standard which is distinctly different from the primary standard in averaging time, level and form. Developing a biologically-relevant ozone air quality index would be directly responsive to the 2004 National Research Council (NRC) recommendations on Air Quality Management in the United States (NAS, 1994) and will help support important new Agency initiatives to enhance ecosystem-related program tracking and accountability.
>
> …[T]he compelling weight of evidence provided in Chapter 7 of the 2nd Draft Ozone Staff Paper results from the convergence of results from many various and disparate assessment methods including chamber and free air exposure, crop yield and tree seedling biomass experimental studies, foliar injury data from biomonitoring plots, and modeled mature tree growth.
>
> Based on the Ozone Panel's review of Chapters 7 and 8, the CASAC unanimously agrees that it is not appropriate to try to protect vegetation from the substantial, known or anticipated, direct and/or indirect, adverse effects of ambient ozone by continuing to promulgate identical primary and secondary standards for ozone. Moreover, the members of the Committee and a substantial majority of the Ozone Panel agrees with EPA staff conclusions and encourages the Administrator to establish an alternative cumulative secondary standard for ozone and related photochemical oxidants that is distinctly different in averaging time, form and

> level from the currently existing or potentially revised 8-hour primary standard." (Henderson, 2006, pp. 5-7).

In a subsequent letter sent to offer advice to aid the Administrator and Agency staff in developing the 2007 O_3 proposal, the CASAC reiterated its unanimous support for the recommendation in the Final Ozone Staff Paper "that protection of managed agricultural crops and natural terrestrial ecosystems requires a secondary Ozone NAAQS that is substantially different from the primary ozone standard in averaging time, level and form" (Henderson, 2007, p. 3).

Following the 2008 decision on the O_3 standards, the members of the CASAC Ozone Review Panel sent a letter to EPA in April 2008 stating "[i]n our most-recent letters to you on this subject - dated October 2006 and March 2007 - … the Committee recommended an alternative secondary standard of cumulative form that is substantially different from the primary Ozone NAAQS in averaging time, level and form — specifically, the W126 index within the range of 7 to 15 ppm-hours, accumulated over at least the 12 'daylight' hours and the three maximum ozone months of the summer growing season . . . [t]he CASAC now wishes to convey, by means of this letter, its additional, unsolicited advice with regard to the primary and secondary Ozone NAAQS. In doing so, the participating members of the CASAC Ozone Review Panel are unanimous in strongly urging you or your successor as EPA Administrator to ensure that these recommendations be considered during the next review cycle for the Ozone NAAQS that will begin next year" (Henderson, 2008). The letter further stated the following views:

> The CASAC was … greatly disappointed that you failed to change the form of the secondary standard to make it different from the primary standard. As stated in the preamble to the Final Rule, even in the previous 1996 ozone review, 'there was general agreement between the EPA staff, CASAC, and the Administrator, … that a cumulative, seasonal form was more biologically relevant than the previous 1-hour and new 8-hour average forms (61 FR 65716)' for the secondary standard. Therefore, in both the previous review and in this review, the Agency staff and its advisors agreed that a change in the form of the secondary standard was scientifically well-justified.
>
> Unfortunately, this scientifically-sound approach of using a cumulative exposure index for welfare effects was not adopted, and the default position of using the primary standard for the secondary standard was once again instituted. Keeping the same form for the secondary Ozone NAAQS as for the primary standard is not supported by current scientific knowledge indicating that different indicator variables are needed to protect vegetation compared to public health. The CASAC was further disappointed that a secondary standard of the W126 form

> was not considered from within the Committee's previously-recommended range of 7 to 15 ppm-hours. The CASAC sincerely hopes that, in the next round of Ozone NAAQS review, the Agency will be able to support and establish a reasonable and scientifically-defensible cumulative form for the secondary standard. (Henderson, 2008).

Following EPA's proposed reconsideration of the 2008 NAAQS, CASAC responded to EPA's request for CASAC's views on the proposal by stating the following:

> CASAC also supports EPA's secondary ozone standard as proposed: a new cumulative, seasonal standard expressed as an annual index of the sum of weighted hourly concentrations (i.e., the W126 form), cumulated over 12 hours per day (8am to 8pm) during the consecutive 3-month period within the ozone season with the maximum index value, set as a level within the range of 7 to [1]5 ppm-hours. This W126 metric can be supported as an appropriate option for relating ozone exposure to vegetation responses, such as visible foliar injury and reductions in plant growth. We found the Agency's reasoning, as stated in the *Federal Register* notice of January 19, 2010, to be supported by the extensive scientific evidence considered in the last review cycle. In choosing the W126 form for the secondary standard, the Agency acknowledges the distinction between the effects of acute exposures to ozone on human health and the effects of chronic ozone exposures on welfare, namely that vegetation effects are more dependent on the cumulative exposure to, and uptake of, ozone over the course of the entire growing season (defined to be a minimum of at least three months). In this proposal, the Agency is responding to the clear need for a secondary standard that is different from the primary standard in averaging time, level and form. (Samet, 2010)

In reaching staff conclusions in the next draft of the PA, in addition to taking note of this advice provided by CASAC in the last review, we will consider advice and recommendations from CASAC based on their reviews of the first drafts of the Welfare REA and this first draft PA.

7.2.4 Preliminary Staff Conclusions on the Current Secondary O_3 Standard

In this section, we present staff's preliminary conclusions regarding the adequacy and appropriateness of the public welfare protection provided by the current 8-hour secondary O_3 standard. In discussing these preliminary conclusions, we address the following questions:

- **To what extent does the available scientific evidence and exposure/risk information support or call into question the adequacy of the public welfare protection afforded by the current O_3 secondary standard?**

- **To what extent does the available scientific evidence, and in particular vegetation exposure-response information, support or call into question the appropriateness of the form and/or averaging time of the current O_3 secondary standard?**

As discussed above, in addressing these questions we have considered the available scientific evidence assessed in the third draft ISA, as discussed above in chapter 5, and the available exposure and risk information assessed in the first draft REA, as discussed above in chapter 6, and considered in section 7.2.1; considerations related to a biologically relevant exposure index discussed in section 7.2.2 and the advice and recommendations received from CASAC during the last review and following the proposal to reconsider the 2008 decision, as discussed above in section 7.2.3.

With regard to the scientific evidence, we reach the preliminary conclusion that the available evidence clearly calls into question the adequacy and appropriateness of the current standard and provides strong support for considering potential alternative standards to increase public welfare protection, especially for sensitive vegetation and ecosystems occurring in federally protected Class I and similar areas. This preliminary conclusion places considerable weight on the array of O_3-related vegetation and ecosystem level effects that have been reported following cumulative, seasonal exposures to O_3 in studies or areas that have air quality that would be allowed by the current standard, including visible foliar injury and growth and productivity reductions in sensitive trees and natural terrestrial ecosystems, as well as changes in community composition, below ground processes, and water cycling as discussed above in chapter 5. In emphasizing such effects, this preliminary conclusion also places considerable weight on the linkages between the evidence for these vegetation and ecosystem-level effects and the broader body of evidence available at the molecular, biochemical, and physiological levels demonstrating biologically plausible mechanisms for O_3 as the causal agent in these higher order effects. In reaching this preliminary conclusion, we acknowledge that uncertainties persist in the welfare evidence; however, in staff's view the broad array of welfare effects reported following cumulative, seasonal exposures to O_3 in studies or areas with air quality that would be allowed by the current standard, combined with the plausible linkages between these effects and the much larger body of molecular, biochemical, and physiological evidence, supports the appropriateness of considering revising the current secondary O_3 standard in order to increase public welfare protection.

With regard to the exposure and risk information we reach the preliminary conclusion that the available exposure and risk information from the first draft REA and from assessments in the last review support the appropriateness of considering alternative standards that would increase public welfare protection against vegetation and ecosystem effects.

With regard to CASAC advice, we note that the CASAC O_3 Panel has repeatedly recommended setting a secondary standard distinctly different from the primary standard in averaging time, level and form. Since this advice was provided, based on evidence available in the last review, the available evidence in this review for the importance of cumulative, concentration weighted exposures in inducing adverse welfare effects has been confirmed and strengthened.

Based on the above considerations, staff reaches the preliminary conclusion that the body of information now available supports consideration of revising the current 8-hour secondary O_3 standard, so as to afford greater and more appropriate public welfare protection by selecting a different form, averaging time and level than that of the primary standard, and that it does not support retention of the current secondary O_3 standard.

7.3 POTENTIAL ALTERNATIVE STANDARDS FOR FURTHER ANALYSIS

Given our preliminary conclusion that the body of information now available supports consideration of revising the current 8-hour secondary O_3 standard so as to afford greater and more appropriate public welfare protection from the adverse effects of cumulative, seasonal O_3 exposures, we next consider the following overarching question:

- **What additional analyses would be appropriate to help inform consideration of potential alternative standards in the second draft of the PA?**

In considering this question, we specifically consider additional exposure and risk analyses of alternative standards that would provide increased and more appropriate public welfare protection relative to that provided by the current secondary O_3 standard. In this first draft PA, the purpose of such considerations is to identify alternative standards appropriate for additional analyses in the second draft REA. In the second draft PA, we will consider the available scientific evidence and exposure/risk information in drawing conclusions about a range of potential alternative standards that would be appropriate for consideration by the Administrator in this review.

In identifying alternative standards appropriate for additional exposure and risk analyses, we note that the scientific evidence can provide meaningful insights into such alternative standards when all the elements of the standard (i.e., indicator, averaging time, form, and level) are considered together. With regard to the O_3 indicator, in this review the available evidence continues to support the current O_3 indicator. Given the available scientific evidence as described in US EPA, 2012a, Chapter 9, the following sections identify potential alternative cumulative, seasonal standard forms (7.3.1), averaging times (7.3.2), and levels (7.3.3), for further analyses.

7.3.1 Form

As discussed above, a secondary O_3 standard should provide an appropriate degree of protection against cumulative, seasonal exposures to O_3 that are known or anticipated to harm sensitive vegetation or ecosystems. In considering alternative cumulative, seasonal forms that have been assessed and evaluated in the ISA, chapter 9, section 9.5.2, we reach the preliminary conclusion that the W126 exposure index is the best cumulative, seasonal, concentration-weighted form to consider, consistent with conclusions reached by EPA staff, CASAC, and the Agency in the last review.

This conclusion is based on considering features of the W126 index that most closely align with our current understanding of the science at this time. First, the cumulative nature of the W126 is clearly supported by the basic biological understanding of how most plants in the U.S. are most biologically active during the warm season and are exposed to ambient O_3 throughout this biologically active period. Second, it has been clearly shown in the scientific literature that, all else being equal, plants respond more to higher concentrations, though there continues to be no evidence of an exposure threshold for vegetation effects. The W126 sigmoidal weighting function reflects both of these understandings, by not including a threshold below which concentrations are not included and by differentially weighting concentrations to give greater weight to higher concentrations and less weight to lower ones. Specifically, this index assigns increasing weight to each increase in hourly O_3 concentrations between 0 and 100 ppb, though the sigmoid shape of the weighting scheme illustrates the point that lower concentrations (below 40 ppb) are de-emphasized by assigning a very low weight, while concentrations between 40 ppb and 100 ppb are given more emphasis by assigning unique and increasing higher weights, and all peaks above 100 ppb receive a weight of 1.

By contrast, other cumulative indices such as the SUM06 or AOT40 weight every concentration below a defined threshold (i.e. 60 ppb and 40 ppb, respectively) with a weight of 0 and every concentration above that given threshold with a weight of 1, without any differential weighting of concentrations above the index threshold. Because there is less refinement in these latter weighting schemes (each concentration can only be assigned either a 0 or 1), such threshold weighting schemes are less able to reflect more subtle differences in O_3 exposure profiles that could account for observed differences in plant response.

Therefore, since the W126 form has a strong biological underpinning, and given the strength of the scientific record, CASAC support, and evidence that it performs consistently well over a wide range of conditions, we again conclude that a secondary standard form defined in terms of the W126 exposure index is best suited and most appropriate to consider for inclusion in additional analyses in the second draft REA on alternative secondary O_3 standards.

7.3.2 Averaging Times

For a standard with a form defined in terms of the W126 exposure index, the NAAQS element of "averaging time" is appropriately considered in terms of exposure periods – diurnal and seasonal -- over which the index would be summed in any given year. This element also reflects consideration of whether the exposure index would be compared to the level of the standard on an annual basis or averaged over three years, as is the case for most other NAAQS. These considerations are discussed below.

7.3.2.1 Diurnal exposure period

As discussed above in chapter 5, section 5.4.1.1 and more fully in the ISA, chapter 9, section 9.5.3.2, the diurnal conditions for maximum uptake of O_3 into the plant for the majority of plants, occur mainly during the daytime hours. This is because, in general, (1) plants have the highest stomatal conductance during the daytime; (2) atmospheric turbulent mixing is greatest during the day in many areas; (3) the high temperature and high light conditions that typically promote the formation of tropospheric O_3 also promote physiological activity in vegetation.

In addition to daytime uptake, a number of studies have also reported O_3 uptake at night in some species. Typically the rate of stomatal conductance at night is much lower than during the day. Several field studies have attempted to quantify night-time O_3 uptake with a variety of methods. Across the studies discussed in the ISA, nocturnal conductance ranged from negligible to 25% of daytime values (US EPA, 2012a, section 9.5.3). In some studies the percent of nocturnal uptake varied by season and drought conditions. However, many of these studies did not link the night-time flux to measured effects on plants. Thus, it is difficult to know whether the impacts on the plant from nocturnal exposures are greater or less than those from similar daytime exposures, and whether or not they should be considered as separate impacts or as additive or synergistic with impacts from the preceding daytime exposure.

In addition to the uncertainties associated with understanding the plant response to nocturnal uptake, there are also uncertainties associated with the extent of its occurrence. This is because for significant nocturnal stomatal flux and O_3 effects to occur, the right combination of specific conditions must exist. In particular, a susceptible plant with nocturnal stomatal conductance and low defenses must be growing in an area with relatively high night-time O_3 concentrations (often high elevation sites) and appreciable nocturnal atmospheric turbulence. It is unclear how many areas there are in the U.S. where these conditions occur. It may be possible that these conditions exist in mountainous areas of southern California, front-range of Colorado and the Great Smoky Mountains of North Carolina and Tennessee. More information is needed

in locations with high night-time O_3 to assess the local O_3 patterns, micrometeorology and responses of potentially vulnerable plant species.

Therefore, due to the substantial uncertainties that remain regarding the importance and extent of nocturnal exposures associated with plant uptake, and whether and how they might be incorporated into a national index, EPA staff continues to focus on the 12-hour daytime exposure period of 8:00 am to 8:00 pm, consistent with CASAC advice in the last review. In so doing, we recognize, as did CASAC (Henderson, 2007, p. 3) that in some parts of the country this daytime period represents a minimum acceptable period and may not include all daytime hours or exposures of importance to vegetation. On this basis, we reach the preliminary conclusion that a 12-hour diurnal window (8:00 am to 8:00 pm) is appropriate to use in defining alternative W126 standards for additional analyses in the second draft REA

7.3.2.2 Seasonal exposure period

The selection of any single window of time over which to cumulate O_3 exposures for a national standard necessarily will represent a balance of factors, given the significant variability in growth patterns and lengths of growing season among the wide range of vegetation species that may experience detrimental effects associated with O_3 exposure. Various intra-annual averaging and accumulation time periods have been considered for the protection of vegetation. In 2007, EPA proposed use of the maximum consecutive 3-month period within the O_3 season as a surrogate for vegetation growing seasons nationally. A 3-month exposure period was also supported by CASAC both in advice provided during the last review and on the 2010 proposed reconsideration, as noted above in section 7.2.3. Alternatively, the U.S. Forest Service and federal land managers have used a 24-hour W126 accumulated for 6 months from April through September.

As an initial matter, in considering the alternatives of 3- or 6-month seasonal exposure periods, we note that the exposure period in the vast majority of O_3 exposure studies conducted in the U.S. has been much shorter than 6 months, ranging from an average of 77 days in most NCLAN crop studies to 145 days in the Aspen FACE experiment which represented the entire growing season at that site. As a result, analyses of effects studies done in terms of the W126 exposure index have typically defined the index in terms of a 3-month exposure period or at least in terms of periods shorter than 6 months. In addition, the O_3 season within which O_3 monitoring is required is shorter than 6 months in many areas in the country.

To further help inform consideration of 3- and 6-month seasonal periods, the ISA presented the results of an analysis conducted by EPA staff of the relationship between 3- and 6-month maximum W126 values calculated for over 1,200 AQS and CASTNET EPA monitoring

sites for the years 2008-2009. This analysis found that these two accumulation periods resulted in highly correlated metrics (US EPA, 2012a, Figure 9-13). As discussed in the ISA (section 9.5.3), the two accumulation periods were centered on the yearly maximum for each monitoring site, and it is possible that this correlation would be weaker if the two periods were not temporally aligned. In the U.S., W126 cumulated over 3 months and W126 cumulated over 6 months are proxies of one another, as long as the period in which daily W126 is accumulated corresponds to the seasonal maximum. Therefore, it is expected that either statistic will predict vegetation response equally well.

Based on the above considerations, we reach the preliminary conclusion that the maximum consecutive 3-month period within the O_3 growing season for vegetation remains an appropriate and useful surrogate for seasonal exposures for vegetation throughout the U.S., and that a 3-month seasonal window is appropriate to use in defining alternative W126 standards for additional analyses in the second draft REA.

7.3.2.3 Annual or 3-year average

In considering whether an annual or 3-year averaging period is more appropriate, we recognize, as was recognized by EPA in the last review and in the 2010 proposed reconsideration, that though most cumulative, seasonal exposure levels of concern for vegetation have been expressed in terms of an annual timeframe, it is also appropriate to consider a 3-year averaging period for purposes of standard stability. In so doing, we note that for certain welfare effects of concern, including visible foliar injury and decreased growth and productivity effects on perennial and annual vegetation, an annual time frame may be a more appropriate period in which to assess what level would provide the requisite degree of protection, while for other welfare effects, such as effects on mature tree biomass loss and effects at the ecosystem level, a 3-year averaging period may also be appropriate.

Consistent with past consideration of this issue, we again recognize that should a 3-year average of the 3-month, 12-hour W126 form be used in defining an alternative secondary O_3 standard, a potentially lower level should be considered to reduce the potential of adverse impacts to annual species from a single high O_3 year that could still occur while attaining a standard on average over 3-years. In considering this issue in the last review, the CASAC Panel concluded that multi-year averaging to promote a “stable” secondary standard is less appropriate for a cumulative, seasonal secondary standard than for a primary standard based on maximum 8-hour concentrations, and further concluded that if multi-year averaging is employed to increase the stability of the secondary standard, the level of the standard should be revised downward to

assure that the desired degree of protection is not exceeded in individual years (Henderson, 2007; p. 3).

In considering whether alternative W126 standards to be analyzed in the second draft REA should be based on an annual or 3-year average index, we reach the preliminary conclusion that while a 3-year average may be the most appropriate choice from a standard stability perspective, it would also be useful to conduct an analysis of the sensitivity of the exposures and risks to a standard defined in terms of an annual index. Such a sensitivity analysis may help inform consideration of the extent to which it might be appropriate to consider lower standard levels in conjunction with a standard specified in terms of a 3-year average index.

7.3.3 Level

In our consideration of what alternative range of levels would be appropriate to consider in conducting exposure and risk analyses of alternative secondary O_3 standards in the second draft REA, we build on the preliminary conclusions reached above on the W126 form and 12-hour and 3-month diurnal and seasonal exposure windows. In so doing, we give preliminary consideration to the nature and degree of effects of O_3 to the public welfare, including what constitutes an adverse effect and the strengths and limitations of the evidence that is available regarding known or anticipated adverse effects from cumulative, seasonal exposures and its usefulness in informing selection of a range of levels appropriate for further analyses. We also consider CASAC's views from the last review and the reconsideration of the 2008 NAAQS regarding the strength of the evidence and its adequacy to inform a range of alternative levels that would be appropriate for further analyses.

In considering the nature and degree of effects of O_3 on the public welfare, we recognize that the significance to the public welfare of O_3-induced effects on sensitive vegetation growing within the U.S. can vary, depending on the nature of the effect, the intended use of the sensitive plants or ecosystems, the degree to which the vegetation is managed for certain attributes and uses, and the types of environments in which the sensitive vegetation and ecosystems are located. Any given O_3-related effect on vegetation and ecosystems (e.g., biomass loss, foliar injury), therefore, may be judged to have a different degree of impact on the public welfare depending, for example, on whether that effect occurs in a Class I area or a city park, or whether the effect occurs in commercial crops or unmanaged forests. In our view, it is appropriate that this variation in the significance of O_3-related vegetation effects should be taken into consideration in identifying a range of alternative levels that may be appropriate to consider in additional exposure and risk analyses. In this regard, we agree with the definition of adversity discussed above in chapter 5 (section 5.6), which draws from the discussion in section IV.A.3 of the 2010

proposed reconsideration and in the 2008 rulemaking. As a result, we conclude that the primary focus of a secondary O_3 standard should be on those effects that occur on sensitive species that are known to or are likely to occur in federally protected areas such as Class I areas[4] or on lands set aside by States, Tribes and public interest groups to provide similar benefits to the public welfare, for residents on those lands, as well as visitors to those areas. In addition to the primary focus as described above, we also consider impacts on private lands where there is less opportunity to offset the degree of damage from O_3 exposure, for example in commercial forests on private lands, trees grown in urban settings, or foliar damage in ornamental plants in residential areas.

We recognize that the same known or anticipated O_3-induced effects may call for less protection if they occur in other areas or on vegetation used for certain purpose, such as crops grown commerically on privately held lands. For example, the maintenance of adequate agricultural crop yields is extremely important to the public welfare and is currently achieved through the application of intensive management practices, including plant breeding for tolerance to various environmental factors, extensive application of fertilizer, and irrigation. These management practices, in conjunction with market forces and government programs, assure an appropriate balance between costs of production and market availability. In light of such intensive management practice there is substantially more uncertainty in characterizing the extent to which O_3 exposures are detrimental to commercial crops than for other senstive vegetation. Thus, while research on agricultural crop species remains useful in illuminating mechanisms of action and physiological processes, we consider information from this sector on O_3-induced effects less useful in informing judgments on alternative standards levels that are appropriate for further analysis. With respect to commercial production of commodities, we note that judgments about the extent to which O_3-related effects on commercially managed vegetation are adverse from a public welfare perspective are particularly difficult to reach, given that what is known about the relationship between O_3 exposures and agricultural crop yield response derives largely from data generated almost 20 years ago. We recognize that there is substantial uncertainty at this time as to whether these data remain relevant to the majority of species and cultivars of crops being grown in the field today. In addition, the extensive management of such vegetation may to some degree mitigate potential O_3-related effects, and the experiments from decades ago do not reflect recent advances in precision management of agricultural inputs to maximize potential yield. The management practices used on these lands are highly variable and

[4] For example, the level of protection granted by Congress under the Wilderness Act of 1964 for designated "wilderness areas" requires that these areas "shall be administered for the use and enjoyment of the American people in such manner as will leave them unimpaired for future use as wilderness, and so as to provide for the protection of these areas, the preservation of their wilderness character" (The Wilderness Act, 1964).

are designed to achieve optimal yields, taking into consideration various environmental conditions. Thus, overall we expect that O_3 exposure would present less risk to the public welfare from detrimental effects on agricultural crops than would O_3 exposure to other more sensitive natural vegetation and ecosystems. We draw a distinction between crops grown on agricultural lands and commercial forests, which while managed for timber yields are less amenable to the types of daily and seasonal intensive management practices available to agricultural farm managers. As such, adverse effects on these commercial forests can still be substantial and not likely fully captured by markets. In addition, commercial forests are often used for multiple purposes, providing recreational services as well as timber production.

While our focus is appropriately on non-agricultural vegetation, we note that providing adequate protection for other more sensitive natural vegetation and ecosytems should tend to provide protection for agricultural crops as well. Based on this, we conclude that such effects should not beconsidered as a primary basis for identifying alterntative standard levels that are appropriate for further analysis.

We also recognize that O_3-related effects on sensitive vegetation can occur in other areas that have not been afforded special federal protections, ranging from effects on vegetation growing in residential or commercial settings, such as ornamentals used in urban/suburban landscaping, to vegetation grown in land use categories that are managed for commercial production of commodities such as timber. For vegetation used for residential or commercial ornamental purposes, such as urban/suburban landscaping, we believe that there is not adequate information at this time to identify alternative standard levels for further analysis based specifically on impairment of urban/suburban landscaping and other uses of ornamental vegetation, but we note that alternative secondary standard levels that would provide protection for sensitive natural vegetation and ecosystems would likely also provide some degree of protection for such ornamental vegetation. Furtherr, we recognize there is substantial data available on the number and types of trees growing in urban areas, including urban parks as well as trees planted along roadways and in other public places. The volume of trees in urban areas can be substantial, and as discussed in the first draft REA, provide important ecosystem services including air pollution removal and carbon storage. As noted in above in chapter 6, the results of the analysis of impacts on urban tree related ecosystem services will be considered in the second draft PA in terms of the relevance of those results for informing potential alternative standards.

Based on the above, we find that the type of information most useful in informing the identification of a range of alternative standard levels appropriate for further analysis is appropriately focused on information regarding exposures and responses of sensitive trees and other native species known or anticipated to occur in protected areas such as Class I areas or on

lands set aside by States, Tribes and public interest groups to provide similar benefits to the public welfare, for residents on those lands, as well as visitors to those areas.

With regard to the available evidence, we find that the newly available evidence in this review is consistent with and reinforces the coherence and strength of the evidence available in the last review. As summarized above in chapter 5, and evaluated in chapter 9 of the ISA, this evidence addresses a broad array of O_3-induced effects on a variety of tree species across a range of growth stages (i.e., seedlings, saplings and mature trees) using diverse field-based (e.g. free air, gradient and ambient) and OTC exposure methods. It demonstrates that significant numbers of forest tree species are potentially experiencing O_3-induced stress under levels of ambient air quality that would be allowed under the current secondary O_3 standard.

In considering the advice of CASAC from the last review and on the proposed recnsideration, we note that in its 2007 letter to the Administrator, the CASAC O_3 Panel agreed with past EPA staff recommendations that the lower bound of the range within which a seasonal W126 O_3 standard should be considered is approximately 7 ppm-hour. However, "it *does not* agree with Staff's recommendations that the upper bound of the range should be as high as 21 ppm-hour. Rather, the Panel recommends that the upper bound of the range considered should be no higher than 15 ppm-hour, which the Panel estimates is approximately equivalent to a seasonal 12-hour SUM06 level of 20 ppm-hour" (Henderson, 2007). The CASAC provided the same advice in its support of the 2010 proposed reconsideration, which proposed a range of levels from 7 to 15 ppm-hours (Samet, 2010).

In also considering the recommendations from the 1996 Consensus Workshop, we recognize that the 1997 Workshop Report did not clearly document the basis for its recommendations, which included a consensus recommendation for a range equivalent to a W126 range of 7 to 13 ppm-hours that would be protective for tree seedlings in natural forest stands. While the absence of such documentation calls for caution in placing weight on this recommendation, the recommendation was an important consideration in the standard level ranges proposed in the last two reviews and in the reconsideration.

Based on the above considerations, we reach the preliminary conclusion that for a secondary O_3 standard defined in terms of a W126 index, with 12-hour and 3-month exposure periods, based on either an annual or 3-year average index, it appropriate to further analyze alternative standard levels in the range of 7 to 15 ppm-hours in the second draft REA.

While the upper end of this range is lower than the upper end of 21 ppm-hour recommended in the 2007 Staff Paper, this upper level of 21 ppm-hour was originally put forward in the 1997 review in terms of a SUM06 of 25 ppm-hour (W126 of 21 ppm-hour) and

was justified on the basis that it was predicted to allow up to 10% biomass loss annually in 50% of studied commercial crops and tree seedling species. Recognizing the significant uncertainties that are associated with evaluating effects on commercial crops from a public welfare perspective, we now believe that commercial crop data are not appropriate to use as a basis for identiying a range of alternative standard levels for further analysis, such that we conclude that a level of 15 ppm-hours is the upper end of the range of levels that is appropriate for further analyses in the second draft REA.

With regard to the lower end of this range, we acknowledge that growth effects and visible foliar injury can still occur in sensitive species at levels below 7 ppm-hours. However, we also recognize that significant uncertainties remain regarding the risk of such effects. For example, we conclude that remaining uncertainties make it difficult to judge the point at which visible foliar injury becomes adverse to the public welfare in various types of specially protected areas. Uncertainties associated with monitoring ambient exposures must be considered in evaluating the strength of predictions regarding the degree of tree seedling growth impairment estimated to occur at varying ambient exposures. These uncertainties add to the challenge of judging which exposure levels are expected to be associated with levels of tree seedling growth effects considered adverse to public welfare.

7.4 SUMMARY OF STAFF CONCLUSIONS ON THE SECONDARY O_3 STANDARD

[To be added in the second draft PA.]

7.5 KEY AREAS FOR FUTURE RESEARCH AND DATA COLLECTION

[To be added in the second draft PA.]

7.6 REFERENCES

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