ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 50 and 58

[EPA–HQ–OAR–2005–0172; FRL–9102–1]

RIN 2060–AP98

National Ambient Air Quality Standards for Ozone

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: Based on its reconsideration of the primary and secondary national ambient air quality standards (NAAQS) for ozone (O_3) set in March 2008, EPA proposes to set different primary and secondary standards than those set in 2008 to provide requisite protection of public health and welfare, respectively. With regard to the primary standard for O_3, EPA proposes that the level of the 8-hour primary standard, which was set at 0.075 ppm in the 2008 final rule, should instead be set at a lower level within the range of 0.060 to 0.070 parts per million (ppm), to provide increased protection for children and other "at risk" populations against an array of O_3-related adverse health effects that range from decreased lung function and increased respiratory symptoms to serious indicators of respiratory morbidity including emergency department visits and hospital admissions for respiratory causes, and possibly cardiovascular-related morbidity as well as total non-accidental and cardiopulmonary mortality. With regard to the secondary standard for O_3, EPA proposes that the secondary O_3 standard, which was set identical to the revised primary standard in the 2008 final rule, should instead be a new cumulative, seasonal standard expressed as an annual index of the sum of weighted hourly concentrations, cumulated over 12 hours per day (8 am to 8 pm) 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 15 ppm-hours, to provide increased protection against O_3-related adverse impacts on vegetation and forested ecosystems.

DATES: Written comments on this proposed rule must be received by March 22, 2010.

Public Hearings: Three public hearings are scheduled for this proposed rule. Two of the public hearings will be held on February 2, 2010 in Arlington, Virginia, and Houston, Texas. The third public hearing will be held on February 4, 2010 in Sacramento, California.

ADDRESSES: Submit your comments, identified by Docket ID No. EPA–HQ–OAR–2005–0172, by one of the following methods:

- *http://www.regulations.gov:* Follow the on-line instructions for submitting comments.
- *E-mail: a-and-r-Docket@epa.gov.*
- *Fax:* 202–566–9744.
- *Mail:* Docket No. EPA–HQ–OAR–2005–0172, Environmental Protection Agency, Mail code 6102T, 1200 Pennsylvania Ave., NW., Washington, DC 20460. Please include a total of two copies.
- *Hand Delivery:* Docket No. EPA–HQ–OAR–2005–0172, Environmental Protection Agency, EPA West, Room 3334, 1301 Constitution Ave., NW., Washington, DC. Such deliveries are only accepted during the Docket's normal hours of operation, and special arrangements should be made for deliveries of boxed information.

Public Hearings: Three public hearings are scheduled for this proposed rule. Two of the public hearings will be held on February 2, 2010 in Arlington, Virginia and Houston, Texas. The third public hearing will be held on February 4, 2010 in Sacramento, California. The hearings will be held at the following locations:

Arlington, Virginia—February 2, 2010

Hyatt Regency Crystal City @ Reagan National Airport, Washington Room (located on the Ballroom Level), 2799 Jefferson Davis Highway, Arlington, Virginia 22202, Telephone: 703–418–1234.

Houston, Texas—February 2, 2010

Hilton Houston Hobby Airport, Moody Ballroom (located on the ground floor), 8181 Airport Boulevard, Houston, Texas 77061, Telephone: 713–645–3000.

Sacramento, California—February 4, 2010

Four Points by Sheraton Sacramento International Airport, Natomas Ballroom, 4900 Duckhorn Drive, Sacramento, California 95834, Telephone: 916–263–9000.

See the **SUPPLEMENTARY INFORMATION** under "Public Hearings" for further information.

Instructions: Direct your comments to Docket ID No. EPA–HQ–OAR–2005–0172. The EPA's policy is that all comments received will be included in the public docket without change and may be made available online at *www.regulations.gov*, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through *www.regulations.gov* or e-mail. The *www.regulations.gov* Web site is an "anonymous access" system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA without going through *www.regulations.gov,* your e-mail address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD–ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

Docket: All documents in the docket are listed in the *www.regulations.gov* index. Although listed in the index, some information is not publicly available, *e.g.,* CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in *www.regulations.gov* or in hard copy at the Air and Radiation Docket and Information Center, EPA/DC, EPA West, Room 3334, 1301 Constitution Ave., NW., Washington, DC. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566–1744 and the telephone number for the Air and Radiation Docket and Information Center is (202) 566–1742.

FOR FURTHER INFORMATION CONTACT: Ms. Susan Lyon Stone, Health and Environmental Impacts Division, Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency, Mail Code C504–06, Research Triangle Park, NC 27711; telephone: 919–541–1146; fax: 919–541–0237; e-mail: *stone.susan@epa.gov.*

SUPPLEMENTARY INFORMATION:

General Information

What Should I Consider as I Prepare My Comments for EPA?

1. *Submitting CBI.* Do not submit this information to EPA through *http://www.regulations.gov* or e-mail. Clearly mark the part or all of the information that you claim to be CBI. For CBI information in a disk or CD–ROM that you mail to EPA, mark the outside of the disk or CD–ROM as CBI and then identify electronically within the disk or CD–ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that includes information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

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

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

Availability of Related Information

A number of documents relevant to this rulemaking are available on EPA web sites. The Air Quality Criteria for Ozone and Related Photochemical Oxidants (2006 Criteria Document) (two volumes, EPA/and EPA/, date) is available on EPA's National Center for Environmental Assessment Web site. To obtain this document, go to *http://www.epa.gov/ncea,* and click on Ozone in the Quick Finder section. This will open a page with a link to the March 2006 Air Quality Criteria Document. The 2007 Staff Paper, human exposure and health risk assessments, vegetation exposure and impact assessment, and other related technical documents are available on EPA's Office of Air Quality Planning and Standards (OAQPS) Technology Transfer Network (TTN) web site. The updated final 2007 Staff Paper is available at: *http://epa.gov/ttn/naaqs/standards/ozone/s_o3_cr_sp.html* and the exposure and risk assessments and other related technical documents are available at *http://www.epa.gov/ttn/naaqs/standards/ozone/s_o3_cr_td.html.* The Response to Significant Comments Document is available at: *http://www.epa.gov/ttn/naaqs/standards/ozone/s_o3_cr_rc.html.* These and other related documents are also available for inspection and copying in the EPA docket identified above.

Public Hearings

The public hearings on February 2, 2010 and February 4, 2010 will provide interested parties the opportunity to present data, views, or arguments concerning the proposed rule. The EPA may ask clarifying questions during the oral presentations, but will not respond to the presentations at that time. Written statements and supporting information submitted during the comment period will be considered with the same weight as any oral comments and supporting information presented at the public hearing. Written comments must be received by the last day of the comment period, as specified in this proposed rulemaking.

The public hearings will begin at 9:30 a.m. and continue until 7:30 p.m. (local time) or later, if necessary, depending on the number of speakers wishing to participate. The EPA will make every effort to accommodate all speakers that arrive and register before 7:30 p.m. A lunch break is scheduled from 12:30 p.m. until 2 p.m.

If you would like to present oral testimony at the hearings, please notify Ms. Tricia Crabtree (C504–02), U.S. EPA, Research Triangle Park, NC 27711. The preferred method for registering is by e-mail (*crabtree.tricia@epa.gov*). Ms. Crabtree may be reached by telephone at (919) 541–5688. She will arrange a general time slot for you to speak. The EPA will make every effort to follow the schedule as closely as possible on the day of the hearing.

Oral testimony will be limited to five (5) minutes for each commenter to address the proposal. We will not be providing equipment for commenters to show overhead slides or make computerized slide presentations unless we receive special requests in advance. Commenters should notify Ms. Crabtree if they will need specific audiovisual (AV) equipment. Commenters should also notify Ms. Crabtree if they need specific translation services for non-English speaking commenters. The EPA encourages commenters to provide written versions of their oral testimonies either electronically on computer disk, CD–ROM, or in paper copy.

The hearing schedules, including lists of speakers, will be posted on EPA's Web site for the proposal at *http://www.epa.gov/ttn/naaqs/standards/ozone/s_o3_cr_fr.html* prior to the hearing. Verbatim transcripts of the hearings and written statements will be included in the rulemaking docket.

Children's Environmental Health

Consideration of children's environmental health plays a central role in the reconsideration of the 2008 final decision on the O_3 NAAQS and EPA's decision to propose to set the 8-hour primary O_3 standard at a level within the range of 0.060 to 0.070 ppm. Technical information that pertains to children, including the evaluation of scientific evidence, policy considerations, and exposure and risk assessments, is discussed in all of the documents listed above in the section on the availability of related information. These documents include: the Air Quality Criteria for Ozone and Other Related Photochemical Oxidants; the 2007 Staff Paper; exposure and risk assessments and other related documents; and the Response to Significant Comments. All of these documents are available on the Web, as described above, and are in the public docket for this rulemaking. The public is invited to submit comments or identify peer-reviewed studies and data that assess effects of early life exposure to O_3.

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I. Background

The proposed decisions presented in this notice are based on a reconsideration of the 2008 O_3 NAAQS final rule (73 FR 16436, March 27, 2008), which revised the level of the 8-hour primary O_3 standard to 0.075 ppm and revised the secondary O_3 standard by making it identical to the revised primary standard. This reconsideration is based on the scientific and technical information and analyses on which the March 2008 O_3 NAAQS rulemaking was based. Therefore, much of the information included in this notice is drawn directly from information included in the 2007 proposed rule (72 FR 37818, July 11, 2007) and the 2008 final rule (73 FR 16436).

A. 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. * * *"

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." [1] A secondary standard, as defined in section 109(b)(2), must "specify a level of air quality the attainment and maintenance of which, in the judgment of the Administrator, based on such criteria, is requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of such air pollutant in the ambient air." [2]

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 (DC Cir 1980), *cert. denied,* 449 U.S. 1042 (1980); *American Petroleum Institute* v. *Costle,* 665 F.2d 1176, 1186 (DC 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

[1] 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)].

[2] 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."

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 standards that are "requisite" to protect public health and welfare, 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. *Whitman* v. *America Trucking Associations,* 531 U.S. 457, 473. In establishing "requisite" primary and secondary standards, EPA may not consider the costs of implementing the standards. *Id.* at 471.

Section 109(d)(1) of the CAA 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.

B. Related Control Requirements

States have primary responsibility for ensuring attainment and maintenance of ambient air quality standards once EPA has established them. Under section 110 of the Act (42 U.S.C. 7410) and related provisions, States are to submit, for EPA approval, State implementation plans (SIPs) that provide for the attainment and maintenance of such standards through control programs directed to emission sources.

The majority of man-made nitrogen oxides (NO_X) and volatile organic compounds (VOC) emissions that contribute to O_3 formation in the United States come from three types of sources: Mobile sources, industrial processes (which include consumer and commercial products), and the electric power industry.[3] Mobile sources and the electric power industry were responsible for 78 percent of annual NO_X emissions in 2004. That same year, 99 percent of man-made VOC emissions came from industrial processes (including solvents) and mobile sources. Emissions from natural sources, such as trees, may also comprise a significant portion of total VOC emissions in certain regions of the country, especially during the O_3 season, which are considered natural background emissions.

The EPA has developed new emissions standards for many types of stationary sources and for nearly every class of mobile sources in the last decade to reduce O_3 by decreasing emissions of NO_X and VOC. These programs complement State and local efforts to improve O_3 air quality and meet the 0.084 ppm 8-hour national standards. Under title II of the CAA, 42 U.S.C. 7521–7574), EPA has established new emissions standards for nearly every type of automobile, truck, bus, motorcycle, earth mover, and aircraft engine, and for the fuels used to power these engines. EPA also established new standards for the smaller engines used in small watercraft, lawn and garden equipment. In March 2008, EPA promulgated new standards for locomotive and marine diesel engines and in August 2009, proposed to control emissions from ocean-going vessels.

Benefits from engine standards increase modestly each year as older, more-polluting vehicles and engines are replaced with newer, cleaner models. In time, these programs will yield substantial emission reductions. Benefits from fuel programs generally begin as soon as a new fuel is available.

The reduction of VOC emissions from industrial processes has been achieved either directly or indirectly through implementation of control technology standards, including maximum achievable control technology, reasonably available control technology, and best available control technology standards; or are anticipated due to proposed or upcoming proposals based on generally available control technology or best available controls under provisions related to consumer and commercial products. These standards have resulted in VOC emission reductions of almost a million tons per year accumulated starting in 1997 from a variety of sources including combustion sources, coating categories, and chemical manufacturing. EPA has also finalized emission standards and fuel requirements for new stationary engines. In the area of consumer and commercial products, EPA has finalized new national VOC emission standards for aerosol coatings and is working toward amending existing rules to establish new nationwide VOC content limits for household and institutional consumer products and architectural and industrial maintenance coatings. The aerosol coatings rule took effect in July 2009; the compliance date for both the amended consumer product rule and architectural coatings rule is anticipated to be January 2011. These actions are expected to yield significant new VOC reductions—about 200,000 tons per year. Additionally, in ozone nonattainment areas, we anticipate reductions of an additional 25,000 tons per year as States adopt rules this year implementing control techniques recommendations issued in 2008 for 4 additional categories of consumer and commercial products, typically surface coatings and adhesives used in industrial manufacturing operations. These emission reductions primarily result from solvent controls and typically occur where and when the solvent is used, such as during manufacturing processes.

The power industry is one of the largest emitters of NO_X in the United States. Power industry emission sources include large electric generating units (EGU) and some large industrial boilers and turbines. The EPA's landmark Clean Air Interstate Rule (CAIR), issued on March 10, 2005, was designed to permanently cap power industry emissions of NO_X in the eastern United States. The first phase of the cap was to begin in 2009, and a lower second phase cap was to begin in 2015. The EPA had projected that by 2015, the CAIR and other programs would reduce NO_X emissions during the O_3 season by about 50 percent and annual NO_X emissions by about 60 percent from 2003 levels in the Eastern U.S. However, on July 11, 2008 and December 23, 2008, the U.S. Court of Appeals for the DC Circuit issued decisions on petitions for review of the CAIR. In its July 11 opinion, the court found CAIR unlawful and decided to vacate CAIR and its associated Federal implementation plans (FIPs) in their entirety. On December 23, the court granted EPA's petition for rehearing to the extent that it remanded without vacatur for EPA to conduct further proceedings consistent with the Court's prior opinion. Under this decision, CAIR will remain in place only until replaced by EPA with a rule that is consistent with the Court's July

[3] See EPA report, *Evaluating Ozone Control Programs in the Eastern United States: Focus on the NO_X Budget Trading Program, 2004.*

11 opinion. The EPA recognizes the need in our CAIR replacement effort to address the reconsidered ozone standard, and we are currently assessing our options for the best way to accomplish this. It should also be noted that new electric generating units (EGUs) are also subject to NO_X limits under New Source Performance Standards (NSPS) under CAA section 111, as well as either nonattainment new source review or prevention of significant deterioration requirements.

With respect to agricultural sources, the U.S. Department of Agriculture (USDA) has approved conservation systems and activities that reduce agricultural emissions of NO_X and VOC. Current practices that may reduce emissions of NO_X and VOC include engine replacement programs, diesel retrofit programs, manipulation of pesticide applications including timing of applications, and animal feeding operations waste management techniques. The EPA recognizes that USDA has been working with the agricultural community to develop conservation systems and activities to control emissions of O_3 precursors.

These conservation activities are voluntarily adopted through the use of incentives provided to the agricultural producer. In cases where the States need these measures to attain the standard, the measures could be adopted. The EPA will continue to work with USDA on these activities with efforts to identify and/or improve the control efficiencies, prioritize the adoption of these conservation systems and activities, and ensure that appropriate criteria are used for identifying the most effective application of conservation systems and activities.

The EPA will work together with USDA and with States to identify appropriate measures to meet the primary and secondary standards, including site-specific conservation systems and activities. Based on prior experience identifying conservation measures and practices to meet the PM NAAQS requirements, the EPA will use a similar process to identify measures that could meet the O_3 requirements. The EPA anticipates that certain USDA-approved conservation systems and activities that reduce agricultural emissions of NO_X and VOC may be able to satisfy the requirements for applicable sources to implement reasonably available control measures for purposes of attaining the primary and secondary O_3 NAAQS.

C. Review of Air Quality Criteria and Standards for O_3

In 1971, EPA first established primary and secondary NAAQS for photochemical oxidants (36 FR 8186). 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 hr per year. In 1977, EPA announced the first periodic review of the air quality criteria in accordance with section 109(d)(1) of the Act. The EPA published a final decision in 1979 (44 FR 8202). Both primary and secondary standard levels were 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 1983, EPA announced that the second periodic review of the primary and secondary standards for O_3 had been initiated. Following review and publication of air quality criteria and a supplement, EPA published a proposed decision (57 FR 35542) in August 1992 that 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-hr O_3 exposures. In March 1993, EPA concluded the review by deciding that revisions to the standards were not warranted at that time (58 FR 13008).

In August 1992 (57 FR 35542), EPA announced plans to initiate the third periodic review of the air quality criteria and O_3 NAAQS. On the basis of the scientific evidence contained in the 1996 CD (U.S. EPA 1996a) and 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 in December 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, in the alternative, to establish a new distinct secondary standard using a biologically based cumulative seasonal form. The EPA completed the review in July 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.

The EPA initiated the most recent periodic review of the air quality criteria and standards for O_3 in September 2000 with a call for information (65 FR 57810; September 26, 2000) for the development of a revised Air Quality Criteria Document for O_3 and Other Photochemical Oxidants (henceforth the "2006 Criteria Document"). A project work plan (EPA, 2002) for the preparation of the Criteria Document was released in November 2002 for CASAC and public review. The EPA held a series of workshops in mid-2003 on several draft chapters of the Criteria Document to obtain broad input from the relevant scientific communities. These workshops helped to inform the preparation of the first draft Criteria Document (EPA, 2005a), which was released for CASAC and public review on January 31, 2005; a CASAC meeting was held on May 4–5, 2005 to review the first draft Criteria Document. A second draft Criteria Document (EPA, 2005b) was released for CASAC and public review on August 31, 2005, and was discussed along with a first draft Staff Paper (EPA, 2005c) at a CASAC meeting held on December 6–8, 2005. In a February 16, 2006 letter to the Administrator, CASAC provided comments on the second draft Criteria Document (Henderson, 2006a), and the final 2006 Criteria Document (EPA, 2006a) was released on March 21, 2006. In a June 8, 2006 letter to the Administrator (Henderson, 2006b), CASAC provided additional advice to the Agency concerning chapter 8 of the final 2006 Criteria Document (Integrative Synthesis) to help inform the second draft Staff Paper.

A second draft Staff Paper (EPA, 2006b) was released on July 17, 2006 and reviewed by CASAC on August 24–25, 2006. In an October 24, 2006 letter to the Administrator, CASAC provided advice and recommendations to the Agency concerning the second draft Staff Paper (Henderson, 2006c). A final 2007 Staff Paper (EPA, 2007a) was released on January 31, 2007. In a March 26, 2007 letter (Henderson, 2007), CASAC offered additional advice to the Administrator with regard to recommendations and revisions to the primary and secondary O_3 NAAQS.

The schedule for completion of the 2008 rulemaking was governed by a consent decree resolving a lawsuit filed in March 2003 by a group of plaintiffs representing national environmental

and public health organizations, alleging that EPA had failed to complete the review within the period provided by statute.[4] The modified consent decree that governed the 2008 rulemaking, entered by the court on December 16, 2004, provided that EPA sign for publication notices of proposed and final rulemaking concerning its review of the O_3 NAAQS no later than March 28, 2007 and December 19, 2007, respectively. That consent decree was further modified in October 2006 to change these proposed and final rulemaking dates to no later than May 30, 2007 and February 20, 2008, respectively. These dates for signing the publication notices of proposed and final rulemaking were further extended to no later than June 20, 2007 and March 12, 2008, respectively. The proposed decision was signed on June 20, 2007 and published in the **Federal Register** on July 11, 2007 (72 FR 37818).

Public hearings on the proposed decision were held on Thursday, August 30, 2007 in Philadelphia, PA and Los Angeles, CA. On Wednesday, September 5, 2007, hearings were held in Atlanta, GA, Chicago, IL, and Houston, TX. A large number of comments were received from various commenters on the 2007 proposed revisions to the O_3 NAAQS. A comprehensive summary of all significant comments, along with EPA's responses (henceforth "Response to Comments"), can be found in the docket for the 2008 rulemaking, which is also the docket for this reconsideration rulemaking.

The EPA's final decision on the O_3 NAAAQS was published in the **Federal Register** on March 27, 2008 (73 FR 16436). In the 2008 rulemaking, EPA revised the level of the 8-hour primary standard for O_3 to 0.075 parts per million (ppm), expressed to three decimal places. With regard to the secondary standard for O_3, EPA revised the 8-hour standard by making it identical to the revised primary standard. The EPA also made conforming changes to the Air Quality Index (AQI) for O_3, setting an AQI value of 100 equal to 0.075 ppm, 8-hour average, and making proportional changes to the AQI values of 50, 150 and 200.

D. Reconsideration of the 2008 O_3 NAAQS Final Rule

Consistent with a directive of the new Administration regarding the review of new and pending regulations (Emanuel memorandum, 74 FR 4435; January 26, 2009), the Administrator reviewed a number of actions that were taken in the last year by the previous Administration. The 2008 final rule was included in this review in recognition of the central role that the NAAQS play in enabling EPA to fulfill its mission to protect the nation's public health and welfare. In her review, the Administrator was mindful of the need for judgments concerning the NAAQS to be based on a strong scientific foundation which is developed through a transparent and credible NAAQS review process, consistent with the core values highlighted in President Obama's memorandum on scientific integrity (March 9, 2009).

1. Decision To Initiate a Rulemaking To Reconsider

In her review of the 2008 final rule, several aspects of the final rule related to the primary and secondary standards stood out to the Administrator. As an initial matter, the Administrator noted that the 2008 final rule concluded that the 1997 primary and secondary O_3 standards were not adequate to protect public health and public welfare, and that revisions were necessary to provide increased protection. With respect to revision of the primary standard, the Administrator noted that the revised level established in the 2008 final rule was above the range that had been unanimously recommended by CASAC.[5] She also noted that EPA received comments from a large number of commenters from the medical and public health communities, including EPA's Children's Health Protection Advisory Committee, all of which endorsed levels within CASAC's recommended range.

With respect to revision of the secondary O_3 standard, the Administrator noted that the 2008 final rule differed substantially from CASAC's recommendations that EPA adopt a new secondary O_3 standard based on a cumulative, seasonal measure of exposure. The 2008 final rule revised the secondary standard to be identical to the revised primary standard, which is based on an 8-hour daily maximum measure of exposure. She also noted that EPA received comments from a number of commenters representing environmental interests, all of which endorsed CASAC;s recommendation for a new cumulative, seasonal secondary standard.[6]

Subsequent to issuance of the 2008 final rule, in April 2008, CASAC took the unusual step of sending EPA a letter expressing strong, unanimous disagreement with EPA's decisions on both the primary and secondary standards (Henderson, 2008). The CASAC explained that it did not endorse the revised primary O_3 standard as being sufficiently protective of public health because it failed to satisfy the explicit stipulation of the Act to provide an adequate margin of safety. The CASAC also expressed the view that failing to revise the secondary standard to a cumulative, seasonal form was not supported by the available science. In addition to CASAC's letter, the Administrator noted a recent adverse ruling issued by the U.S. Court of Appeals for the District of Columbia Circuit on another NAAQS decision. In February 2009, the DC Circuit remanded the Agency's decisions on the primary annual and secondary standards for fine particles ($PM_{2.5}$). In so doing, the Court found that EPA had not adequately explained the basis for its decisions, including why CASAC's recommendations for a more health-protective primary annual standard and for secondary standards different from the primary standards were not accepted. *American Farm Bureau* v. *EPA,* 559 F.3d. 512 (DC Cir. 2009).

Based on her review of the information described above, the Administrator is initiating a rulemaking to reconsider parts of the 2008 final rule. Specifically, the Administrator is reconsidering the level of the primary standard to ensure that it is sufficiently protective of public health, as discussed in section II below, and is reconsidering all aspects of the secondary standard to ensure that it appropriately reflects the available science and is sufficiently protective of public welfare, as discussed in section IV below. Based on her review, the Administrator has serious cause for concern regarding whether the revisions to the primary and secondary O_3 standards adopted in the 2008 final rule satisfy the requirements of the CAA, in light of the body of scientific evidence before the Agency. In addition, the importance of the O_3 NAAQS to public health and welfare weigh heavily in favor of reconsidering parts of the 2008 final rule as soon as possible, based on the scientific and technical information upon which the 2008 final rule was based.

[4] *American Lung Association* v. *Whitman* (No. 1:03CV00778, D.DC 2003).

[5] The level of the 8-hour primary ozone standard was set at 0.075 ppm, while CASAC unanimously recommended a range between 0.060 and 0.070 ppm.

[6] The Administrator also noted the exchange that had occurred between EPA and the Office of Management and Budget (OMB) with regard to the final decision on the secondary standard, as discussed in the 2008 final rule (73 FR 16497).

Also, EPA conducted a provisional assessment of "new" scientific papers (EPA, 2009) of scientific literature evaluating health and ecological effects of O_3 exposure published since the close of the 2006 Criteria Document upon which the 2008 O_3 NAAQS were based. The Administrator notes that the provisional assessment of "new" science found that such studies did not materially change the conclusions in the 2006 Criteria Document. This provisional assessment is supportive of the Administrator's decision to reconsider parts of the 2008 final rule at this time, based on the scientific and technical information available for the 2008 final rule, as compared to foregoing such reconsideration and taking appropriate action in the future as part of the next periodic review of the air quality criteria and NAAQS, which will include such scientific and technical information.

The reconsideration of parts of the 2008 final rule discussed in this notice is based on the scientific and technical record from the 2008 rulemaking, including public comments and CASAC advice and recommendations. The information that was assessed during the 2008 rulemaking includes information in the 2006 Criteria Document (EPA, 2006a), the 2007 Policy Assessment of Scientific and Technical Information, referred to as the 2007 Staff Paper (EPA, 2007b), and related technical support documents including the 2007 REAs (U.S. EPA, 2007c; Abt Associates, 2007a,b). Scientific and technical information developed since the 2006 Criteria Document will be considered in the next periodic review, instead of this reconsideration rulemaking, allowing the new information to receive careful and comprehensive review by CASAC and the public before it is used as a basis in a rulemaking that determines whether to revise the NAAQS.

2. Ongoing Litigation

In May 2008, following publication of the 2008 final rule, numerous groups, including state, public health, environmental, and industry petitioners, challenged EPA's decisions in federal court. The challenges were consolidated as *State of Mississippi, et al.* v. *EPA* (No. 08–1200, DC Cir. 2008). On March 10, 2009, EPA filed an unopposed motion requesting that the Court vacate the briefing schedule and hold the consolidated cases in abeyance. The Agency stated its desire to allow time for appropriate officials from the new Administration to review the O_3 standards to determine whether they should be maintained, modified or otherwise reconsidered. The EPA further requested that it be directed to notify the Court and all the parties of any actions it has taken or intends to take, if any, within 180 days of the Court vacating the briefing schedule. On March 19, 2009, the Court granted EPA's motion. Pursuant to the Court's order, on September 16, 2009 EPA notified the Court and the parties of its decision to initiate a rulemaking to reconsider the primary and secondary O_3 standards set in March 2008 to ensure they satisfy the requirements of the CAA.[7] In its notice to the Court, EPA stated that this notice of proposed rulemaking would be signed by December 21, 2009, and that the final rule will be signed by August 31, 2010.

II. Rationale for Proposed Decision on the Level of the Primary Standard

As an initial matter, the Administrator notes that the 2008 final rule concluded that the 1997 primary O_3 standard was "not sufficient and thus not requisite to protect public health with an adequate margin of safety, and that revision is needed to provide increased public health protection" (73 FR 16472). The Administrator is not reconsidering this aspect of the 2008 decision, which is based on the reasons discussed in section II.B of the 2008 final rule (73 FR 16443–16472). The Administrator also notes that the 2008 final rule concluded that it was appropriate to retain the O_3 indicator, the 8-hour averaging time, and form of the primary O_3 standard (specified as the annual fourth-highest daily maximum 8-hour concentration, averaged over 3 years), while concluding that revision of the standard level was appropriate.[8] The Administrator is not reconsidering these aspects of the 2008 decision, which are based on the reasons discussed in sections II.C.1–3 of the 2008 final rule, which address the indicator, averaging time, and form, respectively, of the primary O_3 standard (73 FR 16472–16475). For these reasons, the Administrator is not reopening the 2008 decision with regard to the need to revise the 1997 primary O_3 standard nor with regard to the indicator, averaging time, and form of the 2008 primary O_3 standard. Thus, the information that follows in this section specifically focuses on a reconsideration of level of the primary O_3 standard.

This section presents the rationale for the Administrator's proposed decision that the O_3 primary standard, which was set at a level of 0.075 ppm in the 2008 final rule, should instead be set at a lower level within the range from 0.060 to 0.070 ppm. As discussed more fully below, the rationale for the proposed range of standard levels is based on a thorough review of the latest scientific information on human health effects associated with the presence of O_3 in the ambient air presented in the 2006 Criteria Document. This rationale also takes into account: (1) Staff assessments of the most policy-relevant information in the 2006 Criteria Document and staff analyses of air quality, human exposure, and health risks, presented in the 2007 Staff Paper, upon which staff recommendations for revisions to the primary O_3 standard in the 2008 rulemaking were based; (2) CASAC advice and recommendations, as reflected in discussions of drafts of the 2006 Criteria Document and 2007 Staff Paper at public meetings, in separate written comments, and in CASAC's letters to the Administrator both before and after the 2008 rulemaking; and (3) public comments received during the development of these documents, either in connection with CASAC meetings or separately, and on the 2007 proposed rule.

In developing this rationale, the Administrator recognizes that the CAA requires her to reach a public health policy judgment as to what standard would be requisite to protect public health with an adequate margin of safety, based on scientific evidence and technical assessments that have inherent uncertainties and limitations. This judgment requires making reasoned decisions as to what weight to place on various types of evidence and assessments, and on the related uncertainties and limitations. Thus, in selecting standard levels to propose, and subsequently in selecting a final level, the Administrator is seeking not only to prevent O_3 levels that have been demonstrated to be harmful but also to prevent lower O_3 levels that may pose an unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree.

In this proposed rule, EPA has drawn upon an integrative synthesis of the entire body of evidence, published

[7] The EPA also separately announced that it will move quickly to implement any new standards that might result from this reconsideration. To reduce the workload for states during the interim period of reconsideration, the Agency intends to propose to defer compliance with the CAA requirement to designate areas as attainment or nonattainment. EPA will work with states, local governments and tribes to ensure that air quality is protected during that time.

[8] The use of O_3 as the indicator for photochemical oxidants was adopted in the 1979 final rule and retained in subsequent rulemaking. An 8-hour averaging time and a form based on the annual fourth-highest daily maximum 8-hour concentration, averaged over 3 years, were adopted in the 1997 final rule and retained in the 2008 rulemaking.

through early 2006, on human health effects associated with the presence of O_3 in the ambient air. As discussed below in section II.A, this body of evidence addresses a broad range of health endpoints associated with exposure to ambient levels of O_3 (EPA, 2006a, chapter 8), and includes over one hundred epidemiologic studies conducted in the U.S., Canada, and many countries around the world.[9] In reconsidering this evidence, EPA focuses on those health endpoints that have been demonstrated to be caused by exposure to O_3, or for which the 2006 Criteria Document judges associations with O_3 to be causal, likely causal, or for which the evidence is highly suggestive that O_3 contributes to the reported effects. This rationale also draws upon the results of quantitative exposure and risk assessments, discussed below in section II.B. Section II.C focuses on the considerations upon which the Administrator's proposed conclusions on the level of the primary standard are based. Policy-relevant evidence-based and exposure/risk-based considerations are discussed, and the rationale for the 2008 final rulemaking on the primary standard and CASAC advice, given both prior to the development of the 2007 proposed rule and following the 2008 final rule, are summarized. Finally, the Administrator's proposed conclusions on the level of the primary standard are presented. Section II.D summarizes the proposed decision on the level of the primary O_3 standard and the solicitation of public comments.

Judgments made in the 2006 Criteria Document and 2007 Staff Paper about the extent to which relationships between various health endpoints and short-term exposures to ambient O_3 are likely causal have been informed by several factors. As discussed below in section II.A, these factors include the nature of the evidence (*i.e.,* controlled human exposure, epidemiological, and/or toxicological studies) and the weight of evidence, which takes into account such considerations as biological plausibility, coherence of evidence, strength of association, and consistency of evidence.

In assessing the health effects data base for O_3, it is clear that human studies provide the most directly applicable information for determining causality because they are not limited by the uncertainties of dosimetry differences and species sensitivity differences, which would need to be addressed in extrapolating animal toxicology data to human health effects. Controlled human exposure studies provide data with the highest level of confidence since they provide human health effects data under closely monitored conditions and can provide exposure-response relationships. Epidemiological data provide evidence of associations between ambient O_3 levels and more serious acute and chronic health effects (*e.g.,* hospital admissions and mortality) that cannot be assessed in controlled human exposure studies. For these studies the degree of uncertainty introduced by potentially confounding variables (*e.g.,* other pollutants, temperature) and other factors affects the level of confidence that the health effects being investigated are attributable to O_3 exposures, alone and in combination with other copollutants.

In using a weight of evidence approach to inform judgments about the degree of confidence that various health effects are likely to be caused by exposure to O_3, confidence increases as the number of studies consistently reporting a particular health endpoint grows and as other factors, such as biological plausibility and strength, consistency, and coherence of evidence, increase. Conclusions regarding biological plausibility, consistency, and coherence of evidence of O_3-related health effects are drawn from the integration of epidemiological studies with mechanistic information from controlled human exposure studies and animal toxicological studies. As discussed below, this type of mechanistic linkage has been firmly established for several respiratory endpoints (*e.g.,* lung function decrements, lung inflammation) but remains far more equivocal for cardiovascular endpoints (*e.g.,* cardiovascular-related hospital admissions). For epidemiological studies, strength of association refers to the magnitude of the association and its statistical strength, which includes assessment of both effects estimate size and precision. In general, when associations yield large relative risk estimates, it is less likely that the association could be completely accounted for by a potential confounder or some other bias. Consistency refers to the persistent finding of an association between exposure and outcome in multiple studies of adequate power in different persons, places, circumstances and times. For example, the magnitude of effect estimates is relatively consistent across recent studies showing association between short-term, but not long-term, O_3 exposure and mortality.

Based on the information discussed below in sections II.A.1–II.A.3, judgments concerning the extent to which relationships between various health endpoints and ambient O_3 exposures are likely causal are summarized below in section II.A.3.c. These judgments reflect the nature of the evidence and the overall weight of the evidence, and are taken into consideration in the quantitative exposure and risk assessments, discussed below in section II.B.

To put judgments about health effects that have been demonstrated to be caused by exposure to O_3, or for which the 2006 Criteria Document judges associations with O_3 to be causal, likely causal, or for which the evidence is highly suggestive that O_3 contributes to the reported effects into a broader public health context, EPA has drawn upon the results of the quantitative exposure and risk assessments. These assessments provide estimates of the likelihood that individuals in particular population groups that are at risk for various O_3-related physiological health effects would experience "exposures of concern" and specific health endpoints under varying air quality scenarios (*i.e.,* just meeting various standards[10]), as well as characterizations of the kind and degree of uncertainties inherent in such estimates.

In the 2008 final rulemaking and in this reconsideration, the term "exposures of concern" is defined as personal exposures while at moderate or greater exertion to 8-hour average ambient O_3 levels at and above specific benchmark levels which represent exposure levels at which O_3-related health effects are known or can reasonably be inferred to occur in some individuals, as discussed below in section II.B.1.[11] The EPA emphasizes

[9] In its assessment of the epidemiological evidence judged to be most relevant to making decisions on the level of the O_3 primary standard, EPA has placed greater weight on U.S. and Canadian epidemiologic studies, since studies conducted in other countries may well reflect different demographic and air pollution characteristics.

[10] The exposure assessment done as part of the 2008 final rulemaking considered several air quality scenarios, including just meeting what was then the current standard set at a level of 0.084 ppm, as well as just meeting alternative standards at levels of 0.080, 0.074, 0.070, and 0.064 ppm.

[11] Exposures of concern were also considered in the 1997 review of the O_3 NAAQS, and were judged by EPA to be an important indicator of the public health impacts of those O_3-related effects for which information was too limited to develop quantitative estimates of risk but which had been observed in humans at and above the benchmark level of 0.08 ppm for 6- to 8-hour exposures * * * including increased nonspecific bronchial responsiveness (for example, aggravation of asthma), decreased pulmonary defense mechanisms (suggestive of increased susceptibility to respiratory infection), and indicators of pulmonary inflammation (related

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that although the analysis of "exposures of concern" was conducted using three discrete benchmark levels (*i.e.,* 0.080, 0.070, and 0.060 ppm), 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. The EPA recognizes that there is no sharp breakpoint within the continuum ranging from at and above 0.080 ppm down to 0.060 ppm. In considering the concept of exposures of concern, 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 at lower O_3 levels.

Within the context of this continuum, estimates of exposures of concern at discrete benchmark levels 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 cannot be evaluated in quantitative risk assessments, such as lung inflammation, increased airway responsiveness, and changes in host defenses. They also help in understanding the extent to which such impacts have the potential to be reduced by meeting various standards. These O_3-related physiological effects are plausibly linked to the increased morbidity seen in epidemiological studies (*e.g.,* as indicated by increased medication use in asthmatics, school absences in all children, and emergency department visits and hospital admissions in people with lung disease). Estimates of the number of people likely to experience exposures of concern cannot be directly translated into quantitative estimates of the number of people likely to experience specific health effects, since sufficient information to draw such comparisons is not available—if such information were available, these health outcomes would have been included in the quantitative risk assessment. Due to individual variability in responsiveness, only a subset of individuals who have exposures at and above a specific benchmark level can be expected to experience such adverse health effects, and susceptible subpopulations such as those with asthma are expected to be affected more by such exposures than healthy individuals. The amount of weight to place on the estimates of exposures of concern at any of these benchmark levels depends in part on the weight of the scientific evidence concerning health effects associated with O_3 exposures at and above that benchmark level. It also depends on judgments about the importance from a public health perspective of the health effects that are known or can reasonably be inferred to occur as a result of exposures at and above the benchmark level. Such public health policy judgments are embodied in the NAAQS standard setting criteria (*i.e.,* standards that, in the judgment of the Administrator, are requisite to protect public health with an adequate margin of safety).

As discussed below in section II.B.2, the quantitative health risk assessment conducted as part of the 2008 final rulemaking includes estimates of risks of lung function decrements in asthmatic and all school age children, respiratory symptoms in asthmatic children, respiratory-related hospital admissions, and non-accidental and cardiorespiratory-related mortality associated with recent ambient O_3 levels, as well as risk reductions and remaining risks associated with just meeting the then current 0.084 ppm standard and various alternative O_3 standards in a number of example urban areas. There are two parts to this risk assessment: one part is based on combining information from controlled human exposure studies with modeled population exposure, and the other part is based on combining information from community epidemiological studies with either monitored or adjusted ambient concentrations levels. This assessment provides estimates of the potential magnitude of O_3-related health effects, as well as a characterization of the uncertainties and variability inherent in such estimates. This assessment also provides insights into the distribution of risks and patterns of risk reductions associated with meeting alternative O_3 standards.

As discussed below, a substantial amount of new research conducted since the 1997 review of the O_3 NAAQS was available to inform the 2008 final rulemaking, with important new information coming from epidemiologic studies as well as from controlled human exposure, toxicological, and dosimetric studies. The research studies newly available in the 2008 final rulemaking that were evaluated in the 2006 Criteria Document and the exposure and risk assessments presented in the 2007 Staff Paper have undergone intensive scrutiny through multiple layers of peer review and many opportunities for public review and comment. While important uncertainties remain in the qualitative and quantitative characterizations of health effects attributable to exposure to ambient O_3, and while different interpretations of these uncertainties can result in different public health policy judgments, the review of this information has been extensive and deliberate. In the judgment of the Administrator, this intensive evaluation of the scientific evidence provides an adequate basis for this reconsideration of the 2008 final rulemaking.

A. Health Effects Information

This section outlines key information contained in the 2006 Criteria Document (chapters 4–8) and in the 2007 Staff Paper (chapter 3) on known or potential effects on public health which may be expected from the presence of O_3 in ambient air. The information highlighted here summarizes: (1) New information available on potential mechanisms for health effects associated with exposure to O_3; (2) the nature of effects that have been associated directly with exposure to O_3 and indirectly with the presence of O_3 in ambient air; (3) an integrative interpretation of the evidence, focusing on the biological plausibility and coherence of the evidence; and (4) considerations in characterizing the public health impact of O_3, including the identification of "at risk" populations.

The decision in the 1997 review focused primarily on evidence from short-term (*e.g.,* 1 to 3 hours) and prolonged (6 to 8 hours) controlled-exposure studies reporting lung function decrements, respiratory symptoms, and respiratory inflammation in humans, as well as epidemiology studies reporting excess hospital admissions and emergency department (ED) visits for respiratory causes. The 2006 Criteria Document prepared for the 2008 rulemaking emphasized the large number of epidemiological studies published since the last review with these and additional health endpoints, including the effects of acute (short-term and prolonged) and chronic exposures to O_3 on lung function decrements and enhanced respiratory symptoms in asthmatic individuals, school absences, and premature mortality. It also emphasized important new information from toxicology, dosimetry, and controlled human exposure studies. Highlights of the evidence include:

(1) Two new controlled human-exposure studies are now available that examine respiratory effects associated with prolonged O_3 exposures at levels below 0.080 ppm, which was the lowest

to potential aggravation of chronic bronchitis or long-term damage to the lungs). (62 FR 38868)

exposure level that had been examined in the 1997 review.

(2) Numerous controlled human-exposure studies have examined indicators of O_3-induced inflammatory response in both the upper respiratory tract (URT) and lower respiratory tract (LRT), and increased airway responsiveness to allergens in subjects with allergic asthma and allergic rhinitis exposed to O_3, while other studies have examined changes in host defense capability following O_3 exposure of healthy young adults.

(3) Animal toxicology studies provide new information regarding mechanisms of action, increased susceptibility to respiratory infection, and the biological plausibility of acute effects and chronic, irreversible respiratory damage.

(4) Numerous acute exposure epidemiological studies published during the past decade offer added evidence of ambient O_3-related lung function decrements and respiratory symptoms in physically active healthy subjects and greater responses in asthmatic subjects, as well as evidence on new health endpoints, such as the relationships between ambient O_3 concentrations and asthma medication use and school absenteeism, and between ambient O_3 and cardiac-related physiological endpoints.

(5) Several additional studies have been published over the last decade examining the temporal associations between O_3 exposures and emergency department visits for asthma and other respiratory diseases and respiratory-related hospital admissions.

(6) A large number of newly available epidemiological studies have examined the effects of acute exposure to PM and O_3 on mortality, notably including large multicity studies that provide much more robust and credible information than was available in the 1997 review, as well as recent meta-analyses that have evaluated potential sources of heterogeneity in O_3-mortality associations.

1. Overview of Mechanisms

Evidence on possible mechanisms by which exposure to O_3 may result in acute and chronic health effects is discussed in chapters 5 and 6 of the 2006 Criteria Document.[12] Evidence from dosimetry, toxicological, and human exposure studies has contributed to an understanding of the mechanisms that help to explain the biological plausibility and coherence of evidence for O_3-induced respiratory health effects reported in epidemiological studies. More detailed information about the physiological mechanisms related to the respiratory effects of short- and long-term exposure to O_3 can be found in section II.A.3.b.i and II.A.3.b.iii, respectively. In the past, however, little information was available to help explain potential biological mechanisms which linked O_3 exposure to premature mortality or cardiovascular effects. As discussed more fully in section II.A.3.b.ii below, since the 1997 review an emerging body of animal toxicology and controlled human exposure evidence is beginning to suggest mechanisms that may mediate acute O_3 cardiovascular effects. While much is known about mechanisms that play a role in O_3-related respiratory effects, additional research is needed to more clearly understand the role that O_3 may have in contributing to cardiovascular effects.

With regard to the mechanisms related to short-term respiratory effects, scientific evidence discussed in the 2006 Criteria Document (section 5.2) indicates that reactions of O_3 with lipids and antioxidants in the epithelial lining fluid and the epithelial cell membranes of the lung can be the initial step in mediating deleterious health effects of O_3. This initial step activates a cascade of events that lead to oxidative stress, injury, inflammation, airway epithelial damage and increased alveolar permeability to vascular fluids. Inflammation can be accompanied by increased airway responsiveness, which is an increased bronchoconstrictive response to airway irritants and allergens. Continued respiratory inflammation also can alter the ability of the body to respond to infectious agents, allergens and toxins. Acute inflammatory responses to O_3 in some healthy people are well documented, and precursors to lung injury are observed within 3 hours after exposure in humans. Repeated respiratory inflammation can lead to a chronic inflammatory state with altered lung structure and lung function and may lead to chronic respiratory diseases such as fibrosis and emphysema (EPA, 2006a, section 8.6.2). The severity of symptoms and magnitude of response to acute exposures depend on inhaled dose, as well as on individual susceptibility to O_3, as discussed below. At the same O_3 dose, individuals who are more susceptible to O_3 will have a larger response than those who are less susceptible; among individuals with similar susceptibility, those who receive a larger dose will have a larger response to O_3.

The inhaled dose is the product of O_3 concentration (C), minute ventilation or ventilation rate, and duration of exposure (T), or (C × ventilation rate × T). A large body of data regarding the interdependent effect of these components of inhaled dose on pulmonary responses was assessed in the 1986 and 1996 O_3 Criteria Documents. In an attempt to describe O_3 dose-response characteristics, acute responses were modeled as a function of total inhaled O_3 dose, which was generally found to be a better predictor of response than O_3 concentration, ventilation rate, or duration of exposure, alone, or as a combination of any two of these factors (EPA 2006a, section 6.2). Predicted O_3-induced decrements in lung function have been shown to be a function of exposure concentration, duration and exercise level for healthy, young adults (McDonnell *et al.,* 1997). A meta-analysis of 21 studies (Mudway and Kelly, 2004) showed that markers of inflammation and increased cellular permeability in healthy subjects are associated with total O_3 dose.

The 2006 Criteria Document summarizes information on potentially susceptible and vulnerable groups in section 8.7. As described there, the term *susceptibility* refers to innate (*e.g.,* genetic or developmental) or acquired (*e.g.,* personal risk factors, age) factors that make individuals more likely to experience effects with exposure to pollutants. A number of population groups and lifestages have been identified as potentially susceptible to health effects as a result of O_3 exposure, including people with existing lung diseases, including asthma, children and older adults, and people who have larger than normal lung function responses that may be due to genetic susceptibility. In addition, some population groups and lifestages have been identified as having increased *vulnerability* to O_3-related effects due to increased likelihood of exposure while at elevated ventilation rates, including healthy children and adults who are active outdoors, for example, outdoor workers, and joggers. Taken together, the susceptible and vulnerable groups are more commonly referred to as "at-risk" groups,[13] as discussed more fully below in section II.A.4.b.

[12] While most of the available evidence addresses mechanisms for O_3, O_3 clearly serves as an indicator for the total photochemical oxidant mixture found in the ambient air. Some effects may be caused by one or more components in the overall pollutant mix, either separately or in combination with O_3. However, O_3 clearly dominates these other oxidants with their concentrations only being a few percent of the O_3 concentration.

[13] In previous Staff Papers and Federal Register notices announcing proposed and final decisions on the O_3 and other NAAQS, EPA has used the phrase

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Based on a substantial body of new evidence from animal, controlled human exposure and epidemiological studies, the 2006 Criteria Document concludes that people with asthma and other preexisting pulmonary diseases are likely to be among those at increased risk from O_3 exposure. Altered physiological, morphological and biochemical states typical of respiratory diseases like asthma, COPD and chronic bronchitis may render people sensitive to additional oxidative burden induced by O_3 exposure (EPA 2006a, section 8.7). Children and adults with asthma are the group that has been studied most extensively. Evidence from controlled human exposure studies indicates that asthmatics may exhibit larger lung function decrements in response to O_3 exposure than healthy controls. As discussed more fully in section II.A.4.b.ii below, asthmatics present a differential response profile for cellular, molecular, and biochemical parameters (EPA, 2006a, section 8.7.1) that are altered in response to acute O_3 exposure. They can have larger inflammatory responses, as manifested by larger increases in markers of inflammation such as white bloods cells (*e.g.,* PMNs) or inflammatory cytokines. Asthmatics, and people with allergic rhinitis, are more likely to mount an allergic-type response upon exposure to O_3, as manifested by increases in white blood cells associated with allergy (*i.e.,* eosinophils) and related molecules, which increase inflammation in the airways. The increased inflammatory and allergic responses also may be associated with the larger late-phase responses that asthmatics can experience, which can include increased bronchoconstrictor responses to irritant substances or allergens and additional inflammation. In addition to the experimental evidence of lung function decrements, respiratory symptoms, and other respiratory effects in asthmatic populations, two large U.S. epidemiological studies as well as several smaller U.S. and international studies, have reported fairly robust associations between ambient O_3 concentrations and measures of lung function and daily symptoms (*e.g.,* chest tightness, wheeze, shortness of breath) in children with moderate to severe asthma and between O_3 and increased asthma medication use (EPA, 2007a, chapter 6). These responses in asthmatics and others with lung disease provide biological plausibility for the more serious respiratory morbidity effects observed in epidemiological studies, such as emergency department visits and hospital admissions.

Children with and without asthma were found to be particularly susceptible to O_3 effects on lung function and generally have greater lung function responses than older people. The American Academy of Pediatrics (2004) notes that children and infants are among the population groups most susceptible to many air pollutants, including O_3. This is in part because their lungs are still developing. For example, eighty percent of alveoli are formed after birth, and changes in lung development continue through adolescence (Dietert *et al.,* 2000). Moreover, children have high minute ventilation rates and relatively high levels of physical activity which also increases their O_3 dose (*Plunkett et al.,* 1992). Thus, children are at-risk due to both their susceptibility and vulnerability.

Looking more broadly at age-related differences in susceptibility, several mortality studies have investigated age-related differences in O_3 effects (EPA, 2006a, section 7.6.7.2), primarily in the older adult population. Among the studies that observed positive associations between O_3 and mortality, a comparison of all age or younger age (65 years of age) O_3-mortality effect estimates to that of the elderly population (>65 years) indicates that, in general, the elderly population is more susceptible to O_3 mortality effects. There is supporting evidence of age-related differences in susceptibility to O_3 lung function effects. The 2006 Criteria Document (section 7.6.7.2) concludes that the elderly population (>65 years of age) appear to be at greater risk of O_3-related mortality and hospitalizations compared to all ages or younger populations, and children (<18 years of age) experience other potentially adverse respiratory health outcomes with increased O_3 exposure.

Controlled human exposure studies have also indicated a high degree of interindividual variability in some of the pulmonary physiological parameters, such as lung function decrements. The variable effects in individuals have been found to be reproducible, in other words, a person who has a large lung function response after exposure to O_3 will likely have about the same response if exposed again to the same dose of O_3 (EPA 2006a, section 6.1). In controlled human exposure studies, group mean responses are not representative of this segment of the population that has much larger than average responses to O_3. Recent studies, discussed in section II.A.4.b.iv below, reported a role for genetic polymorphism (*i.e.,* the occurrence together in the same population of more than one allele or genetic marker at the same locus with the least frequent allele or marker occurring more frequently than can be accounted for by mutation alone) in observed differences in antioxidant enzymes and genes involved in inflammation to modulate pulmonary function and inflammatory responses to O_3 exposure. These observations suggest a potential role for these markers in the innate susceptibility to O_3, however, the validity of these markers and their relevance in the context of prediction to population studies needs additional experimentation.

Controlled human exposure studies that provide information about mechanisms of the initial response to O_3 (*e.g.,* lung function decrements, inflammation, and injury to the lung) also inform the selection of appropriate lag times to analyze in epidemiological studies through elucidation of the time course of these responses (EPA 2006a, section 8.4.3). Based on the results of these studies, it would be reasonable to expect that lung function decrements could be detected epidemiologically within lags of 0 (same day) or 1 to 2 days following O_3 exposure, given the rapid onset of lung function changes and their persistence for 24 to 48 hours among more responsive human subjects in controlled human exposure studies. Other responses take longer to develop and can persist for longer periods of time. For example, although asthmatic individuals may begin to experience symptoms soon after O_3 exposure, it may take anywhere from 1 to 3 days after exposure for these subjects to seek medical attention as a result of increased airway responsiveness or inflammation that may persist for 2 to 3 days. This may be reflected by epidemiologic observations of significantly increased risk for asthma-related emergency department visits or hospital admissions with 1- to 3-day lags, or, perhaps, enhanced distributed lag risks (combined across 3 days) for such morbidity indicators. Analogously, one might project increased mortality within 0- to 3-day lags as a possible consequence of O_3-induced increases in clotting agents arising from the cascade of events, starting with cell injury described above, occurring within 12 to 24 hours of O_3 exposure. The time course for many of these initial responses to O_3 is highly variable.

"sensitive population groups" to include both population groups that are at increased risk because they are more intrinsically susceptible and population groups that are more vulnerable due to an increased potential for exposure. In this notice, we use the phrase, "at risk" populations to include both types of population groups.

Moreover these observations pertain only to the initial response to O_3. Consequent responses can follow. For example, Jörres *et al.,* (1996) found that in subjects with asthma and allergic rhinitis, a maximum percent fall in FEV_1 of 27.9% and 7.8%, respectively, occurred 3 days after O_3 exposure when they were challenged with of the highest common dose of allergen.

2. Nature of Effects

The 2006 Criteria Document provides new evidence that notably enhances our understanding of short-term and prolonged exposure effects, including effects on lung function, symptoms, and inflammatory effects reported in controlled exposure studies. These studies support and extend the findings of the previous Criteria Document. There is also a significant body of new epidemiological evidence of associations between short-term and prolonged exposure to O_3 and effects such as premature mortality, hospital admissions and emergency department visits for respiratory (*e.g.,* asthma) causes. Key epidemiological and controlled human exposure studies are summarized below and discussed in chapter 3 of the 2007 Staff Paper, which is based on scientific evidence critically reviewed in chapters 5, 6, and 7 of the 2006 Criteria Document, as well as the Criteria Document's integration of scientific evidence contained in chapter 8.[14] Conclusions drawn about O_3-related health effects are based upon the full body of evidence from controlled human exposure, epidemiological and toxicological data contained in the 2006 Criteria Document.

a. Morbidity

This section summarizes scientific information on the effects of inhalation of O_3, including public health effects of short-term, prolonged, and long-term exposures on respiratory morbidity and cardiovascular system effects, as discussed in chapters 6, 7 and 8 of the 2006 Criteria Document and chapter 3 of the 2007 Staff Paper. This section also summarizes the uncertainty about the potential indirect effects on public health associated with changes due to increases in UV–B radiation exposure, such as UV–B radiation-related skin cancers, that may be associated with reductions in ambient levels of ground-level O_3, as discussed in chapter 10 of the 2006 Criteria Document and chapter 3 of the 2007 Staff Paper.

[14] Health effects discussions are also drawn from the more detailed information and tables presented in the Criteria Document's annexes.

i. Effects on the Respiratory System From Short-term and Prolonged O_3 Exposures

Controlled human exposure studies have shown that O_3 induces a variety of health effects, including: Lung function decrements, respiratory symptoms, increased airway responsiveness, respiratory inflammation and permeability, increased susceptibility to respiratory infection, and acute morphological effects. Epidemiology studies have reported associations between O_3 exposures (*i.e.,* 1-hour, 8-hour and 24-hour) and a wide range of respiratory-related health effects including: pulmonary function decrements; respiratory symptoms; increased asthma medication use; increased school absences; increased emergency department visits and hospital admissions.

(a) Pulmonary Function Decrements, Respiratory Symptoms, and Asthma Medication Use

(i) Results From Controlled Human Exposure Studies

A large number of studies published prior to 1996 that investigated short-term O_3 exposure health effects on the respiratory system from short-term O_3 exposures were reviewed in the 1986 and 1996 Criteria Documents (EPA, 1986, 1996a). In the 1997 review, 0.50 ppm was the lowest O_3 concentration at which statistically significant reductions in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) were reported in sedentary subjects. During exercise, spirometric (lung function) and symptomatic responses were observed at much lower O_3 exposures. When minute ventilation was considerably increased by continuous exercise (CE) during O_3 exposures lasting 2 hour or less at ≥ 0.12 ppm, healthy subjects generally experienced decreases in FEV_1, FVC, and other measures of lung function; increases in specific airway resistance (sRaw), breathing frequency, and airway responsiveness; and symptoms such as cough, pain on deep inspiration, shortness of breath, throat irritation, and wheezing. When exposures were increased to 4- to 8-hours in duration, statistically significant lung function and symptom responses were reported at O_3 concentrations as low as 0.08 ppm and at lower minute ventilation (*i.e.,* moderate rather than high level exercise) than the shorter duration studies.

The most important observations drawn from studies reviewed in the 1996 Criteria Document were that: (1) Young healthy adults exposed to O_3 concentrations ≥ 0.080 ppm develop significant, reversible, transient decrements in pulmonary function if minute ventilation or duration of exposure is increased sufficiently; (2) children experience similar lung function responses but report lesser symptoms from O_3 exposure relative to young adults; (3) O_3-induced lung function responses are decreased in the elderly relative to young adults; (4) there is a large degree of intersubject variability in physiological and symptomatic responses to O_3 but responses tend to be reproducible within a given individual over a period of several months; (5) subjects exposed repeatedly to O_3 for several days show an attenuation of response upon successive exposures, but this attenuation is lost after about a week without exposure; and (6) acute O_3 exposure initiates an inflammatory response which may persist for at least 18 to 24 hours post exposure.

The development of these respiratory effects is time-dependent during both exposure and recovery periods, with great overlap for development and disappearance of the effects. In healthy human subjects exposed to typical ambient O_3 levels near 0.120 ppm, lung function responses largely resolve within 4 to 6 hours postexposure, but cellular effects persist for about 24 hours. In these healthy subjects, small residual lung function effects are almost completely gone within 24 hours, while in hyperresponsive subjects, recovery can take as much as 48 hour to return to baseline. The majority of these responses are attenuated after repeated consecutive exposures, but such attenuation to O_3 is lost one week postexposure.

Since 1996, there have been a number of studies published investigating lung function and symptomatic responses that generally support the observations previously drawn. Recent studies for acute exposures of 1 to 2 hours and 6 to 8 hours in duration are compiled in the 2007 Staff Paper (Appendix 3C). As summarized in more detail in the 2007 Staff Paper (section 3.3.1.1), among the more important of the recent studies that examined changes in FEV_1 in large numbers of subjects over a range of 1–2 hours at exposure levels of 0.080 to 0.40 ppm were studies by McDonnell *et al.* (1997) and Ultman *et al.* (2004). These studies observed considerable intersubject variability in FEV_1 decrements, which was consistent with findings in the 1996 Criteria Document.

For prolonged exposures (4 to 8 hours) in the range of 0.080 to 0.160 ppm O_3 using moderate intermittent

exercise and typically using square-wave exposure patterns (*i.e.,* a constant exposure level during time of exposure), several pre- and post-1996 studies (Folinsbee *et al.,* 1988,1994; Horstman *et al.,* 1990; Adams, 2002, 2003a, 2006) have reported statistically significant lung function responses and increased symptoms in healthy adults with increasing duration of exposure, O_3 concentration, and minute ventilation. Studies that employed triangular exposure patterns (*i.e.,* integrated exposures that begin at a low level, rise to a peak, and return to a low level during the exposure) (Hazucha *et al.,* 1992; Adams 2003a, 2006) suggest that the triangular exposure pattern can potentially lead to greater FEV_1 decrements and respiratory symptoms than square-wave exposures (when the overall O_3 doses are equal). These results suggest that peak exposures, reflective of the pattern of ambient O_3 concentrations in some locations, are important in terms of O_3 health effects.

McDonnell (1996) used data from a series of studies to investigate the frequency distributions of FEV_1 decrements following 6.6 hour exposures and found statistically significant, but relatively small, group mean decreases in average FEV_1 responses (between 5 and 10 percent) at 0.080 ppm O_3.[15] Notably, about 26 percent of the 60 exposed subjects had lung function decrements > 10 percent, including about 8 percent of the subjects that experienced large decrements (> 20 percent) (EPA, 2007b, Figure 3–1A). These results (which were not corrected for exercise in filtered air responses) demonstrate that while average responses may be relatively small at the 0.080 ppm exposure level, some individuals experience more severe effects that may be clinically significant. Similar results at the 0.080 ppm exposure level (for 6.6 hours during intermittent exercise) were seen in more recent studies of 30 healthy young adults by Adams (2002, 2006).[16] In Adams (2006), relatively small but statistically significant lung function decrements and respiratory symptom responses were found (for both square-wave and triangular exposure patterns), with 17 percent of the subjects (5 of 30) experiencing ≥ 10 percent FEV_1 decrements (comparing pre- and post-exposures) when the results were not corrected for the effects of exercise alone in filtered air (EPA, 2007b, Figure 3–1B) and with 23 percent of subjects (7 of 30) experiencing such effects when the results were corrected (EPA, 2007b, p. 3–6).[17]

These studies by Adams (2002, 2006) were notable in that they were the only controlled exposure human studies available at the time of the 2008 rulemaking that examined respiratory effects associated with prolonged O_3 exposures at levels below 0.080 ppm, which was the lowest exposure level that had been examined in the 1997 review. The Adams (2006) study investigated a range of exposure levels (0.000, 0.040, 0.060, and 0.080 ppm O_3) using square-wave and triangular exposure patterns. The study was designed to examine hour-by-hour changes in pulmonary function (FEV_1) and respiratory symptom responses (total subjective symptoms (TSS) and pain on deep inspiration (PDI)) between these various exposure protocols at six different time points within the exposure periods to investigate the effects of different patterns of exposure. At the 0.060 ppm exposure level, the author reported no statistically significant differences for FEV_1 decrements nor for most respiratory symptoms responses. Statistically significant responses were reported only for TSS for the triangular exposure pattern toward the end of the exposure period, with the PDI responses being noted as following a closely similar pattern (Adams, 2006, p. 131–132). EPA's reanalysis of the data from the Adams (2006) study addressed the more fundamental question of whether there were statistically significant differences in responses before and after the 6.6 hour exposure period (Brown, 2007), and used a standard statistical method appropriate for a simple before-and-after comparison. The statistical method used by EPA had been used previously by other researchers to address this same question. EPA's reanalysis of the data from the Adams (2006) study, comparing FEV_1 responses pre- and post-exposure at the 0.060 ppm exposure level, found small group mean differences from responses to filtered air that were statistically significant (Brown, 2007).[18]

Further examination of the post-exposure FEV_1 data and mean data at other time points and concentrations also suggest a pattern of response at 0.06 ppm that is consistent with a dose-response relationship rather than random variability. For example, the response at 5.6 hours was similar to that of the post-exposure 6.6 hour response and appeared to also differ from the FA response. At the 0.08 ppm level, the subjects in this study did not appear to be more responsive to O_3 than subjects in previous studies, as the observed response was similar to that of previous studies (Adams, 2003a,b; Horstman *et al.,* 1990; McDonnell *et al.,* 1991). Although of much smaller magnitude, the temporal pattern of the 0.06 ppm response was generally consistent with the temporal patterns of response to higher concentrations of O_3 in this and other studies. These findings are not unexpected because the previously observed group mean FEV_1 responses to 0.08 ppm were in the range of 6–9% suggesting that exposure to lower concentrations of O_3 would result in smaller, but real group mean FEV_1 decrements, *i.e.,* the responses to 0.060 ppm O_3 are consistent with the presence of a smooth exposure-response curve with responses that do not end abruptly below 0.080 ppm.

Moreover, the Adams studies (2002, 2006) also report a small percentage of subjects experiencing moderate lung function decrements (≥ 10 percent) at the 0.060 ppm exposure level. Based on study data (Adams, 2006) provided by the author, 7 percent of the subjects (2 of 30 subjects) experienced notable FEV_1 decrements (≥ 10 percent) with the square wave exposure pattern at the 0.060 ppm exposure level (comparing pre- and post-exposures) when the results were corrected for the effects of exercise alone in filtered air (EPA, 2007b, p. 3–6). Furthermore, in a prior publication (Adams, 2002), the author stated that, "some sensitive subjects experience notable effects at 0.06 ppm," based on the observation that 20% of subjects exposed to 0.06 ppm O_3 (in a face mask exposure study) had greater than a 10% decrement in FEV_1 even though the group mean response was not statistically different from the filtered air response. The effects described by Adams (2002), along with

[15] This study and other studies (Folinsbee *et al.,* 1988; Horstman *et al.,* 1990; and McDonnell *et al.,* 1991), conducted in EPA's human studies research facility in Chapel Hill, NC, measured ozone concentrations to within +/− 5 percent or +/− 0.004 ppm at the 0.080 ppm exposure level.

[16] These studies, conducted at a facility at the University of California, in Davis, CA, reported O_3 concentrations to be accurate within +/− 0.003 ppm over the range of concentrations included in these studies.

[17] These distributional results presented in the Criteria Document and Staff Paper for the Adams (2006) study are based on data for squate-wave exposures to 0.080 ppm that were not included in the publication but were obtained from the author.

[18] Dr. Adams submitted comments on EPA's reanalysis in which he concluded that the FEV_1 response in healthy young adults at the 0.060 ppm exposure level in his study (Adams, 2006a) does not demonstrate a significant mean effect by ordinarily acceptable statistical analysis, but is rather in somewhat of a gray area, both in terms of a biologically meaningful response and a statistically significant response (Adams, 2007). The EPA responded to these comments in the 2008 final rule (73 FR 16455) and in the Response to Comments (EPA, 2008, pp. 26–28).

the reanalysis of the Adams (2006) data as described above, demonstrate considerable inter-individual variability in responses of healthy adults at the 0.060 ppm level with some individuals experiencing greater than 10% decrements in FEV_1. The observation of statistically significant small group mean lung function decrements in healthy adults at 0.060 ppm O_3 lowers the lowest-observed-effects level found in controlled human exposure studies for lung function decrements and respiratory symptoms.

Of potentially greater concern is the magnitude of the lung function decrements in the small group of healthy subjects who had the largest responses (*i.e.,* FEV_1 decrements ≥ 10%). This is a concern because for active healthy people, moderate levels of functional responses (*e.g.,* FEV_1 decrements of ≥ 10% but < 20%) and/or moderate symptomatic responses would likely interfere with normal activity for relatively few responsive individuals. However, for people with lung disease, even moderate functional or symptomatic responses would likely interfere with normal activity for many individuals, and would likely result in more frequent use of medication (see section II.A.4 below).

(ii) Results of Epidemiological and Field Studies

A relatively large number of field studies investigating the effects of ambient O_3 concentrations, in combination with other air pollutants, on lung function decrements and respiratory symptoms has been published over the last decade that support the major findings of the 1996 Criteria Document that lung function changes, as measured by decrements in FEV_1 or peak expiratory flow (PEF), and respiratory symptoms in healthy adults and asthmatic children are closely correlated to ambient O_3 concentrations. Pre-1996 field studies focused primarily on children attending summer camps and found O_3-related impacts on measures of lung function, but not respiratory symptoms, in healthy children. The newer studies have expanded to evaluate O_3-related effects on outdoor workers, athletes, the elderly, hikers, school children, and asthmatics. Collectively, these studies confirm and extend clinical observations that prolonged (*i.e.,* 6–8 hour) exposure periods, combined with elevated levels of exertion or exercise, increase the dose of O_3 to the lungs at a given ambient exposure level and result in larger lung function effects. The results of one large study of hikers (Korrick *et al.,* 1998), which reported outcome measures stratified by several factors (*e.g.,* gender, age, smoking status, presence of asthma) within a population capable of more than normal exertion, provide useful insight. In this study, lung function was measured before and after hiking, and individual O_3 exposures were estimated by averaging hourly O_3 concentrations from ambient monitors located at the base and summit. The mean 8-hour average O_3 concentration was 0.040 ppm (8-hour average concentration range of 0.021 ppm to 0.074 ppm O_3). Decreased lung function was associated with O_3 exposure, with the greatest effect estimates reported for the subgroup that reported having asthma or wheezing, and for those who hiked for longer periods of time.

Asthma panel studies conducted both in the U.S. and in other countries have reported that decrements in PEF are associated with routine O_3 exposures among asthmatic and healthy people. One large U.S. multicity study, the National Cooperative Inner City Asthma Study or NCICAS, (Mortimer *et al.,* 2002) examined O_3-related changes in PEF in 846 asthmatic children from 8 urban areas and reported that the incidence of ≥ 10 percent decrements in morning PEF are associated with increases in 8-hour average O_3 for a 5-day cumulative lag, suggesting that O_3 exposure may be associated with clinically significant changes in PEF in asthmatic children; however, no associations were reported with evening PEF. The mean 8-hour average O_3 was 0.048 ppm across the 8 cities. Excluding days when 8-hour average O_3 was greater than 0.080 ppm (less than 5 percent of days), the associations with morning PEF remained statistically significant. Mortimer *et al.* (2002) discussed potential biological mechanisms for delayed effects on pulmonary function in asthma, which included increased nonspecific airway responsiveness secondary to airway inflammation due to O_3 exposure. Two other panel studies (Romieu *et al.,* 1996, 1997) carried out simultaneously in northern and southwestern Mexico City with mildly asthmatic school children reported statistically significant O_3-related reductions in PEF, with variations in effect depending on lag time and time of day. Mean 1-hour maximum O_3 concentrations in these locations ranged from 0.190 ppm in northern Mexico City to 0.196 ppm in southwestern Mexico City. While several studies report statistically significant associations between O_3 exposure and reduced PEF in asthmatics, other studies did not, possibly due to low levels of O_3 exposure. EPA concludes that these studies collectively indicate that O_3 may be associated with short-term declines in lung function in asthmatic individuals and that the Mortimer *et al.* (2002) study showed statistically significant effects at concentrations in the range below 0.080 ppm O_3.

Most of the panel studies which have investigated associations between O_3 exposure and respiratory symptoms or increased use of asthma medication are focused on asthmatic children. Two large U.S. studies (Mortimer *et al.,* 2002; Gent *et al.,* 2003) have reported associations between ambient O_3 concentrations and daily symptoms/asthma medication use, even after adjustment for copollutants. Results were more mixed, meaning that a greater proportion of studies were not both positive and statistically significant, across smaller U.S. and international studies that focused on these health endpoints.

The NCICAS reported morning symptoms in 846 asthmatic children from 8 U.S. urban areas to be most strongly associated with a cumulative 1- to 4-day lag of O_3 concentrations (Mortimer *et al.,* 2002). The NCICAS used standard protocols that included instructing caretakers of the subjects to record symptoms (including cough, chest tightness, and wheeze) in the daily diary by observing or asking the child. While these associations were not statistically significant in several cities, when the individual data are pooled from all eight cities, statistically significant effects were observed for the incidence of symptoms. The authors also reported that the odds ratios remained essentially the same and statistically significant for the incidence of morning symptoms when days with 8-hour O_3 concentrations above 0.080 ppm were excluded. These days represented less than 5 percent of days in the study.

Gent and colleagues (2003) followed 271 asthmatic children under age 12 and living in southern New England for 6 months (April through September) using a daily symptom diary. They found that mean 1-hour max O_3 and 8-hour max O_3 concentrations were 0.0586 ppm and 0.0513 ppm, respectively. The data were analyzed for two separate groups of subjects, those who used maintenance asthma medications during the follow-up period and those who did not. The need for regular medication was considered to be a proxy for more severe asthma. Not taking any medication on a regular basis and not needing to use a bronchodilator would suggest the

presence of very mild asthma. Statistically significant effects of 1-day lag O_3 were observed on a variety of respiratory symptoms only in the medication user group. Both daily 1-hour max and 8-hour max O_3 concentrations were similarly related to symptoms such as chest tightness and shortness of breath. Effects of O_3, but not $PM_{2.5}$, remained significant and even increased in magnitude in two-pollutant models. Some of the associations were noted at 1-hour max O_3 levels below 0.060 ppm. In contrast, no effects were observed among asthmatics not using maintenance medication. In terms of person-days of follow-up, this is one of the larger studies currently available that address symptom outcomes in relation to O_3 and provides supportive evidence for effects of O_3 independent of $PM_{2.5}$. Study limitations include the post-hoc nature of the population stratification by medication use. Also, the study did not account for all of the important meteorological factors that might influence these results, such as relative humidity or dew point.

The multicity study by Mortimer *et al.* (2002), which examined an asthmatic population representative of the United States, and several single-city studies indicate a robust association of O_3 concentrations with respiratory symptoms and increased medication use in asthmatics. While there are a number of well-conducted, albeit relatively smaller, U.S. studies which showed only limited or a lack of evidence for symptom increases associated with O_3 exposure, these studies had less statistical power and/or were conducted in areas with relatively low 1-hour maximum average O_3 levels, in the range of 0.03 to 0.09 ppm. The 2006 Criteria Document concludes that the asthma panel studies, as a group, and the NCICAS in particular, indicate a positive association between ambient concentrations and respiratory symptoms and increased medication use in asthmatics. The evidence has continued to expand since 1996 and now is considered to be much stronger than in the 1997 review of the O_3 primary standard.

School absenteeism is another potential surrogate for the health implications of O_3 exposure in children. The association between school absenteeism and ambient O_3 concentrations was assessed in two relatively large field studies. The first study, Chen *et al.* (2000), examined total daily school absenteeism in about 28,000 elementary school students in Nevada over a 2-year period (after adjusting for PM_{10} and CO concentrations) and found that ambient O_3 concentrations with a distributed lag of 14 days were statistically significantly associated with an increased rate of school absences. The second study, Gilliland *et al.* (2001), studied O_3-related absences among about 2,000 4th grade students in 12 southern California communities and found statistically significant associations between 8-hour average O_3 concentrations (with a distributed lag out to 30 days) and all absence categories, and particularly for respiratory causes. Neither PM_{10} nor NO_2 were associated with any respiratory or nonrespiratory illness-related absences in single pollutant models. The 2006 Criteria Document concludes that these studies of school absences suggest that ambient O_3 concentrations, accumulated over two to four weeks, may be associated with school absenteeism, and particularly illness-related absences, but further replication is needed before firm conclusions can be reached regarding the effect of O_3 on school absences. In addition, more research is needed to help shed light on the implications of variation in the duration of the lag structures (*i.e.,* 1 day, 5 days, 14 days, and 30 days) found both across studies and within data sets by health endpoint and exposure metric.

(b) Increased Airway Responsiveness

As discussed in more detail in the 2006 Criteria Document (section 6.8) and the 2007 Staff Paper (section 3.3.1.1.2), increased airway responsiveness, also known as airway hyperresponsiveness (AHR) or bronchial hyperreactivity, refers to a condition in which the propensity for the airways to bronchoconstrict due to a variety of stimuli (*e.g.,* exposure to cold air, allergens, or exercise) becomes augmented. This condition is typically quantified by measuring the decrement in pulmonary function after inhalation exposure to specific (*e.g.,* antigen, allergen) or nonspecific (*e.g.,* methacholine, histamine) bronchoconstrictor stimuli. Exposure to O_3 causes an increase in airway responsiveness as indicated by a reduction in the concentration of stimuli required to produce a given reduction in FEV_1 or increase in airway obstruction. Increased airway responsiveness is an important consequence of exposure to O_3 because its presence means that the airways are predisposed to narrowing on exposure to various stimuli, such as specific allergens, cold air or SO_2. Statistically significant and clinically relevant decreases in pulmonary function have been observed in early phase allergen response in subjects with allergic rhinitis after consecutive (4-day) 3-hour exposures to 0.125 ppm O_3 (Holz *et al.,* 2002). Similar increased airway responsiveness in asthmatics to house dust mite antigen 16 to 18 hours after exposure to a single dose of O_3 (0.160 ppm for 7.6 hours) was observed. These observations, based on O_3 exposures to levels much higher than the 0.084 ppm standard level suggest that O_3 exposure may be a clinically important factor that can exacerbate the response to ambient bronchoconstrictor substances in individuals with preexisting allergic asthma or rhinitis. Further, O_3 may have an immediate impact on the lung function of asthmatics as well as contribute to effects that persist for longer periods.

Kreit *et al.* (1989) found that O_3 can induce increased airway responsiveness in asthmatic subjects to O_3, who typically have increased airway responsiveness at baseline. A subsequent study (Jörres *et al.,* 1996) suggested an increase in specific (*i.e.,* allergen-induced) airway reactivity in subjects with allergic asthma, and to a lesser extent in subjects with allergic rhinitis after short-term exposure to higher O_3 levels; other studies reported similar results. According to one study (Folinsbee and Hazucha, 2000), changes in airway responsiveness after O_3 exposure resolve more slowly than changes in FEV_1 or respiratory symptoms. Other studies of repeated exposure to O_3 suggest that changes in airway responsiveness tend to be somewhat less affected by attenuation with consecutive exposures than changes in FEV_1 (EPA, 2006a, section 6.8).

The 2006 Criteria Document (section 6.8) concludes that O_3 exposure is linked with increased airway responsiveness. Both human and animal studies indicate that increased airway responsiveness is not mechanistically associated with inflammation, and does not appear to be strongly associated with initial decrements in lung function or increases in symptoms. As a result of increased airway responsiveness induced by O_3 exposure, human airways may be more susceptible to a variety of stimuli, including antigens, chemicals, and particles. Because asthmatic subjects typically have increased airway responsiveness at baseline, enhanced bronchial response to antigens in asthmatics raises potential public health concerns as they could lead to increased morbidity (*e.g.,* medication usage, school absences, emergency room visits, hospital admissions) or to more persistent alterations in airway

responsiveness (EPA 2006a, p. 8–21). As such, increased airway responsiveness after O_3 exposure represents a plausible link between O_3 exposure and increased hospital admissions.

(c) Respiratory Inflammation and Increased Permeability

Based on evidence from the 1997 review, acute inflammatory responses in the lung have been observed subsequent to 6.6 hour O_3 exposures to the lowest tested level—0.080 ppm—in healthy adults engaged in moderately high exercise (section 6.9 of the 2006 Criteria Document and section 3.3.1.3 of the 2007 Staff Paper). Some of these prior studies suggest that inflammatory responses may be detected in some individuals following O_3 exposures in the absence of O_3-induced pulmonary decrements in those subjects. These studies also demonstrate that short-term exposures to O_3 also can cause increased permeability in the lungs of humans and experimental animals. Inflammatory responses and epithelial permeability have been seen to be independent of spirometric responses. Not only are the newer lung inflammation and increased cellular permeability findings discussed in the 2006 Criteria Document (section 8.4.2) consistent with the 1997 review, but they provide better characterization of the physiological mechanisms by which O_3 causes these effects.

Lung inflammation and increased permeability, which are distinct events controlled by different mechanisms, are two commonly observed effects of O_3 exposure observed in all of the species studied. Increased cellular permeability is a disruption of the lung barrier that leads to leakage of serum proteins, influx of polymorphonuclear leukocytes (neutrophils or PMNs), release of bioactive mediators, and movement of compounds from the airspaces into the blood.

A number of controlled human exposure studies have analyzed bronchoalveolar lavage (BAL) and nasal lavage (NL) [19] fluids and cells for markers of inflammation and lung damage (EPA, 2006a, Annex AX6). Increased lung inflammation is demonstrated by the presence of neutrophils found in BAL fluid in the lungs, which has long been accepted as a hallmark of inflammation. It is apparent, however, that inflammation within airway tissues may persist beyond the point that inflammatory cells are found in the BAL fluid. Soluble mediators of inflammation, such as cytokines and arachidonic acid metabolites have been measured in the BAL fluid of humans exposed to O_3. In addition to their role in inflammation, many of these compounds have bronchoconstrictive properties and may be involved in increased airway responsiveness following O_3 exposure. An in vitro study of epithelial cells from nonatopic and atopic asthmatics exposed to 0.010 to 0.100 ppm O_3 showed significantly increased permeability compared to cells from normal persons. This indicates a potentially inherent susceptibility of cells from asthmatic individuals for O_3-induced permeability.

In the 1996 Criteria Document, assessment of controlled human exposure studies indicated that a single, acute (1 to 4 hours) O_3 exposure (≥ 0.080 to 0.100 ppm) of subjects engaged in moderate to heavy exercise could induce a number of cellular and biochemical changes suggestive of pulmonary inflammation and lung permeability (EPA, 2006a, p. 8–22). These changes persisted for at least 18 hours. Markers from BAL fluid following both 2-hour and 4-hour O_3 exposures repeated up to 5 days indicate that there is ongoing cellular damage irrespective of attenuation of some cellular inflammatory responses of the airways, pulmonary function, and symptom scores (EPA, 2006a, p. 8–22). Acute airway inflammation was shown in Devlin *et al.* (1990) to occur among adults exposed to 0.080 ppm O_3 for 6.6 hours with exercise. McBride *et al.* (1994) reported that asthmatic subjects were more sensitive than non-asthmatics to upper airway inflammation for O_3 exposures that did not affect pulmonary function (EPA, 2006a, p. 6–33). However, the public health significance of these changes is not entirely clear.

The studies reporting inflammatory responses and markers of lung injury have clearly demonstrated that there is significant variation in response of subjects exposed, especially to 6.6 hours O_3 exposures at 0.080 and 0.100 ppm. To provide some perspective on the public health impact for these effects, the 2007 Staff Paper (section 3.3.1.1.3) notes that one study (Devlin *et al.,* 1991) showed that roughly 10 to 50 percent of the 18 young healthy adult subjects experienced notable increases (*i.e.*, ≥ 2 fold increase) in most of the inflammatory and cellular injury indicators analyzed, associated with 6.6-hour exposures at 0.080 ppm. Similar, although in some cases higher, fractions of the population of 10 healthy adults tested saw > 2 fold increases associated with 6.6-hour exposures to 0.100 ppm. The authors of this study expressed the view that "susceptible subpopulations such as the very young, elderly, and people with pulmonary impairment or disease may be even more affected" (Devlin *et al.,* 1991).

Since 1996, a substantial number of human exposure studies have been published which have provided important new information on lung inflammation and epithelial permeability. Mudway and Kelly (2004) examined O_3-induced inflammatory responses and epithelial permeability with a meta-analysis of 21 controlled human exposure studies and showed that an influx in neutrophils and protein in healthy subjects is associated with total O_3 dose (product of O_3 concentration, exposure duration, and minute ventilation) (EPA, 2006a, p. 6–34). Results of the analysis suggest that the time course for inflammatory responses (including recruitment of neutrophils and other soluble mediators) is not clearly established, but there is evidence that attenuation profiles for many of these parameters are different (EPA, 2006a, p. 8–22).

The 2006 Criteria Document (chapter 8) concludes that interaction of O_3 with lipid constituents of epithelial lining fluid (ELF) and cell membranes and the induction of oxidative stress is implicated in injury and inflammation. Alterations in the expression of cytokines, chemokines, and adhesion molecules, indicative of an ongoing oxidative stress response, as well as injury repair and regeneration processes, have been reported in animal toxicology and human in vitro studies evaluating biochemical mediators implicated in injury and inflammation. While antioxidants in ELF confer some protection, O_3 reactivity is not eliminated at environmentally relevant exposures (2006 Criteria Document, p. 8–24). Further, antioxidant reactivity with O_3 is both species-specific and dose-dependent.

(d) Increased Susceptibility to Respiratory Infection

As discussed in more detail in the 2006 Criteria Document (sections 5.2.2, 6.9.6, and 8.4.2), short-term exposures to O_3 have been shown to impair physiological defense capabilities in experimental animals by depressing alveolar macrophage (AM) functions and by altering the mucociliary clearance of inhaled particles and microbes resulting in increased susceptibility to respiratory infection.

[19] Graham and Koren (1990) compared inflammatory mediators present in NL and BAL fluids of humans exposed to 0.4 ppm O_3 for 2 hours and found similar increases in PMNs in both fluids, suggesting a qualitative correlation between inflammatory changes in the lower airways (BAL) and upper respiratory tract (NL).

Short-term O_3 exposures also interfere with the clearance process by accelerating clearance for low doses and slowing clearance for high doses. Animal toxicological studies have reported that acute O_3 exposures suppress alveolar phagocytosis and immune system functions. Impairment of host defenses and subsequent increased susceptibility to bacterial lung infection in laboratory animals has been induced by short-term exposures to O_3 levels as low as 0.080 ppm.

A single controlled human exposure study reviewed in the 1996 Criteria Document (p. 8–26) reported that exposure to 0.080 to 0.100 ppm O_3 for 6.6 hours (with moderate exercise) induced decrements in the ability of AMs to phagocytose microorganisms. Integrating the recent animal study results with human exposure evidence available in the 1996 Criteria Document, the 2006 Criteria Document concludes that available evidence indicates that short-term O_3 exposures have the potential to impair host defenses in humans, primarily by interfering with AM function. Any impairment in AM function may lead to decreased clearance of microorganisms or nonviable particles. Compromised AM functions in asthmatics may increase their susceptibility to other O_3 effects, the effects of particles, and respiratory infections (EPA, 2006a, p. 8–26).

(e) Morphological Effects

The 1996 Criteria Document found that short-term O_3 exposures cause similar alterations in lung morphology in all laboratory animal species studied, including primates. As discussed in the 2007 Staff Paper (section 3.3.1.1.5), cells in the centriacinar region (CAR) of the lung (the segment between the last conducting airway and the gas exchange region) have been recognized as a primary target of O_3-induced damage (epithelial cell necrosis and remodeling of respiratory bronchioles), possibly because epithelium in this region receives the greatest dose of O_3 delivered to the lower respiratory tract. Following chronic O_3 exposure, structural changes have been observed in the CAR, the region typically affected in most chronic airway diseases of the human lung (EPA, 2006a, p. 8–24).

Ciliated cells in the nasal cavity and airways, as well as Type I cells in the gas-exchange region, are also identified as targets. While short-term O_3 exposures can cause epithelial cell profileration and fibrolitic changes in the CAR, these changes appear to be transient with recovery occurring after exposure, depending on species and O_3 dose. The potential impacts of repeated short-term and chronic morphological effects of O_3 exposure are discussed below in the section on effects from long-term exposures. Long-term or prolonged exposure has been found to cause chronic lesions similar to early lesions found in individuals with respiratory bronchiolitis, which have the potential to progress to fibrotic lung disease (2006 Criteria Document, p. 8–25).

Recent studies continue to show that short-term and sub-chronic exposures to O_3 cause similar alterations in lung structure in a variety of experimental animal species. For example, a series of new studies that used infant rhesus monkeys and simulated seasonal ambient exposure (0.5 ppm 8 hours/day for 5 days, every 14 days for 11 episodes) reported remodeling in the distal airways; abnormalities in tracheal basement membrane; eosinophil accumulation in conducting airways; and decrements in airway innervation (2006 Criteria Document, p. 8–25). Based on evidence from animal toxicological studies, short-term and sub-chronic exposures to O_3 can cause morphological changes in the respiratory systems, particularly in the CAR, of a number of laboratory animal species (EPA, 2006a, section 5.2.4).

(f) Emergency Department Visits/ Hospital Admissions for Respiratory Causes

Increased summertime emergency department visits and hospital admissions for respiratory causes have been associated with ambient exposures to O_3. As discussed in section 3.3.1.1.6 of the 2007 Staff Paper, numerous studies conducted in various locations in the U.S. and Canada consistently have shown a relationship between ambient O_3 levels and increased incidence of emergency department visits and hospital admissions for respiratory causes, even after controlling for modifying factors, such as weather and copollutants. Such associations between elevated ambient O_3 during summer months and increased hospital admissions have a plausible biological basis in the human and animal evidence of functional, symptomatic, and physiologic effects discussed above and in the increased susceptibility to respiratory infections observed in laboratory animals.

In the 1997 review of the O_3 NAAQS, the Criteria Document evaluated emergency department visits and hospital admissions as possible outcomes following exposure to O_3 (EPA, 2006a, section 7.3). The evidence was limited for emergency department visits, but results of several studies generally indicated that short-term exposures to O_3 were associated with respiratory emergency department visits. The strongest and most consistent evidence, at both lower levels (*i.e.,* below 0.120 ppm 1-hour max O_3) and at higher levels (above 0.120 ppm 1-hour max O_3), was found in the group of studies which investigated summertime [20] daily hospital admissions for respiratory causes in different eastern North American cities. These studies consistently demonstrated that ambient O_3 levels were associated with increased hospital admissions and accounted for about one to three excess respiratory hospital admissions per million persons with each 0.100 ppm increase in 1-hour max O_3, after adjustment for possible confounding effects of temperature and copollutants. Overall, the 1996 Criteria Document concluded that there was strong evidence that ambient O_3 exposures can cause significant exacerbations of preexisting respiratory disease in the general public. Excess respiratory-related hospital admissions associated with O_3 exposures for the New York City area (based on Thurston *et al.,* 1992) were included in the quantitative risk assessment in the 1997 review and are included in the current assessment along with estimates for respiratory-related hospital admissions in Cleveland, Detroit, and Los Angeles based on more recent studies (2007 Staff Paper, chapter 5). Significant uncertainties and the difficulty of obtaining reliable baseline incidence numbers resulted in emergency department visits not being used in the quantitative risk assessment in either the 1997 or the 2008 O_3 NAAQS review.

In the past decade, a number of studies have examined the temporal pattern associations between O_3 exposures and emergency department visits for respiratory causes (EPA, 2006a, section 7.3.2). These studies are summarized in the 2006 Criteria Document (chapter 7 Annex) and some are shown in Figure 1 (in section II.A.3). Respiratory causes for emergency department visits include asthma, bronchitis, emphysema, pneumonia, and other upper and lower respiratory infections, such as influenza, but asthma visits typically dominate the daily incidence counts. Most studies report positive associations with O_3. Among studies with adequate controls for seasonal patterns, many reported at least one significant positive association involving O_3.

[20] Discussion of the reasons for focusing on warm season studies is found in the section 2.A.3.a below.

In reviewing evidence for associations between emergency department visits for asthma and short-term O_3 exposures, the 2006 Criteria Document (Figure 7–8, p. 7–68) notes that in general, O_3 effect estimates from summer only analyses tended to be positive and larger compared to results from cool season or all year analyses. Several of the studies reported significant associations between O_3 concentrations and emergency department visits for respiratory causes, in particular asthma. However, inconsistencies were observed which were at least partially attributable to differences in model specifications and analysis approach among various studies. For example, ambient O_3 concentrations, length of the study period, and statistical methods used to control confounding by seasonal patterns and copollutants appear to affect the observed O_3 effect on emergency department visits.

Hospital admissions studies focus specifically on unscheduled admissions because unscheduled hospital admissions occur in response to unanticipated disease exacerbations and are more likely than scheduled admissions to be affected by variations in environmental factors, such as daily O_3 levels. Results of a fairly large number of these studies published during the past decade are summarized in 2006 Criteria Document (chapter 7 Annex), and results of U.S. and Canadian studies are shown in Figure 1 below (in section II.A.3). As a group, these hospital admissions studies tend to be larger geographically and temporally than the emergency department visit studies and provide results that are generally more consistent. The strongest associations of respiratory hospital admissions with O_3 concentrations were observed using short lag periods, in particular for a 0-day lag (same day exposure) and a 1-day lag (previous day exposure). Most studies in the United States and Canada indicated positive, statistically significant associations between ambient O_3 concentrations and respiratory hospital admissions in the warm season. However, not all studies found a statistically significant relationship with O_3, possibly because of very low ambient O_3 levels. Analyses for confounding using multipollutant regression models suggest that copollutants generally do not confound the association between O_3 and respiratory hospitalizations. Ozone effect estimates were robust to PM adjustment in all-year and warm-season only data.

Overall, the 2006 Criteria Document concludes that positive and robust associations were found between ambient O_3 concentrations and various respiratory disease hospitalization outcomes, when focusing particularly on results of warm-season analyses. Recent studies also generally indicate a positive association between O_3 concentrations and emergency department visits for asthma during the warm season (EPA, 2006a, p. 7–175). These positive and robust associations are supported by the controlled human exposure, animal toxicological, and epidemiological evidence for lung function decrements, increased respiratory symptoms, airway inflammation, and increased airway responsiveness. Taken together, the overall evidence supports a causal relationship between acute ambient O_3 exposures and increased respiratory morbidity outcomes resulting in increased emergency department visits and hospitalizations during the warm season (EPA, 2006a, p. 8–77).

ii. Effects on the Respiratory System of Long-Term O_3 Exposures

The 1996 Criteria Document concluded that there was insufficient evidence from the limited number of studies to determine whether long-term O_3 exposures resulted in chronic health effects at ambient levels observed in the U.S. However, the aggregate evidence suggested that O_3 exposure, along with other environmental factors, could be responsible for health effects in exposed populations. Animal toxicological studies carried out in the 1980's and 1990's demonstrated that long-term exposures can result in a variety of morphological effects, including permanent changes in the small airways of the lungs, including remodeling of the distal airways and CAR and deposition of collagen, possibly representing fibrotic changes. These changes result from the damage and repair processes that occur with repeated exposure. Fibrotic changes were also found to persist after months of exposure providing a potential pathophysiologic basis for changes in airway function observed in children in some recent epidemiological studies. It appears that variable seasonal ambient patterns of exposure may be of greater concern than continuous daily exposures.

Several studies published since 1996 have investigated lung function changes over seasonal time periods (EPA, 2006a, section 7.5.3). The 2006 Criteria Document (p. 7–114) summarizes these studies which collectively indicate that seasonal O_3 exposure is associated with smaller growth-related increases in lung function in children than they would have experienced living in areas with lower O_3 levels. There is some limited evidence that seasonal O_3 also may affect lung function growth in young adults, although the uncertainty about the role of copollutants makes it difficult to attribute the effects to O_3 alone.

Lung capacity grows during childhood and adolescence as body size increases, reaches a maximum during the twenties, and then begins to decline steadily and progressively with age. Long-term exposure to air pollution has long been thought to contribute to slower growth in lung capacity, diminished maximally attained capacity, and/or more rapid decline in lung capacity with age (EPA, 2006a, section 7.5.4). Toxicological findings evaluated in the 1996 Criteria Document demonstrated that repeated daily exposure of rats to an episodic profile of O_3 caused small, but significant, decrements in growth-related lung function that were consistent with early indicators of focal fibrogenesis in the proximal alveolar region, without overt fibrosis. Because O_3 at sufficient concentrations is a strong respiratory irritant and has been shown to cause inflammation and restructuring of the respiratory airways, it is plausible that long-term O_3 exposures might have a negative impact on baseline lung function, particularly during childhood when these exposures might be associated with long-term risks.

Several epidemiological studies published since 1996 have examined the relationship between lung function development and long-term O_3 exposure. The most extensive and robust study of respiratory effects in relation to long-term air pollution exposures among children in the U.S. is the Children's Health Study carried out in 12 communities of southern California starting in 1993. One analysis (Peters *et al.,* 1999a) examined the relationship between long-term O_3 exposures and self-reports of respiratory symptoms and asthma in a cross sectional analysis and found a limited relationship between outcomes of current asthma, bronchitis, cough and wheeze and a 0.040 ppm increase in 1-hour max O_3 (EPA, 2006a, p. 7–115). Another analysis (Peters *et al.,* 1999b) examined the relationship between lung function at baseline and levels of air pollution in the community. They reported evidence that annual mean O_3 levels were associated with decreases in FVC, FEV_1, PEF and forced expiratory flow (FEF_{25-75}) (the latter two being statistically significant) among females but not males. In a separate analysis (Gauderman *et al.,* 2000) of 4th, 7th, and

10th grade students, a longitudinal analysis of lung function development over four years found no association with O_3 exposure. The Children's Health Study enrolled a second cohort of more than 1500 fourth graders in 1996 (Gauderman *et al.,* 2002). While the strongest associations with negative lung function growth were observed with acid vapors in this cohort, children from communities with higher 4-year average O_3 levels also experienced smaller increases in various lung function parameters. The strongest relationship with O_3 was with PEF. Specifically, children from the least-polluted community had a small but statistically significant increase in PEF as compared to those from the most-polluted communities. In two-pollutant models, only 8-hour average O_3 and NO_2 were significant joint predictors of FEV_1 and maximal midexpiratory flow (MMEF). Although results from the second cohort of children are supportive of a weak association, the definitive 8-year follow-up analysis of the first cohort (Gauderman *et al.,* 2004a) provides 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. Avol *et al.* (2001) examined children who had moved away from participating communities in southern California to other states with improved air quality. They found that a negative, but not statistically significant, association was observed between O_3 and lung function parameters. Collectively, the results of these reports from the children's health cohorts provide little evidence to support an impact of long-term O_3 exposures on lung function development.

Evidence for a significant relationship between long-term O_3 exposures and decrements in maximally attained lung function was reported in a nationwide study of first year Yale students (Kinney *et al.,* 1998; Galizia and Kinney, 1999) (EPA, 2006a, p. 7–120). Males had much larger effect estimates than females, which might reflect higher outdoor activity levels and correspondingly higher O_3 exposures during childhood. A similar study of college freshmen at University of California at Berkeley also reported significant effects of long-term O_3 exposures on lung function (Künzli *et al.,* 1997; Tager *et al.,* 1998). In a comparison of students whose city of origin was either Los Angeles or San Francisco, long-term O_3 exposures were associated with significant changes in mid- and end-expiratory flow measures, which could be considered early indicators for pathologic changes that might progress to COPD.

There have been a few studies that investigated associations between long-term O_3 exposures and the onset of new cases of asthma (EPA, 2006a, section 7.5.6). The Adventist Health and Smog (AHSMOG) study cohort of about 4,000 was drawn from nonsmoking, non-Hispanic white adult Seventh Day Adventists living in California (Greer *et al.,* 1993; McDonnell *et al.,* 1999). During the ten-year follow-up in 1987, a statistically significant increased relative risk of asthma development was observed in males, compared to a nonsignificant relative risk in females (Greer *et al.,* 1993). In the 15-year follow-up in 1992, it was reported that for males, there was a statistically significant increased relative risk of developing asthma associated with 8-hour average O_3 exposures, but there was no evidence of an association in females. Consistency of results in the two studies with different follow-up times provides supportive evidence of the potential for an association between long-term O_3 exposure and asthma incidence in adult males; however, representativeness of this cohort to the general U.S. population may be limited (EPA, 2006a, p. 7–125).

In a similar study (McConnell *et al.,* 2002) of incident asthma among children (ages 9 to 16 at enrollment), annual surveys of 3,535 children initially without asthma were used to identify new-onset asthma cases as part of the Children's Health Study. Six high-O_3 and six low-O_3 communities were identified where the children resided. There were 265 children who reported new-onset asthma during the follow-up period. Although asthma risk was no higher for all residents of the six high-O_3 communities versus the six low-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 within the high-O_3 communities. This association was absent in the communities with lower O_3 concentrations. No other pollutants were found to be associated with new-onset asthma (EPA, 2006a, p. 7–125). Playing sports may result in extended outdoor activity and exposure occurring during periods when O_3 levels are higher. It should be noted, however, that the results of the Children's Health Study were based on a small number of new-onset asthma cases among children who played three or more sports. Future replication of these findings in other cohorts would help determine whether a causal interpretation is appropriate.

In animal toxicology studies, the progression of morphological effects reported during and after a chronic exposure in the range of 0.50 to 1.00 ppm O_3 (well above current ambient levels) is complex, with inflammation peaking over the first few days of exposure, then dropping, then plateauing, and finally, largely disappearing (EPA, 2006a, section 5.2.4.4). By contrast, fibrotic changes in the tissue increase very slowly over months of exposure, and, after exposure ceases, the changes sometimes persist or increase. Epithelial hyperplasia peaks soon after the inflammatory response but is usually maintained in both the nose and lungs with continuous exposure; it also does not return to pre-exposure levels after the end of exposure. Patterns of exposure in this same concentration range determine effects, with 18 months of daily exposure, causing less morphologic damage than exposures on alternating months. This is important as environmental O_3 exposure is typically seasonal. Long-term studies by Plopper and colleagues (Evans *et al.,* 2003; Schelegle *et al.,* 2003; Chen *et al.,* 2003; Plopper and Fanucchi, 2000) investigated infant rhesus monkeys exposed to simulated, seasonal O_3 and demonstrated: (1) Remodeling in the distal airways, (2) abnormalities in tracheal basement membrane; (3) eosinophil accumulation in conducting airways; and (4) decrements in airway innervation (EPA, 2006a, p. 5–45). These findings provide additional information regarding possible injury-repair processes occurring with long-term O_3 exposures suggesting that these processes are only partially reversible and may progress following cessation of O_3 exposure. Further, these processes may lead to nonreversible structural damage to lung tissue; however, there is still too much uncertainty to characterize the significance of these findings to human exposure profiles and effect levels (EPA, 2006a, p. 8–25).

In summary, in the past decade, important new longitudinal studies have examined the effect of chronic O_3 exposure on respiratory health outcomes. Limited evidence from recent long-term morbidity studies have suggested in some cases that chronic exposure to O_3 may be associated with seasonal declines in lung function or reduced lung function development, increases in inflammation, and development of asthma in children and adults. Seasonal decrements or smaller increases in lung function measures have been reported in several studies; however, the extent to which these

changes are transient remains uncertain. While there is supportive evidence from animal studies involving effects from chronic exposures, large uncertainties still remain as to whether current ambient levels and exposure patterns might cause these same effects in human populations. The 2006 Criteria Document concludes that epidemiological studies of new asthma development and longer-term lung function declines remain inconclusive at present (EPA, 2006a, p. 7–134).

iii. Effects on the Cardiovascular System of O_3 Exposure

At the time of the 1997 review, the possibility of O_3-induced cardiovascular effects was largely unrecognized. Since then, a very limited body of evidence from animal, controlled human exposure, and epidemiologic studies has emerged that provides evidence for some potential plausible mechanisms for how O_3 exposures might exert cardiovascular system effects, however further research is needed to substantiate these potential mechanisms. Possible mechanisms may involve O_3-induced secretions of vasoconstrictive substances and/or effects on neuronal reflexes that may result in increased arterial blood pressure and/or altered electrophysiologic control of heart rate or rhythm. Some animal toxicology studies have shown O_3-induced decreases in heart rate, mean arterial pressure, and core temperature. One controlled human exposure study that evaluated effects of O_3 exposure on cardiovascular health outcomes found no significant O_3-induced differences in ECG or blood pressure in healthy or hypertensive subjects but did observe a significant O_3-induced increase the alveolar-to-arterial PO_2 gradient and heart rate in both groups resulting in an overall increase in myocardial work and impairment in pulmonary gas exchange (Gong *et al.,* 1998). In another controlled human exposure study, inhalation of a mixture of $PM_{2.5}$ and O_3 by healthy subjects increased brachial artery vasoconstriction and reactivity (Brook *et al.,* 2002).

The evidence from a few animal studies also includes potential direct effects such as O_3-induced release from lung epithelial cells of platelet activating factor (PAF) that may contribute to blood clot formation that would have the potential to increase the risk of serious cardiovascular outcomes (*e.g.,* heart attack, stroke, mortality). Also, interactions of O_3 with surfactant components in epithelial lining fluid of the lung may result in production of oxysterols and reactive oxygen species that may exhibit PAF-like activity contributing to clotting and also may exert cytotoxic effects on lung and heart muscle cells.

Epidemiological panel and field studies that examined associations between O_3 and various cardiac physiologic endpoints have yielded limited evidence suggestive of a potential association between acute O_3 exposure and altered heart rate variability (HRV), ventricular arrhythmias, and incidence of heart attacks (myocardial infarction or MI). A number of epidemiological studies have also reported associations between short-term exposures and hospitalization for cardiovascular diseases. As shown in Figure 7–13 of the 2006 Criteria Document, many of the studies reported negative or inconsistent associations. Some other studies, especially those that examined the relationship when O_3 exposures were higher, have found robust positive associations between O_3 and cardiovascular hospital admissions (EPA, 2006a, p. 7–82). For example, one study reported a positive association between O_3 and cardiovascular hospital admissions in Toronto, Canada in a summer-only analysis (Burnett *et al.,* 1997b). The results were robust to adjustment for various PM indices, whereas the PM effects diminished when adjusted for gaseous pollutants. Other studies stratified their analysis by temperature (*i.e.,* by warms days versus cool days). Several analyses using warm season days consistently produced positive associations.

The epidemiologic evidence for cardiovascular morbidity is much weaker than for respiratory morbidity, with only one of several U.S. and Canadian studies showing statistically significant positive associations of cardiovascular hospitalizations with warm-season O_3 concentrations. Most of the available European and Australian studies, all of which conducted all-year O_3 analyses, did not find an association between short-term O_3 concentrations and cardiovascular hospitalizations. Overall, the currently available evidence is inconclusive regarding an association between cardiovascular hospital admissions and ambient O_3 exposure (EPA, 2006a, p. 7–83).

In summary, based on the evidence from animal toxicology, controlled human exposure, and epidemiological studies, from the 2006 Criteria Document (p. 8–77) concludes that this generally limited body of evidence is suggestive that O_3 can directly and/or indirectly contribute to cardiovascular-related morbidity, but that much needs to be done to more fully integrate links between ambient O_3 exposures and adverse cardiovascular outcomes.

b. Mortality

i. Mortality and Short-term O_3 Exposure

The 1996 Criteria Document concluded that an association between daily mortality and O_3 concentration for areas with high O_3 levels (*e.g.,* Los Angeles) was suggested. However, due to a very limited number of studies available at that time, there was insufficient evidence to conclude that the observed association was likely causal.

The 2006 Criteria Document included results from numerous epidemiological analyses of the relationship between O_3 and mortality. Additional single city analyses have also been conducted since 1996, however, the most pivotal studies in EPA's (and CASAC's) finding of increased support for the relationship between premature mortality and O_3 is in part related to differences in study design—limiting analyses to warm seasons, better control for copollutants, particularly PM, and use of multicity designs (both time series and meta-analytic designs). Key findings are available from multicity time-series studies that report associations between O_3 and mortality. These studies include analyses using data from 90 U.S. cities in the National Mortality, Morbidity and Air Pollution (NMMAPS) study (Dominici *et al.,* 2003) and from 95 U.S. communities in an extension to the NMMAPS analyses (Bell *et al.,* 2004).

The original 90-city NMMAPS analysis, with data from 1987 to 1994, was primarily focused on investigating effects of PM_{10} on mortality. A significant association was reported between mortality and 24-hour average O_3 concentrations in analyses using all available data as well as in the warm season only analyses (Dominici *et al.,* 2003). The estimate using all available data was about half that for the summer-only data at a lag of 1-day. The extended NMMAPS analysis included data from 95 U.S. cities and included an additional 6 years of data, from 1987–2000 (Bell *et al.,* 2004). Significant associations were reported between O_3 and mortality in analyses using all available data. The effect estimate for increased mortality was approximately 0.5 percent per 0.020 ppm change in 24-hour average O_3 measured on the same day, and approximately 1.04 percent per 0.020 ppm change in 24-hour average O_3 in a 7-day distributed lag model (EPA, 2006a, p. 7–88). In analyses using only data from the warm season, the results were not significantly different from the full-year results. The authors also report

that O_3-mortality associations were robust to adjustment for PM (EPA, 2006a, p. 7–100). Using a subset of the NMMAPS data set, Huang *et al.* (2005) focused on associations between cardiopulmonary mortality and O_3 exposure (24-hour average) during the summer season only. The authors report an approximate 1.47 percent increase per 0.020 ppm change in O_3 concentration measured on the same day and an approximate 2.52 percent increase per 0.020 ppm change in O_3 concentration using a 7-day distributed lag model. These findings suggest that the effect of O_3 on mortality is immediate but also persists for several days.

As discussed below in section II.A.3.a, confounding by weather, especially temperature, is complicated by the fact that higher temperatures are associated with the increased photochemical activities that are important for O_3 formation. Using a case-crossover study design, Schwartz (2005) assessed associations between daily maximum concentrations and mortality, matching case and control periods by temperature, and using data only from the warm season. The reported effect estimate of approximately 0.92 percent change in mortality per 0.040 ppm O_3 (1-hour maximum) was similar to time-series analysis results with adjustment for temperature (approximately 0.76 percent per 0.040 ppm O_3), suggesting that associations between O_3 and mortality were robust to the different adjustment methods for temperature.

An initial publication from APHEA, a European multicity study, reported statistically significant associations between daily maximum O_3 concentrations and mortality in four cities in a full year analysis (Toulomi *et al.,* 1997). An extended analysis was done using data from 23 cities throughout Europe (Gryparis *et al.,* 2004). In this report, a positive but not statistically significant association was found between mortality and 1-hour daily maximum O_3 in a full year analysis. Gryparis *et al.* (2004) noted that there was a considerable seasonal difference in the O_3 effect on mortality; thus, the small effect for the all-year data might be attributable to inadequate adjustment for confounding by seasonality. Focusing on analyses using summer measurements, the authors report statistically significant associations with total mortality, cardiovascular mortality and respiratory mortality (EPA, 2006a, p. 7–93, 7–99).

Numerous single-city analyses have also reported associations between mortality and short-term O_3 exposure, especially for those analyses using warm season data. As shown in Figure 7–21 of the 2006 Criteria Document, the results of recent publications show a pattern of positive, often statistically significant associations between short-term O_3 exposure and mortality during the warm season. In considering results from year-round analyses, there remains a pattern of positive results but the findings are less consistent. In most single-city analyses, effect estimates were not substantially changed with adjustment for PM (EPA, 2006a, Figure 7–22).

In addition, several meta-analyses have been conducted on the relationship between O_3 and mortality. As described in section 7.4.4 of the 2006 Criteria Document, these analyses reported fairly consistent and positive combined effect estimates ranging from approximately 1.5 to 2.5 percent increase in mortality for a standardized change in O_3 (EPA, 2006a, Figure 7–20). Three recent meta-analyses evaluated potential sources of heterogeneity in O_3-mortality associations (Bell *et al.,* 2005; Ito *et al.,* 2005; Levy *et al.,* 2005). The 2006 Criteria Document (p. 7–96) observes common findings across all three analyses, in that all reported that effect estimates were larger in warm season analyses, reanalysis of results using default convergence criteria in generalized additive models (GAM) did not change the effect estimates, and there was no strong evidence of confounding by PM. Bell *et al.* (2005) and Ito *et al.* (2005) both provided suggestive evidence of publication bias, but O_3-mortality associations remained after accounting for that potential bias. The 2006 Criteria Document concludes that the "positive O_3 effects estimates, along with the sensitivity analyses in these three meta-analyses, provide evidence of a robust association between ambient O_3 and mortality" (EPA, 2006a, p. 7–97).

Most of the single-pollutant model estimates from single-city studies range from 0.5 to 5 percent excess deaths per standardized increments. Corresponding summary estimates in large U.S. multicity studies ranged between 0.5 to 1 percent with some studies noting heterogeneity across cities and studies (EPA, 2006a, p. 7–110).

Finally, from those studies that included assessment of associations with specific causes of death, it appears that effect estimates for associations with cardiovascular mortality are larger than those for total mortality. The meta-analysis by Bell *et al.* (2005) observed a slightly larger effect estimate for cardiovascular mortality compared to mortality from all causes. The effect estimate for respiratory mortality was approximately one-half that of cardiovascular mortality in the meta-analysis. However, other studies have observed larger effect estimates for respiratory mortality compared to cardiovascular mortality. The apparent inconsistency regarding the effect size of O_3-related respiratory mortality may be due to reduced statistical power in this subcategory of mortality (EPA, 2006a, p. 7–108).

In summary, many single- and multi-city studies observed positive associations of ambient O_3 concentrations with total nonaccidental and cardiopulmonary mortality. The 2006 Criteria Document finds that the results from U.S. multicity time-series studies provide the strongest evidence to date for O_3 effects on acute mortality. Recent meta-analyses also indicate positive risk estimates that are unlikely to be confounded by PM; however, future work is needed to better understand the influence of model specifications on the risk coefficient (EPA, 2006a, p. 7–175). A meta-analysis that examined specific causes of mortality found that the cardiovascular mortality risk estimates were higher than those for total mortality. For cardiovascular mortality, the 2006 Criteria Document (Figure 7–25, p. 7–106) suggests that effect estimates are consistently positive and more likely to be larger and statistically significant in warm season analyses. The findings regarding the effect size for respiratory mortality have been less consistent, possibly because of lower statistical power in this subcategory of mortality. The 2006 Criteria Document (p. 8–78) concludes that these findings are highly suggestive that short-term O_3 exposure directly or indirectly contribute to non-accidental and cardiopulmonary-related mortality, but additional research is needed to more fully establish underlying mechanisms by which such effects occur.[21]

[21] In commenting on the Criteria Document, the CASAC Ozone Panel raised questions about the implications of these time-series results in a policy context, emphasizing that "* * * while the time-series study design is a powerful tool to detect very small effects that could not be detected using other designs, it is also a blunt tool" (Henderson, 2006b). They note that "* * * not only is the interpretation of these associations complicated by the fact that the day-to-day variation in concentrations of these pollutants is, to a varying degree, determined by meteorology, the pollutants are often part of a large and highly correlated mix of pollutants, only a very few of which are measured" (Henderson, 2006b). Even with these uncertainties, the CASAC Ozone Panel, in its review of the Staff Paper, found "* * * premature total non-accidental and cardiorespiratory mortality for inclusion in the quantitative risk assessment to be appropriate." (Henderson, 2006b)

ii. Mortality and Long-Term O_3 Exposure

Little evidence was available in the 1997 review on the potential for associations between mortality and long-term exposure to O_3. In the Harvard Six City prospective cohort analysis, the authors report that mortality was not associated with long-term exposure to O_3 (Dockery *et al.,* 1993). The authors note that the range of O_3 concentrations across the six cities was small, which may have limited the power of the study to detect associations between mortality and O_3 levels (EPA, 2006a, p. 7–127).

As discussed in section 7.5.8 of the 2006 Criteria Document, in this review there are results available from three prospective cohort studies: the American Cancer Society (ACS) study (Pope *et al.,* 2002), the Adventist Health and Smog (AHSMOG) study (Beeson *et al.,* 1998; Abbey *et al.,* 1999), and the U.S. Veterans Cohort study (Lipfert *et al.,* 2000, 2003). In addition, a major reanalysis report includes evaluation of data from the Harvard Six City cohort study (Krewski *et al.,* 2000).[22] This reanalysis also includes additional evaluation of data from the initial ACS cohort study report that had only reported results of associations between mortality and long-term exposure to fine particles and sulfates (Pope *et al.,* 1995). This reanalysis was discussed in the 2007 Staff Paper (section 3.3.2.2) but not in the 2006 Criteria Document.

In this reanalysis of data from the previous Harvard Six City prospective cohort study, the investigators replicated and validated the findings of the original studies, and the report included additional quantitative results beyond those available in the original report (Krewski *et al.,* 2000). In the reanalysis of data from the Harvard Six Cities study, the effect estimate for the association between long-term O_3 concentrations and mortality was negative and nearly statistically significant (relative risk = 0.87, 95 percent CI: 0.76, 1.00).

The ACS study is based on health data from a large prospective cohort of approximately 500,000 adults and air quality data from about 150 U.S. cities. The initial report (Pope *et al.,* 1995) focused on associations with fine particles and sulfates, for which significant associations had been reported in the earlier Harvard Six Cities study (Dockery *et al.,* 1993). As part of the major reanalysis of these data, results for associations with other air pollutants were also reported, and the authors report that no significant associations were found between O_3 and all-cause mortality. However, a significant association was reported for cardiopulmonary mortality in the warm season (Krewski *et al.,* 2000). The ACS II study (Pope *et al.,* 2002) reported results of associations with an extended data base; the mortality records for the cohort had been updated to include 16 years of follow-up (compared with 8 years in the first report) and more recent air quality data were included in the analyses. Similar to the earlier reanalysis, a marginally significant association was observed between long-term exposure to O_3 and cardiopulmonary mortality in the warm season. No other associations with mortality were observed in both the full-year and warm season analyses.

The Adventist Health and Smog (AHSMOG) cohort includes about 6,000 adults living in California. In two studies from this cohort, a significant association has been reported between long-term O_3 exposure and increased risk of lung cancer mortality among males only (Beeson *et al.,* 1998; Abbey *et al.,* 1999). No significant associations were reported between long-term O_3 exposure and mortality from all causes or cardiopulmonary causes. Due to the small numbers of lung cancer deaths (12 for males, 18 for females) and the precision of the effect estimate (*i.e.,* the wide confidence intervals), the 2006 Criteria Document (p. 7–130) discussed concerns about the plausibility of the reported association with lung cancer.

The U.S. Veterans Cohort study (Lipfert *et al.,* 2000, 2003) of approximately 50,000 middle-aged males diagnosed with hypertension, reported some positive associations between mortality and peak O_3 exposures (95th percentile level for several years of data). The study included numerous analyses using subsets of exposure and mortality follow-up periods which spanned the years 1960 to 1996. In the results of analyses using deaths and O_3 exposure estimates concurrently across the study period, there were positive, statistically significant associations between peak O_3 and mortality (EPA, 2006a, p. 7–129).

Overall, the 2006 Criteria Document (p. 7–130) concludes that consistent associations have not been reported between long-term O_3 exposure and all-cause, cardiopulmonary or lung cancer mortality.

c. Role of Ground-Level O_3 in Solar Radiation-Related Human Health Effects

Beyond the direct health effects attributable to inhalation exposure to O_3 in the ambient air discussed above, the 2006 Criteria Document also assesses potential indirect effects related to the presence of O_3 in the ambient air by considering the role of ground-level O_3 in mediating human health effects that may be directly attributable to exposure to solar ultraviolet radiation (UV–B). The 2006 Criteria Document (chapter 10) focuses this assessment on three key factors, including those factors that govern (1) UV–B radiation flux at the earth's surface, (2) human exposure to UV–B radiation, and (3) human health effects due to UV–B radiation. In so doing, the 2006 Criteria Document provides a thorough analysis of the current understanding of the relationship between reducing ground-level O_3 concentrations and the potential impact these reductions might have on increasing UV–B surface fluxes and indirectly contributing to UV–B related health effects.

There are many factors that influence UV–B radiation penetration to the earth's surface, including latitude, altitude, cloud cover, surface albedo, PM concentration and composition, and gas phase pollution. Of these, only latitude and altitude can be defined with small uncertainty in any effort to assess the changes in UV–B flux that may be attributable to any changes in tropospheric O_3 as a result of any revision to the O_3 NAAQS. Such an assessment of UV–B related health effects would also need to take into account human habits, such as outdoor activities (including age- and occupation-related exposure patterns), dress and skin care to adequately estimate UV–B exposure levels. However, little is known about the impact of these factors on individual exposure to UV–B.

Moreover, detailed information does not exist regarding other factors that are relevant to assessing changes in disease incidence, including: Type (*e.g.,* peak or cumulative) and time period (*e.g.,* childhood, lifetime, current) of exposures related to various adverse health outcomes (*e.g.,* damage to the skin, including skin cancer; damage to the eye, such as cataracts; and immune system suppression); wavelength dependency of biological responses; and interindividual variability in UV–B resistance to such health outcomes. Beyond these well recognized adverse health effects associated with various wavelengths of UV radiation, the 2006 Criteria Document (section 10.2.3.6) also

[22] This reanalysis report and the original prospective cohort study findings are discussed in more detail in section 8.2.3 of the *Air Quality Criteria for Particulate Matter* (EPA, 2004).

discusses protective effects of UV–B radiation. Recent reports indicate the necessity of UV–B in producing vitamin D. Vitamin D deficiency can cause metabolic bone disease among children and adults, and may also increase the risk of many common chronic diseases (*e.g.,* type I diabetes and rheumatoid arthritis) as well as the risk of various types of cancers. Thus, the 2006 Criteria Document concludes that any assessment that attempts to quantify the consequences of increased UV–B exposure on humans due to reduced ground-level O_3 must include consideration of both negative and positive effects. However, as with other impacts of UV–B on human health, this beneficial effect of UV–B radiation has not been studied in sufficient detail to allow for a credible health benefits or risk assessment. In conclusion, the effect of changes in surface-level O_3 concentrations on UV–B-induced health outcomes cannot yet be critically assessed within reasonable uncertainty (2006 Criteria Document, p. 10–36).

The Agency last considered indirect effects of O_3 in the ambient air in its 2003 final response to a remand of the Agency's 1997 decision to revise the O_3 NAAQS. In so doing, based on the available information in the 1997 review, EPA determined that the information linking (a) changes in patterns of ground-level O_3 concentrations likely to occur as a result of programs implemented to attain the 1997 O_3 NAAQS to (b) changes in relevant exposures to UV–B radiation of concern to public health was too uncertain at that time to warrant any relaxation in the level of public health protection previously determined to be requisite to protect against the demonstrated direct adverse respiratory effects of exposure to O_3 in the ambient air (68 FR 614). At that time, the more recent information on protective effects of UV–B radiation was not available, such that only adverse UV–B-related effects could be considered. Taking into consideration the more recent information available for the 2008 review, the 2006 Criteria Document and 2007 Staff Paper conclude that the effect of changes in ground-level O_3 concentrations, likely to occur as a result of revising the O_3 NAAQS, on UV–B-induced health outcomes, including whether these changes would ultimately result in increased or decreased incidence of UV–B-related diseases, cannot yet be critically assessed.

3. Interpretation and Integration of Health Evidence

As discussed below, in assessing the health evidence, the 2006 Criteria Document integrates findings from experimental (*e.g.,* toxicological, dosimetric and controlled human exposure) and epidemiological studies, to make judgments about the extent to which causal inferences can be made about observed associations between health endpoints and exposure to O_3. In evaluating the evidence from epidemiological studies, the EPA focuses on well-recognized criteria, including: The strength of reported associations, including the magnitude and precision of reported effect estimates and their statistical significance; the robustness of reported associations, or stability in the effect estimates after considering factors such as alternative models and model specification, potential confounding by co-pollutants, and issues related to the consequences of exposure measurement error; potential aggregation bias in pooling data; and the consistency of the effects associations as observed by looking across results of multiple- and single-city studies conducted by different investigators in different places and times. Consideration is also given to evaluating concentration-response relationships observed in epidemiological studies to inform judgments about the potential for threshold levels for O_3-related effects. Integrating more broadly across epidemiological and experimental evidence, the 2006 Criteria Document also focuses on the coherence and plausibility of observed O_3-related health effects to reach judgments about the extent to which causal inferences can be made about observed associations between health endpoints and exposure to O_3 in the ambient air.

a. Assessment of Evidence From Epidemiological Studies

Key elements of the evaluation of epidemiological studies are briefly summarized below.

(1) The strength of associations most directly refers to the magnitude of the reported relative risk estimates. Taking a broader view, the 2006 Criteria Document draws upon the criteria summarized in a recent report from the U.S. Surgeon General, which define strength of an association as "the magnitude of the association and its statistical strength" which includes assessment of both effect estimate size and precision, which is related to the statistical power of the study (CDC, 2004). In general, when associations are strong in terms of yielding large relative risk estimates, it is less likely that the association could be completely accounted for by a potential confounder or some other source of bias, whereas with associations that yield small relative risk estimates it is especially important to consider potential confounding and other factors in assessing causality. Effect estimates between O_3 and some of the health outcomes are generally small in size and could thus be characterized as weak. For example, effect estimates for associations with mortality generally range from 0.5 to 5 percent increases per 0.040 ppm increase in 1-hour maximum O_3 or equivalent, whereas associations for hospitalization range up to 50 percent increases per standardized O_3 increment. However, the 2006 Criteria Document notes that there are large multicity studies that find small associations between short-term O_3 exposure and mortality or morbidity and have done so with great precision due to the statistical power of the studies (p. 8–40). That is, the power of the studies allows the authors to reliably distinguish even weak relationships from the null hypothesis with statistical confidence.

(2) In evaluating the robustness of associations, the 2006 Criteria Document (sections 7.1.3 and 8.4.4.3) and 2007 Staff Paper (section 3.4.2) have primarily considered the impact of exposure error, potential confounding by copollutants, and alternative models and model specifications.

In time-series and panel studies, the temporal (*e.g.,* daily or hourly) changes in ambient O_3 concentrations measured at centrally-located ambient monitoring stations are generally used to represent a community's exposure to ambient O_3. In prospective cohort or cross-sectional studies, air quality data averaged over a period of months to years are used as indicators of a community's long-term exposure to ambient O_3 and other pollutants. In both types of analyses, exposure error is an important consideration, as actual exposures to individuals in the population will vary across the community.

Ozone concentrations measured at central ambient monitoring sites may explain, at least partially, the variance in individual exposures to ambient O_3; however, this relationship is influenced by various factors related to building ventilation practices and personal behaviors. Further, the pattern of exposure misclassification error and the influence of confounders may differ across the outcomes of interest as well as in susceptible populations. As discussed in the 2006 Criteria Document

(section 3.9), only a limited number of studies have examined the relationship between ambient O_3 concentrations and personal exposures to ambient O_3. One of the strongest predictors of the relationship between ambient concentrations and personal exposures appears to be time spent outdoors. The strongest relationships were observed in outdoor workers (Brauer and Brook, 1995, 1997; O'Neill *et al.,* 2004). Statistically significant correlations between ambient concentrations and personal exposures were also observed for children, who likely spend more time outdoors in the warm season (Linn *et al.,* 1996; Xu *et al.,* 2005). There is some concern about the extent to which ambient concentrations are representative of personal O_3 exposures of another particularly susceptible group of individuals, the debilitated elderly, since those who suffer from chronic cardiovascular or respiratory conditions may tend to protect themselves more than healthy individuals from environmental threats by reducing their exposure to both O_3 and its confounders, such as high temperature and PM. Studies by Sarnat *et al.* (2001, 2005) that included this susceptible group reported mixed results for associations between ambient O_3 concentrations and personal exposures to O_3. Collectively, these studies observed that the daily averaged personal O_3 exposures tend to be well correlated with ambient O_3 concentrations despite the substantial variability that existed among the personal measurements. These studies provide supportive evidence that ambient O_3 concentrations from central monitors may serve as valid surrogate measures for mean personal exposures experienced by the population, which is of most relevance for time-series studies. A better understanding of the relationship between ambient concentrations and personal exposures, as well as of the other factors that affect relationship will improve the interpretation of concentration-population health response associations observed.

The 2006 Criteria Document (section 7.1.3.1) also discusses the potential influence of exposure error on epidemiologic study results. Zeger *et al.* (2000) outlined the components to exposure measurement error, finding that ambient exposure can be assumed to be the product of the ambient concentration and an attenuation factor (*i.e.,* building filter) and that panel studies and time-series studies that use ambient concentrations instead of personal exposure measurements will estimate a health risk that is attenuated by that factor. Navidi *et al.* (1999) used data from a children's cohort study to compare effect estimates from a simulated "true" exposure level to results of analyses from O_3 exposures determined by several methods, finding that O_3 exposures based on the use of ambient monitoring data overestimate the individual's O_3 exposure and thus generally result in O_3 effect estimates that are biased downward (EPA, 2006a, p. 7–8). Similarly, in a reanalysis of a study by Burnett *et al.* (1994) on the acute respiratory effects of ambient air pollution, Zidek *et al.* (1998) reported that accounting for measurement error, as well as making a few additional changes to the analysis, resulted in qualitatively similar conclusions, but the effects estimates were considerably larger in magnitude (EPA, 2006a, p. 7–8). A simulation study by Sheppard *et al.* (2005) also considered attenuation of the risk based on personal behavior, their microenvironment, and the qualities of the pollutant in time-series studies. Of particular interest is their finding that risk estimates were not further attenuated in time-series studies even when the correlations between personal exposures and ambient concentrations were weak. In addition to overestimation of exposure and the resulting underestimation of effects, the use of ambient O_3 concentrations may obscure the presence of thresholds in epidemiologic studies (EPA, 2006a, p. 7–9).

As discussed in the 2006 Criteria Document (section 3.9), using ambient concentrations to determine exposure generally overestimates true personal O_3 exposures by approximately 2- to 4-fold in available studies, resulting in attenuated risk estimates. The implication is that the effects being estimated occur at fairly low exposures and the potency of O_3 is greater than these effects estimates indicate. As very few studies evaluating O_3 health effects with personal O_3 exposure measurements exist in the literature, effect estimates determined from ambient O_3 concentrations must be evaluated and used with caution to assess the health risks of O_3. In the absence of available data on personal O_3 exposure, the use of routinely monitored ambient O_3 concentrations as a surrogate for personal exposures is not generally expected to change the principal conclusions from O_3 epidemiologic studies. Therefore, population health risk estimates derived using ambient O_3 levels from currently available observational studies, with appropriate caveats about personal exposure considerations, remain useful. The 2006 Criteria Document recommends caution in the quantitative use of effect estimates calculated using ambient O_3 concentrations as they may lead to underestimation of the potency of O_3. However, the 2007 Staff Paper observes that the use of these risk estimates for comparing relative risk reductions between alternative ambient O_3 standards considered in the risk assessment (discussed below in section II.B.2) is less likely to suffer from this concern.

Confounding occurs when a health effect that is caused by one risk factor is attributed to another variable that is correlated with the causal risk factor; epidemiological analyses attempt to adjust or control for potential confounders. Copollutants (*e.g.,* PM, CO, SO_2 and NO_2) can meet the criteria for potential confounding in O_3-health associations if they are potential risk factors for the health effect under study and are correlated with O_3. Effect modifiers include variables that may influence the health response to the pollutant exposure (*e.g.,* co-pollutants, individual susceptibility, smoking or age). Both are important considerations for evaluating effects in a mixture of pollutants, but for confounding, the emphasis is on controlling or adjusting for potential confounders in estimating the effects of one pollutant, while the emphasis for effect modification is on identifying and assessing the effects for different modifiers.

The 2006 Criteria Document (p. 7–148) observes that O_3 is generally not highly correlated with other criteria pollutants (*e.g.,* PM_{10}, CO, SO_2 and NO_2), but may be more highly correlated with secondary fine particles, especially during the summer months, and that the degree of correlation between O_3 and other pollutants may vary across seasons. For example, positive associations are observed between O_3 and pollutants such as fine particles during the warmer months, but negative correlations may be observed during the cooler months (EPA, 2006a, p. 7–17). Thus, the 2006 Criteria Document (section 7.6.4) pays particular attention to the results of season-specific analyses and studies that assess effects of PM in potential confounding of O_3-health relationships. The 2006 Criteria Document also discussed the limitations of commonly used multipollutant models that include the difficulty in interpreting results where the copollutants are highly colinear, or where correlations between pollutants change by season (EPA, 2006a, p. 7–150). This is particularly the situation where O_3 and a copollutant, such as

sulfates, are formed under the same atmospheric condition; in such cases multipollutant models would produce unstable and possibly misleading results (EPA, 2006a, p. 7–152).

For mortality, the results from numerous multicity and single-city studies indicate that O_3-mortality associations do not appear to be substantially changed in multipollutant models including PM_{10} or $PM_{2.5}$ (EPA, 2006a, p. 7–101; Figure 7–22). Focusing on results of warm season analyses, effect estimates for O_3-mortality associations are fairly robust to adjustment for PM in multipollutant models (EPA, 2006a, p. 7–102; Figure 7–23). The 2006 Criteria Document concludes that in the few multipollutant analyses conducted for these endpoints, copollutants generally do not confound the relationship between O_3 and respiratory hospitalization (EPA, 2006a, p. 7–79 to 7–80; Figure 7–12). Multipollutant models were not used as commonly in studies of relationships between respiratory symptoms or lung function with O_3, but the 2006 Criteria Document reports that results of available analyses indicate that such associations generally were robust to adjustment for $PM_{2.5}$ (p. 7–154). For example, in a large multicity study of asthmatic children (Mortimer *et al.,* 2002), the O_3 effect was attenuated, but there was still a positive association; in Gent *et al.* (2003), effects of O_3, but not $PM_{2.5}$, remained statistically significant and even increased in magnitude in two-pollutant models (EPA, 2006a, p. 7–53). Considering this body of studies, the 2006 Criteria Document (p. 7–154) concludes: "Multipollultant regression analyses indicated that O_3 risk estimates, in general, were not sensitive to the inclusion of copollutants, including $PM_{2.5}$ and sulfate. These results suggest that the effects of O_3 on respiratory health outcomes appear to be robust and independent of the effects of other copollutants."

The 2006 Criteria Document (p. 7–14) observes that another challenge of time-series epidemiological analysis is assessing the relationship between O_3 and health outcomes while avoiding bias due to confounding by other time-varying factors, particularly seasonal trends and weather variables. These variables are of particular interest because O_3 concentrations have a well-characterized seasonal pattern and are also highly correlated with changes in temperature, such that it can be difficult to distinguish whether effects are associated with O_3 or with seasonal or weather variables in statistical analyses.

The 2006 Criteria Document (section 7.1.3.4) discusses statistical modeling approaches that have been used to adjust for time-varying factors, highlighting a series of analyses that were done in a Health Effects Institute-funded reanalysis of numerous time-series studies. While the focus of these reanalyses was on associations with PM, a number of investigators also examined the sensitivity of O_3 coefficients to the extent of adjustment for temporal trends and weather factors. In addition, several recent studies, including U.S. multicity studies (Bell *et al.,* 2005; Huang *et al.,* 2005; Schwartz *et al.,* 2005) and a meta-analysis study (Ito *et al.,* 2005), evaluated the effect of model specification on O_3-mortality associations. As discussed in the 2006 Criteria Document (section 7.6.3.1), these studies generally report that associations reported with O_3 are not substantially changed with alternative modeling strategies for adjusting for temporal trends and meteorologic effects. In the meta-analysis by Ito *et al.* (2005), a separate multicity analysis was presented that found that alternative adjustments for weather resulted in up to 2-fold difference in the O_3 effect estimate. Significant confounding can occur when strong seasonal cycles are present, suggesting that season-specific results are more generally robust than year-round results in such cases. A number of epidemiological studies have conducted season-specific analyses, and have generally reported stronger and more precise effect estimates for O_3 associations in the warm season than in analyses conducted in the cool seasons or over the full year.

(3) Consistency refers to the persistent finding of an association between exposure and outcome in multiple studies of adequate power in different persons, places, circumstances and times (CDC, 2004). In considering results from multicity studies and single-city studies in different areas, the 2006 Criteria Document (p. 8–41) observes general consistency in effects of short-term O_3 exposure on mortality, respiratory hospitalization and other respiratory health outcomes. The variations in effects that are observed may be attributable to differences in relative personal exposure to O_3, as well as varying concentrations and composition of copollutants present in different regions. Thus, the 2006 Criteria Document (p. 8–41) concludes that "consideration of consistency or heterogeneity of effects is appropriately understood as an evaluation of the similarity or general concordance of results, rather than an expectation of finding quantitative results with a very narrow range."

(4) The 2007 Staff Paper recognizes that it is likely that there are biological thresholds for different health effects in individuals or groups of individuals with similar innate characteristics and health status. For O_3 exposure, individual thresholds would presumably vary substantially from person to person due to individual differences in genetic susceptibility, pre-existing disease conditions and possibly individual risk factors such as diet or exercise levels (and could even vary from one time to another for a given person). Thus, it would be difficult to detect a distinct threshold at the population level below which no individual would experience a given effect, especially if some members of a population are unusually sensitive even down to very low concentrations (EPA, 2004, p. 9–43, 9–44).

Some studies have tested associations between O_3 and health outcomes after removal of days with higher O_3 levels from the data set; such analyses do not necessarily indicate the presence or absence of a threshold, but provide some information on whether the relationship is found using only lower-concentration data. For example, using data from 95 U.S. cities, Bell *et al.* (2004) found that the effect estimate for an association between short-term O_3 exposure and mortality was little changed when days exceeding 0.060 ppm (24-hour average) were excluded in the analysis. Using data from 8 U.S. cities, Mortimer and colleagues (2002) also reported that associations between O_3 and both lung function and respiratory symptoms remained statistically significant and of the same or greater magnitude in effect size when concentrations greater than 0.080 ppm (8-hour average) were excluded (EPA, 2006a, p. 7–46). Several single-city studies also report similar findings of associations that remain or are increased in magnitude and statistical significance when data at the upper end of the concentration range are removed (EPA, 2006a, section 7.6.5).

Other time-series epidemiological studies have used statistical modeling approaches to evaluate whether thresholds exist in associations between short-term O_3 exposure and mortality. As discussed in section 7.6.5 of the 2006 Criteria Document, one European multicity study included evaluation of the shape of the concentration-response curve, and observed no deviation from a linear function across the range of O_3 measurements from the study (Gryparis *et al.,* 2004; EPA, 2006a p. 7–154). Several single-city studies also observed a monotonic increase in associations between O_3 and morbidity that suggest

that no population threshold exists (EPA, 2006a, p. 7–159).

On the other hand, a study in Korea used several different modeling approaches and reported that a threshold model provided the best fit for the data. The results suggested a potential threshold level of about 0.045 ppm (1-hour maximum concentration; < 0.035 ppm, 8-hour average) for an association between mortality and short-term O_3 exposure during the summer months (Kim *et al.,* 2004; EPA, 2006a, p. 8–43). The authors reported larger effect estimates for the association for data above the potential threshold level, suggesting that an O_3-mortality association might be underestimated in the non-threshold model. A threshold analysis recently reported by Bell *et al.* (2006) for 98 U.S. communities, including the same 95 communities in Bell *et al.* (2004), indicated that if a population threshold existed for mortality, it would likely fall below a 24-hour average O_3 concentration of 0.015 ppm (< 0.025 ppm, 8-hour average). In addition, Burnett and colleagues (1997a,b) plotted the relationships between air pollutant concentrations and both respiratory and cardiovascular hospitalization, and it appears in these results that the associations with O_3 are found in the concentration range above about 0.030 ppm (1-hour maximum; < 0.025 ppm, 8-hour average). Vedal and colleagues (2003) reported a significant association between O_3 and mortality in British Columbia where O_3 concentrations were quite low (mean 1-hour maximum concentration of 0.0273 ppm). The authors did not specifically test for threshold levels, but the fact that the association was found in an area with such low O_3 concentrations suggests that any potential threshold level would be quite low in this data set.

In summary, the 2006 Criteria Document finds that, taken together, the available evidence from controlled human exposure and epidemiological studies suggests that no clear conclusion can now be reached with regard to possible threshold levels for O_3-related effects (EPA, 2006a, p. 8–44). Thus, the available epidemiological evidence neither supports nor refutes the existence of thresholds at the population level for effects such as increased hospital admissions and premature mortality. There are limitations in epidemiological studies that make discerning thresholds in populations difficult, including low data density in the lower concentration ranges, the possible influence of exposure measurement error, and interindividual differences in susceptibility to O_3-related effects in populations. There is the possibility that thresholds for individuals may exist in reported associations at fairly low levels within the range of air quality observed in the studies but not be detectable as population thresholds in epidemiological analyses.

b. Biological Plausibility and Coherence of Evidence

The body of epidemiological studies discussed in the 2007 Staff Paper emphasizes the role of O_3 in association with a variety of adverse respiratory and cardiovascular effects. While recognizing a variety of plausible mechanisms, there exists a general consensus suggesting that O_3, could either directly or through initiation, interfere with basic cellular oxidation processes responsible for inflammation, reduced antioxidant capacity, atherosclerosis and other effects. Reasoning that O_3 influences cellular chemistry through basic oxidative properties (as opposed to a unique chemical interaction), other reactive oxidizing species (ROS) in the atmosphere acting either independently or in combination with O_3 may also contribute to a number of adverse respiratory and cardiovascular health effects. Consequently, the role of O_3 should be considered more broadly as O_3 behaves as a generator of numerous oxidative species in the atmosphere.

In considering the biological plausibility of reported O_3-related effects, the 2007 Staff Paper (section 3.4.6) considers this broader question of health effects of pollutant mixtures containing O_3. The potential for O_3-related enhancements of PM formation, particle uptake, and exacerbation of PM-induced cardiovascular effects underscores the importance of considering contributions of O_3 interactions with other often co-occurring air pollutants to health effects due to O_3-containing pollutant mixes. The 2007 Staff Paper summarizes some examples of important pollutant mixture effects from studies that evaluate interactions of O_3 with other co-occurring pollutants, as discussed in chapters 4, 5, and 6 of the 2006 Criteria Document.

All of the types of interactive effects of O_3 with other co-occurring gaseous and nongaseous viable and nonviable PM components of ambient air mixes noted above argue that O_3 acts not only alone but that O_3 also is a surrogate indicator for air pollution mixes which may enhance the risk of adverse effects due to O_3 acting in combination with other pollutants. Viewed from this perspective, those epidemiologic findings of morbidity and mortality associations, with ambient O_3 concentrations extending to quite low levels in many cases, become more understandable and plausible.

The 2006 Criteria Document integrates epidemiological studies with mechanistic information from controlled human exposure studies and animal toxicological studies to draw conclusions regarding the coherence of evidence and biological plausibility of O_3-related health effects to reach judgments about the causal nature of observed associations. As summarized below, coherence and biological plausibility is discussed for each of the following types of O_3-related effects: Short-term effects on the respiratory system, effects on the cardiovascular system, effects related to long-term O_3 exposure, and short-term mortality-related health endpoints.

i. Coherence and Plausibility of Short-Term Effects on the Respiratory System

Acute respiratory morbidity effects that have been associated with short-term exposure to O_3 include such health endpoints as decrements in lung function, increased respiratory symptoms, increased airway responsiveness, airway inflammation, increased permeability related to epithelial injury, immune system effects, emergency department visits for respiratory diseases, and hospitalization due to respiratory illness.

Recent epidemiological studies have supported evidence available in the previous O_3 NAAQS review on associations between ambient O_3 exposure and decline in lung function for children. The 2006 Criteria Document (p. 8–34) concludes that exposure to ambient O_3 has a significant effect on lung function and is associated with increased respiratory symptoms and medication use, particularly in asthmatics. Short-term exposure to O_3 has also been associated with more severe morbidity endpoints, such as emergency department visits and hospital admissions for respiratory cases, including specific respiratory illness (*e.g.*, asthma) (EPA, 2006a, sections 7.3.2 and 7.3.3). In addition, a few epidemiological studies have reported positive associations between short-term O_3 exposure and respiratory mortality, though the associations are not generally statistically significant (EPA, 2006a, p. 7–108).

Considering the evidence from epidemiological studies, the results described above provide evidence for coherence in O_3-related effects on the respiratory system. Effect estimates from U.S. and Canadian studies are shown in

Figure 1, where it can be seen that mostly positive associations have been reported with respiratory effects ranging from respiratory symptoms, such as cough or wheeze, to hospitalization for various respiratory diseases, and there is suggestive evidence for associations with respiratory mortality. Many of the reported associations are statistically significant, particularly in the warm season. In Figure 1, the central effect estimate is indicated by a square for each result, with the vertical bar representing the 95 percent confidence interval around the estimate. In the discussions that follow, an individual study result is considered to be statistically significant if the 95 percent confidence interval does not include zero.[23] Positive effect estimates indicate increases in the health outcome with O_3 exposure. In considering these results as a whole, it is important to consider not only whether statistical significance at the 95 percent confidence level is reported in individual studies but also the general pattern of results, focusing in particular on studies with greater statistical power that report relatively more precise results.

[23] Results for studies of respiratory symptoms are presented as odds ratios; an odds ratio of 1.0 is equivalent to no effect, and thus is presented as equivalent to the zero effect estimate line.

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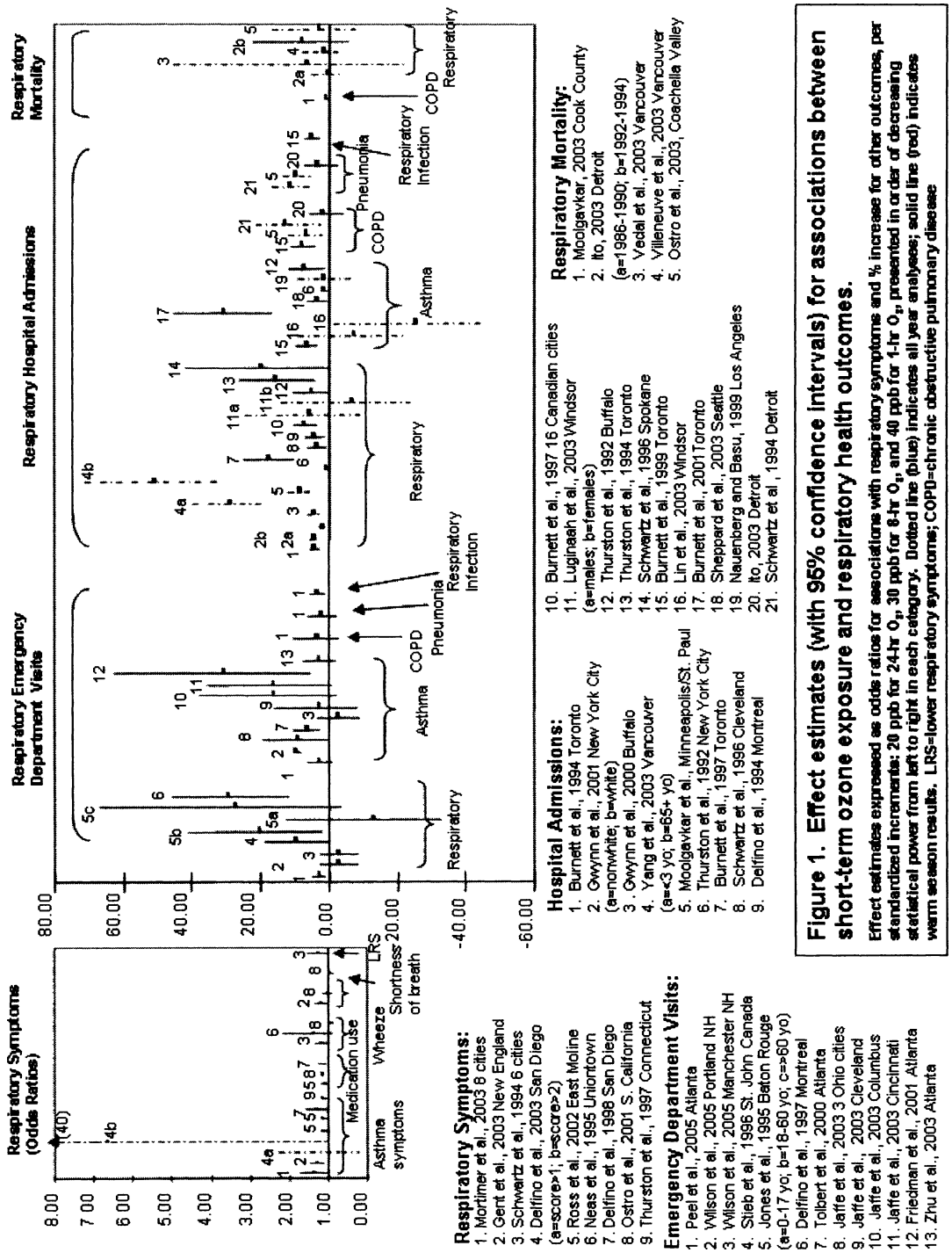

Figure 1. Effect estimates (with 95% confidence intervals) for associations between short-term ozone exposure and respiratory health outcomes.

Effect estimates expressed as odds ratios for associations with respiratory symptoms and % increase for other outcomes, per standardized increments: 20 ppb for 24-hr O_3, 30 ppb for 8-hr O_3, and 40 ppb for 1-hr O_3, presented in order of decreasing statistical power from left to right in each category. Dotted line (blue) indicates all year analyses; solid line (red) indicates warm season results. LRS=lower respiratory symptoms; COPD=chronic obstructive pulmonary disease

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Considering also evidence from toxicological, controlled human exposure, and field studies, the 2006 Criteria Document (section 8.6) discusses biological plausibility and coherence of evidence for acute O_3-induced respiratory health effects. Inhalation of O_3 for several hours while subjects are physically active can elicit both acute adverse pathophysiological changes and subjective respiratory tract symptoms (EPA, 2006a, section 8.4.2). Acute pulmonary responses observed in healthy humans exposed to O_3 at ambient concentrations include: decreased inspiratory capacity; mild bronchoconstriction; rapid, shallow breathing during exercise; subjective symptoms of tracheobronchial airway irritation, including cough and pain on deep inspiration; decreases in measures of lung function; and increased airway resistance. The severity of symptoms and magnitude of response depends on inhaled dose, individual O_3 sensitivity, and the degree of attenuation or enhancement of response resulting from previous O_3 exposures. Lung function studies of several animal species acutely exposed to relatively low O_3 levels from a toxicological perspective (*i.e.,* 0.25 to 0.4 ppm) show responses similar to those observed in humans, including increased breathing frequency, decreased tidal volume, increased resistance, and decreased FVC. Alterations in breathing pattern return to normal within hours of exposure, and

attenuation in functional responses following repeated O_3 exposures is similar to those observed in humans.

Physiological and biochemical alterations investigated in controlled human exposure and animal toxicology studies tend to support certain hypotheses of underlying pathological mechanisms which lead to the development of respiratory-related effects reported in epidemiology studies (*e.g.,* increased hospitalization and medication use). Some of these are: (a) Decrements in lung function, (b) bronchoconstriction, (c) increased airway responsiveness, (d) airway inflammation, (e) epithelial injury, (f) immune system activation, (g) host defense impairment, and (h) sensitivity of individuals, which depends on at least a person's age, disease status, genetic susceptibility, and the degree of attenuation present due to prior exposures. The time sequence, magnitude, and overlap of these complex events, both in terms of development and recovery, illustrate the inherent difficulty of interpreting the biological plausibility of O_3-induced cardiopulmonary health effects (EPA, 2006a, p. 8–48).

The interaction of O_3 with airway epithelial cell membranes and ELF to form lipid ozonation products and ROS is supported by numerous human, animal and in vitro studies. Ozonation products and ROS initiate a cascade of events that lead to oxidative stress, injury, inflammation, airway epithelial damage and increased epithelial damage and increased alveolar permeability to vascular fluids. Repeated respiratory inflammation can lead to a chronic inflammatory state with altered lung structure and lung function and may lead to chronic respiratory diseases such as fibrosis and emphysema (EPA, 2006a, section 8.6.2). Continued respiratory inflammation also can alter the ability to respond to infectious agents, allergens and toxins. Acute inflammatory responses to O_3 are well documented, and lung injury appears within 3 hours after exposure in humans.

Taken together, the 2006 Criteria Document concludes that the evidence from experimental human and animal toxicology studies indicates that acute O_3 exposure is causally associated with respiratory system effects. These effects include O_3-induced pulmonary function decrements; respiratory symptoms; lung inflammation and increased lung permeability; airway hyperresponsiveness; increased uptake of nonviable and viable particles; and consequent increased susceptibility to PM-related toxic effects and respiratory infections (EPA, 2006a, p. 8–48).

ii. Coherence and Plausibility of Effects on the Cardiovascular System

There is very limited experimental evidence of animals and humans that has evaluated possible mechanisms or physiological pathways by which acute O_3 exposures may induce cardiovascular system effects. Ozone induces lung injury, inflammation, and impaired mucociliary clearance, with a host of associated biochemical changes all leading to increased lung epithelial permeability. As noted above in section II.A.2.a, the generation of lipid ozonation products and ROS in lung tissues can influence pulmonary hemodynamics, and ultimately the cardiovascular system. Other potential mechanisms by which O_3 exposure may be associated with cardiovascular disease outcomes have been described. Laboratory animals exposed to relatively high O_3 concentrations (≥ 0.5 ppm) demonstrate tissue edema in the heart and lungs. Ozone-induced changes in heart rate, edema of heart tissue, and increased tissue and serum levels of ANF found with 8-hour 0.5 ppm O_3 exposure in animal toxicology studies (Vesely *et al.,* 1994a,b,c) also raise the possibility of potential cardiovascular effects of acute ambient O_3 exposures.

Animal toxicology studies have found both transient and persistent ventilatory responses with and without progressive decreases in heart rate (Arito *et al.,* 1997). Observations of O_3-induced vasoconstriction in a controlled human exposure study by Brook *et al.* (2002) suggests another possible mechanism for O_3-related exacerbations of preexisting cardiovascular disease. One controlled human study (Gong *et al.,* 1998) evaluated potential cardiovascular health effects of O_3 exposure. The overall results did not indicate acute cardiovascular effects of O_3 in either the hypertensive or control subjects. The authors observed an increase in rate-pressure product and heart rate, a decrement for FEV_1, and a >10 mm Hg increase in the alveolar/arterial pressure difference for O_2 following O_3 exposure. Foster *et al.* (1993) demonstrated that even in relatively young healthy adults, O_3 exposure can cause ventilation to shift away from the well-perfused basal lung. This effect of O_3 on ventilation distribution may persist beyond 24-hours post-exposure (Foster *et al.,* 1997). These findings suggest that O_3 may exert cardiovascular effects indirectly by impairing alveolar-arterial O_2 transfer and potentially reducing O_2 supply to the myocardium. Ozone exposure may increase myocardial work and impair pulmonary gas exchange to a degree that could perhaps be clinically important in persons with significant preexisting cardiovascular impairment.

As noted above in section II.A.2.a, a limited number of new epidemiological studies have reported associations between short-term O_3 exposure and effects on the cardiovascular system. Among these studies, three were population-based and involved relatively large cohorts; two of these studies evaluated associations between O_3 and HRV and the other study evaluated the association between O_3 levels and the relative risk of MI or heart attack. Such studies may offer more informative results based on their large subject-pool and design. Results from these three studies were suggestive of an association between O_3 exposure and the cardiovascular endpoints studied. In other recent studies on the incidence of heart attacks and some more subtle cardiovascular health endpoints, such as changes in HRV or cardiac arrhythmia, some but not all studies reported associations with short-term exposure to O_3 (EPA, 2006a, section 7.2.7.1). From these studies, the 2006 Criteria Document concludes that the "current evidence is rather limited but suggestive of a potential effect on HRV, ventricular arrhythmias, and MI incidence" (EPA, 2006a, p. 7–65).

An increasing number of studies have evaluated the association between O_3 exposure and cardiovascular hospital admissions. As discussed in section 7.3.4 of the 2006 Criteria Document, many reported negative or inconsistent associations, whereas other studies, especially those that examined the relationship when O_3 exposures were higher, have found positive and robust associations between O_3 and cardiovascular hospital admissions. The 2006 Criteria Document (p. 7–83) finds that the overall evidence from these studies remains inconclusive regarding the effect of O_3 on cardiovascular hospitalizations. The 2006 Criteria Document notes that the suggestive positive epidemiologic findings of O_3 exposure on cardiac autonomic control, including effects on HRV, ventricular arrhythmias and heart attacks, and reported associations between O_3 exposure and cardiovascular hospitalizations generally in the warm season gain credibility and scientific support from the results of experimental animal toxicology and controlled human exposure studies, which are indicative of plausible pathways by which O_3 may exert cardiovascular effects (EPA, 2006a, section 8.6.1).

iii. Coherence and Plausibility of Effects Related to Long-Term O_3 Exposure

Controlled human exposure studies cannot evaluate effects of long-term exposures to O_3; there is some evidence available from toxicological studies. While early animal toxicology studies of long-term O_3 exposures were conducted using continuous exposures, more recent studies have focused on exposures which mimic diurnal and seasonal patterns and more realistic O_3 exposure levels (EPA, 2006a, p. 8–50). Studies of monkeys that compared these two exposure scenarios found increased airway pathology only with the latter design. Persistent and irreversible effects reported in chronic animal toxicology studies suggest that additional complementary human data are needed from epidemiologic studies (EPA, 2006a, p. 8–50).

There is limited evidence from human studies for long-term O_3-induced effects on lung function. As discussed in section 8.6.2 of the 2006 Criteria Document, previous epidemiological studies have provided only inconclusive evidence for either mortality or morbidity effects of long-term O_3 exposure. The 2006 Criteria Document (p. 8–50) observes that the inconsistency in findings may be due to a lack of precise exposure information, the possibility of selection bias, and the difficulty of controlling for confounders. Several new longitudinal epidemiology studies have evaluated associations between long-term O_3 exposures and morbidity and mortality and suggest that these long-term exposures may be related to changes in lung function in children; however, little evidence is available to support a relationship between chronic O_3 exposure and mortality or lung cancer incidence (EPA, 2006a, p. 8–50).

The 2006 Criteria Document (p. 8–51) concludes that evidence from animal toxicology studies strongly suggests that chronic O_3 exposure is capable of damaging the distal airways and proximal alveoli, resulting in lung tissue remodeling leading to apparent irreversible changes. Such structural changes and compromised lung function caused by persistent inflammation may exacerbate the progression and development of chronic lung disease. Together with the limited evidence available from epidemiological studies, these findings offer some insight into potential biological mechanisms for suggested associations between long-term or seasonal exposures to O_3 and reduced lung function development in children which have been observed in epidemiologic studies (EPA, 2006a, p. 8–51).

iv. Coherence and Plausibility of Short-Term Mortality-Related Health Endpoints

An extensive epidemiological literature on air pollution related mortality risk estimates from the U.S., Canada, and Europe is discussed in the 2006 Criteria Document (sections 7.4 and 8.6.3). These single- and multicity mortality studies coupled with results from meta-analyses generally indicate associations between acute O_3 exposure and elevated risk for all-cause mortality, even after adjustment for the influence of season and PM exposure. Several single-city studies that specifically evaluated the relationship between O_3 exposure and cardiopulmonary mortality also reported results suggestive of a positive association (EPA, 2006a, p. 8–51). These mortality studies suggest a pattern of effects for causality that have biologically plausible explanations, but our knowledge regarding potential underlying mechanisms is very limited at this time and requires further research. Most of the physiological and biochemical parameters investigated in human and animal studies suggest that O_3-induced biochemical effects are relatively transient and attenuate over time. The 2006 Criteria Document (p. 8–52) hypothesizes a generic pathway of O_3-induced lung damage, potentially involving oxidative lung damage with subsequent inflammation and/or decline in lung function leading to respiratory distress in some sensitive population groups (*e.g.,* asthmatics), or other plausible pathways noted below that may lead to O_3-related contributions to cardiovascular effects that ultimately increase risk of mortality.

The third National Health and Nutrition Examination Survey follow-up data analysis indicates that about 20 percent of the adult population has reduced FEV_1 values, suggesting impaired lung function in a significant portion of the population. Most of these individuals have COPD, asthma or fibrotic lung disease (Manino *et al.,* 2003), which are associated with persistent low-grade inflammation. Furthermore, patients with COPD are at increased risk for cardiovascular disease. Also, lung disease with underlying inflammation may be linked to low-grade systemic inflammation associated with atherosclerosis, independent of cigarette smoking (EPA, 2006a, p. 8–52). Lung function decrements in persons with cardiopulmonary disease have been associated with inflammatory markers, such as C-reactive protein (CRP) in the blood. At a population level it has been found that individuals with the lowest FEV_1 values have the highest levels of CRP, and those with the highest FEV_1 values have the lowest CRP levels (Manino *et al.,* 2003; Sin and Man, 2003). This complex series of physiological and biochemical reactions following O_3 exposure may tilt the biological homeostasis mechanisms which could lead to adverse health effects in people with compromised cardiopulmonary systems.

Several other types of newly available data also support reasonable hypotheses that may help to explain the findings of O_3-related increases in cardiovascular mortality observed in some epidemiological studies. These include the direct effect of O_3 on increasing PAF in lung tissue that can then enter the general circulation and possibly contribute to increased risk of blood clot formation and the consequent increased risk of heart attacks, cerebrovascular events (stroke), or associated cardiovascular-related mortality. Ozone reactions with cholesterol in lung surfactant to form epoxides and oxysterols that are cytotoxic to lung and heart muscles and that contribute to atherosclerotic plaque formation in arterial walls represent another potential pathway. Stimulation of airway irritant receptors may lead to increases in tissue and serum levels of ANF, changes in heart rate, and edema of heart tissue. A few new field and panel studies of human adults have reported associations between ambient O_3 concentrations and changes in cardiac autonomic control (*e.g.,* HRV, ventricular arrhythmias, and MI). These represent plausible pathways that may lead to O_3-related contributions to cardiovascular effects that ultimately increase the risk of mortality.

In addition, O_3-induced increases in lung permeability allow more ready entry for inhaled PM into the blood stream, and thus O_3 exposure may increase the risk of PM-related cardiovascular effects. Furthermore, increased ambient O_3 levels contribute to ultrafine PM formation in the ambient air and indoor environments. Thus, the contributions of elevated ambient O_3 concentrations to ultrafine PM formation and human exposure, along with the enhanced uptake of inhaled fine particles, consequently may contribute to exacerbation of PM-induced cardiovascular effects in addition to those more directly induced by O_3 (EPA, 2006a, p. 8–53).

c. Summary

Judgments concerning the extent to which relationships between various health endpoints and ambient O_3 exposures are likely to be causal are informed by the conclusions and discussion in the 2006 Criteria Document as discussed above and summarized in section 3.7.5 of the 2007 Staff Paper. These judgments reflect the nature of the evidence and the overall weight of the evidence, and are taken into consideration in the quantitative risk assessment discussed below in section II.B.2.

For example, there is a very high level of confidence that O_3 induces lung function decrements in healthy adults and children due in part to the dozens of controlled human exposure and epidemiological studies consistently showing such effects. The 2006 Criteria Document (p. 8–74) states that these studies provide clear evidence of causality for associations between short-term O_3 exposures and statistically significant declines in lung function in children, asthmatics and adults who exercise outdoors. An increase in respiratory symptoms (*e.g.,* cough, shortness of breath) has been observed in controlled human exposure studies of short-term O_3 exposures, and significant associations between ambient O_3 exposures and a wide variety of respiratory symptoms have been reported in epidemiology studies (EPA, 2006a, p. 8–75). Population time-series studies showing robust associations between O_3 exposures and respiratory hospital admissions and emergency department visits are strongly supported by controlled human exposure, animal toxicological, and epidemiological evidence for O_3-related lung function decrements, respiratory symptoms, airway inflammation, and airway hyperreactivity. The 2006 Criteria Document (p. 8–77) concludes that, taken together, the overall evidence supports the inference of a causal relationship between acute ambient O_3 exposures and increased respiratory morbidity outcomes resulting in increased emergency department visits and hospitalizations during the warm season. Further, recent epidemiologic evidence has been characterized in the 2006 Criteria Document (p. 8–78) as highly suggestive that O_3 directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality.

4. O_3-Related Impacts on Public Health

The following discussion draws from chapters 6 and 7 and section 8.7 of the 2006 Criteria Document and section 3.6 of the 2007 Staff Paper to characterize factors which modify responsiveness to O_3, populations potentially at risk for O_3-related health effects, the adversity of O_3-related effects, and the size of the at-risk populations in the U.S. These considerations are all important elements in characterizing the potential public health impacts associated with exposure to ambient O_3.

a. Factors That Modify Responsiveness to Ozone

There are numerous factors that can modify individual responsiveness to O_3. These include: influence of physical activity; age; gender and hormonal influences; racial, ethnic and socioeconomic status (SES) factors; environmental factors; and oxidant-antioxidant balance. These factors are discussed in more detail in section 6.5 of the 2006 Criteria Document.

It is well established that physical activity increases an individual's minute ventilation and will thus increase the dose of O_3 inhaled (EPA, 2006a, section 6.5.4). Increased physical activity results in deeper penetration of O_3 into more distal regions of the lungs, which are more sensitive to acute O_3 response and injury. This will result in greater lung function decrements for acute exposures of individuals during increased physical activity. Research has shown that respiratory effects are observed at lower O_3 concentrations if the level of exertion is increased and/or duration of exposure and exertion are extended. Predicted O_3-induced decrements in lung function have been shown to be a function of exposure concentration, duration and exercise level for healthy, young adults (McDonnell *et al.,* 1997).

Most of the studies investigating the influence of age have used lung function decrements and symptoms as measures of response. For healthy adults, lung function and symptom responses to O_3 decline as age increases. The rate of decline in O_3 responsiveness appears greater in those 18 to 35 years old compared to those 35 to 55 years old, while there is very little change after age 55. In one study (Seal *et al.,* 1996) analyzing a large data set, a 5.4% decrement in FEV_1 on average was estimated for 20-year-old individuals exposed to 0.12 ppm O_3 for 2.3 hours, whereas similar exposure of 35-year-old individuals resulted in a 2.6% decrement on average. While healthy children tend not to report respiratory symptoms when exposed to low levels of O_3, for subjects 18 to 36 years old symptom responses induced by O_3 are observed but tend to decrease with increasing age within this range (McDonnell *et al.,* 1999).

Limited evidence of gender differences in response to O_3 exposure has suggested that females may be predisposed to a greater susceptibility to O_3. Lower plasma and NL fluid levels of the most prevalent antioxidant, uric acid, in females relative to males may be a contributing factor. Consequently, reduced removal of O_3 in the upper airways may promote deeper penetration. However, most of the evidence on gender differences appears to be equivocal, with one study (Hazucha *et al.,* 2003) suggesting that physiological responses of young healthy males and females may be comparable (EPA, 2006a, section 6.5.2).

A few studies have suggested that ethnic minorities might be more responsive to O_3 than Caucasian population groups (EPA, 2006a, section 6.5.3). This may be more the result of a lack of adequate health care and socioeconomic status (SES) than any differences in sensitivity to O_3. The limited data available, which have investigated the influence of race, ethnic or other related factors on responsiveness to O_3, prevent drawing any clear conclusions at this time.

Few human studies have examined the potential influence of environmental factors such as the sensitivity of individuals who voluntarily smoke tobacco (*i.e.,* smokers) and the effect of high temperatures on O_3 responsiveness. New controlled human exposure studies have confirmed that smokers are less responsive to O_3 than nonsmokers; however, time course of development and recovery of these effects, as well as reproducibility, was not different from nonsmokers (EPA, 2006a, section 6.5.5). Influence of ambient temperature on pulmonary effects induced by O_3 has been studied very little, but additive effects of heat and O_3 exposure have been reported.

Antioxidants, which scavenge free radicals and limit lipid peroxidation in the ELF, are the first line of defense against oxidative stress. Ozone exposure leads to absorption of O_3 in the ELF with subsequent depletion of antioxidant in the nasal ELF, but concentration and antioxidant enzyme activity in ELF or plasma do not appear related to O_3 responsiveness (EPA 2006a, section 6.5.6). Controlled studies of dietary antioxidant supplements have shown some protective effects on lung function decrements but not on symptoms and airway inflammatory responses. Dietary antioxidant supplements have provided some protection to asthmatics by attenuating post-exposure airway hyperresponsiveness. Animal studies

have also supported the protective effects of ELF antioxidants.

b. At-Risk Subgroups for O_3-Related Effects

Several characteristics may increase the extent to which a population group shows increased susceptibility or vulnerability. Information on potentially susceptible and vulnerable groups is summarized in section 8.7 of the 2006 Criteria Document. As described there, the term *susceptibility* refers to innate (*e.g.,* genetic or developmental) or acquired (*e.g.,* personal risk factors, age) factors that make individuals more likely to experience effects with exposure to pollutants. A number of population groups have been identified as potentially susceptible to health effects as a result of O_3 exposure, including people with existing lung diseases, including asthma, children and older adults, and people who have larger than normal lung function responses that may be due to genetic susceptibility. In addition, some population groups have been identified as having increased vulnerability to O_3-related effects due to increased likelihood of exposure while at elevated ventilation rates, including healthy children and adults who are active outdoors, for example, outdoor workers and joggers. Taken together, the susceptible and vulnerable groups make up "at-risk" groups.[24]

i. Active People

A large group of individuals at risk from O_3 exposure consists of outdoor workers and children, adolescents, and adults who engage in outdoor activities involving exertion or exercise during summer daylight hours when ambient O_3 concentrations tend to be higher. This conclusion is based on a large number of controlled-human exposure studies and several epidemiologic field/panel studies which have been conducted with healthy children and adults and those with preexisting respiratory diseases (EPA 2006a, sections 6.2, 6.3, 7.2, and 8.4.4). The controlled human exposure studies show a clear O_3 exposure-response relationship with increasing spirometric and symptomatic response as exercise level increases. Furthermore, O_3-induced response increases as time of exposure increases. Studies of outdoor workers and others who participate in outdoor activities indicate that extended exposures to O_3 at elevated exertion levels can produce marked effects on lung function, as discussed above in section IIA.2 (Brauer *et al.,* 1996; Höppe *et al.,* 1995; Korrick *et al.,* 1998; McConnell *et al.,* 2002).

These field studies with subjects at elevated exertion levels support the extensive evidence derived from controlled human exposure studies. The majority of controlled human exposure studies has examined the effects of O_3 exposure in subjects performing continuous or intermittent exercise for variable periods of time and has reported significant O_3-induced respiratory responses. The epidemiologic studies discussed above also indicate that prolonged exposure periods, combined with elevated levels of exertion or exercise, may magnify O_3 effects on lung function. Thus, outdoor workers and others who participate in higher exertion activities outdoors during the time of day when high peak O_3 concentrations occur appear to be particularly vulnerable to O_3 effects on respiratory health. Although these studies show a wide variability of response and sensitivity among subjects and the factors contributing to this variability continue to be incompletely understood, the effect of increased exertion is consistent. It should be noted that this wide variability of response and sensitivity among subjects may be in part due to the wide range of other highly reactive photochemical oxidants coexisting with O_3 in the ambient air.

ii. People With Lung Disease

People with preexisting pulmonary disease are among those at increased risk from O_3 exposure. Altered physiological, morphological, and biochemical states typical of respiratory diseases like asthma, COPD, and chronic bronchitis may render people sensitive to additional oxidative burden induced by O_3 exposure. At the time of the 1997 review, it was concluded that these groups were at greater risk because the impact of O_3-induced responses on already-compromised respiratory systems would noticeably impair an individual's ability to engage in normal activity or would be more likely to result in increased self-medication or medical treatment. At that time there was little evidence that people with pre-existing disease were more responsive than healthy individuals in terms of the magnitude of lung function decrements or symptomatic responses. The new results from controlled exposure and epidemiologic studies continue to indicate that individuals with preexisting pulmonary disease are a sensitive population for O_3-related health effects.

Several controlled human exposure studies reviewed in the 1996 Criteria Document on atopic and asthmatic subjects have suggested but not clearly demonstrated enhanced responsiveness to acute O_3 exposure compared to healthy subjects. The majority of the newer studies reviewed in Chapter 6 of the 2006 Criteria Document indicate that asthmatics are more sensitive than normal subjects in manifesting O_3-induced lung function decrements. In one key study (Horstman *et al.,* 1995), the FEV_1 decrement observed in the asthmatics was significantly larger than in the healthy subjects (19% versus 10%, respectively). There was also a notable tendency for a greater group mean O_3-induced decrease in FEF_{25-75} in asthmatics relative to the healthy subjects (24% versus 15%, respectively). A significant positive correlation in asthmatics was also reported between the magnitude of O_3-induced spirometric responses and baseline lung function, *i.e.,* responses increased with severity of disease.

Asthmatics present a differential response profile for cellular, molecular, and biochemical parameters (2006 Criteria Document, Figure 8–1) that are altered in response to acute O_3 exposure. Ozone-induced increases in neutrophils, IL–8 and protein were found to be significantly higher in the BAL fluid from asthmatics compared to healthy subjects, suggesting mechanisms for the increased sensitivity of asthmatics (Basha *et al.,* 1994; McBride *et al.,* 1994; Scannell *et al.,* 1996; Hiltermann *et al.,* 1999; Holz *et al.,* 1999; Bosson *et al.,* 2003). Neutrophils, or PMNs, are the white blood cells most associated with inflammation. IL–8 is an inflammatory cytokine with a number of biological effects, primarily on neutrophils. The major role of this cytokine is to attract and activate neutrophils. Protein in the airways is leaked from the circulatory system, and is a marker for increased cellular permeability.

Bronchial constriction following provocation with O_3 and/or allergens presents a two-phase response. The early response is mediated by release of histamine and leukotrienes that leads to contraction of smooth muscle cells in the bronchi, narrowing the lumen and decreasing the airflow. In people with allergic airway disease, including people with rhinitis and asthma, these mediators also cause accumulation of eosinophils in the airways (Bascom *et al.,* 1990; Jorres *et al.,* 1996; Peden *et al.,* 1995 and 1997; Frampton *et al.,* 1997; Michelson *et al.,* 1999; Hiltermann *et al.,* 1999; Holz *et al.,* 2002; Vagaggini *et al.,* 2002). In asthma, the eosinophil,

[24] In the Staff Paper and documents from previous O_3 NAAQS reviews, "at-risk" groups have also been called "sensitive" groups, to mean both groups with greater inherent susceptibility and those more likely to be exposed.

which increases inflammation and allergic responses, is the cell most frequently associated with exacerbations of the disease. A study by Bosson *et al.* (2003) evaluated the difference in O_3-induced bronchial epithelial cytokine expression between healthy and asthmatic subjects. After O_3 exposure the epithelial expression of IL–5 and GM–CSF increased significantly in asthmatics, compared to healthy subjects. Asthma is associated with Th2-related airway response (allergic response), and IL–5 is an important Th2-related cytokine. The O_3-induced increase in IL–5, and also in GM–CSF, which affects the growth, activation and survival of eosinophils, may indicate an effect on the Th2-related airway response and on airway eosinophils. The authors reported that the O_3-induced Th2-related cytokine responses that were found within the asthmatic group may indicate a worsening of their asthmatic airway inflammation and thus suggest a plausible link to epidemiological data indicating O_3-associated increases in bronchial reactivity and hospital admissions.

The accumulation of eosinophils in the airways of asthmatics is followed by production of mucus and a late-phase bronchial constriction and reduced airflow. In a study of 16 intermittent asthmatics, Hiltermann *et al.* (1999) found that there was a significant inverse correlation between the O_3-induced change in the percentage of eosinophils in induced sputum and the change in $PC_{20,}$ the concentration of methacholine causing a 20% decrease in FEV_1. Characteristic O_3-induced inflammatory airway neutrophilia at one time was considered a leading mechanism of airway hyperresponsiveness. However, Hiltermann *et al.* (1999) determined that the O_3-induced change in percentage neutrophils in sputum was not significantly related to the change in $PC_{20.}$ These results are consistent with the results of Zhang *et al.* (1995), which found neutrophilia in a murine model to be only coincidentally associated with airway hyperresponsiveness, *i.e.,* there was no cause and effect relationship. (2006 Criteria Document, AX 6–26). Hiltermann *et al.* (1999) concluded that the results point to the role of eosinophils in O_3-induced airway hyperresponsiveness. Increases in O_3-induced nonspecific airway responsiveness incidence and duration could have important clinical implications for asthmatics.

Two studies (Jörres *et al.,* 1996; Holz *et al.,* 2002) observed increased airway responsiveness to O_3 exposure with bronchial allergen challenge in subjects with preexisting allergic airway disease. Jörres *et al.* (1996) found that O_3 causes an increased response to bronchial allergen challenge in subjects with allergic rhinitis and mild allergic asthma. The subjects were exposed to 0.25 ppm O_3 for 3 hours with IE. Airway responsiveness to methacholine was determined 1 hour before and after exposure; responsiveness to allergen was determined 3 hours after exposure. Statistically significant decreases in FEV_1 occurred in subjects with allergic rhinitis (13.8%) and allergic asthma (10.6%), and in healthy controls (7.3%). Methacholine responsiveness was statistically increased in asthmatics, but not in subjects with allergic rhinitis or healthy controls. Airway responsiveness to an individual's historical allergen (either grass and birch pollen, house dust mite, or animal dander) was significantly increased after O_3 exposure when compared to FA exposure. In subjects with asthma and allergic rhinitis, a maximum percent fall in FEV_1 of 27.9% and 7.8%, respectively, occurred 3 days after O_3 exposure when they were challenged with of the highest common dose of allergen. The authors concluded that subjects with asthma or allergic rhinitis, without asthma, could be at risk if a high O_3 exposure is followed by a high dose of allergen. Holz *et al.* (2002) reported an early phase lung function response in subjects with rhinitis after a consecutive 4-day exposure to 0.125 ppm O_3 that resulted in a clinically relevant (>20%) decrease in $FEV_{1.}$ Ozone-induced exacerbation of airway responsiveness persists longer and attenuates more slowly than O_3-induced lung function decrements and respiratory symptom responses and can have important clinical implications for asthmatics.

A small number of in vitro studies corroborate the differences in the responses of asthmatic and healthy subject generally found in controlled human exposure studies. In vitro studies (Schierhorn *et al.,* 1999) of nasal mucosal biopsies from atopic and nonatopic subjects exposed to 0.1 ppm O_3 found significant differences in release of IL–4, IL–6, IL–8, and TNF-α. Another study by Schierhorn *et al.* (2002) found significant differences in the O_3-induced release of the neuropeptides neurokinin A and substance P for allergic patients in comparison to nonallergic controls, suggesting increased activation of sensory nerves by O_3 in the allergic tissues. Another study by Bayram *et al.* (2002) using in vitro culture of bronchial epithelial cells recovered from atopic and nonatopic asthmatics also found significant increases in epithelial permeability in response to O_3 exposure.

The new data on airway responsiveness, inflammation, and various molecular markers of inflammation and bronchoconstriction indicate that people with asthma and allergic rhinitis (with or without asthma) comprise susceptible groups for O_3-induced adverse effects. This body of evidence indicates that controlled human exposure and epidemiological panel studies of lung function decrements and respiratory symptoms that evaluate only healthy, non-asthmatic subjects likely underestimate the effects of O_3 exposure on asthmatics and other susceptible populations. The effects of O_3 on lung function, inflammation, and increased airway responsiveness demonstrated in subjects with asthma and other allergic airway diseases, provide plausible mechanisms underlying the more serious respiratory morbidity effects, such as emergency department visits and hospital admissions, and respiratory mortality effects.

A number of epidemiological studies have been conducted using asthmatic study populations. The majority of epidemiological panel studies that evaluated respiratory symptoms and medication use related to O_3 exposures focused on children. These studies suggest that O_3 exposure is associated with increased respiratory symptoms and medication use in children with asthma. Other reported effects include respiratory symptoms, lung function decrements, and emergency department visits, as discussed in the 2006 Criteria Document (section 7.6.7.1). Strong evidence from a large multicity study (Mortimer *et al.,* 2002), along with support from several single-city studies indicate that O_3 exposure is associated with increased respiratory symptoms and medication use in children with asthma. With regard to ambient O_3 levels and increased hospital admissions and emergency department visits for asthma and other respiratory causes, strong and consistent evidence establishes a correlation between O_3 exposure and increased exacerbations of preexisting respiratory disease for 1-hour maximum O_3 concentrations <0.12 ppm. As discussed above and in the 2006 Criteria Document, section 7.3, several hospital admission and emergency department visit studies in the U.S., Canada, and Europe have reported positive associations between increase in O_3 and increased risk of emergency department visits and hospital admissions for asthma other

respiratory diseases, especially during the warm season.

In summary, based on a substantial new body of evidence from animal, controlled human exposure and epidemiological studies the 2006 Criteria Document (section x.x) concludes that people with asthma and other preexisting pulmonary diseases are among those at increased risk from O_3 exposure. Evidence from controlled human exposure studies indicates that asthmatics may exhibit larger lung function decrements and can have larger inflammatory responses in response to O_3 exposure than healthy controls. Asthmatics present a different response profile for cellular, molecular, and biochemical parameters that are altered in response to acute O_3 exposure. Asthmatics, and people with allergic rhinitis, are more likely to mount an allergic-type response upon exposure to O_3, as manifested by increases in white blood cells associated with allergy and related molecules, which increase inflammation in the airways. The increased inflammatory and allergic responses also may be associated with the larger late-phase responses that asthmatics can experience, which can include increased bronchoconstrictor responses to irritant substances or allergens and additional inflammation. Epidemiological studies have reported fairly robust associations between ambient O_3 concentrations and measures of lung function and daily respiratory symptoms (*e.g.,* chest tightness, wheeze, shortness of breath) in children with moderate to severe asthma and between O_3 and increased asthma medication use. These more serious responses in asthmatics and others with lung disease provide biological plausibility for the respiratory morbidity effects observed in epidemiological studies, such as emergency department visits and hospital admissions. The body of evidence from controlled human exposure and epidemiological studies, which includes asthmatic as well as non-asthmatic subjects, indicates that controlled human exposure studies of lung function decrements and respiratory symptoms that evaluate only healthy, non-asthmatic subjects likely underestimate the effects of O_3 exposure on asthmatics and other susceptible populations.

Newly available reports from controlled human exposure studies (see chapter 6 in the 2006 Criteria Document) utilized subjects with preexisting cardiopulmonary diseases such as COPD, asthma, allergic rhinitis, and hypertension. The data generated from these studies that evaluated changes in spirometry did not find clear differences between filtered air and O_3 exposure in COPD subjects. However, the new data on airway responsiveness, inflammation, and various molecular markers of inflammation and bronchoconstriction indicate that people with atopic asthma and allergic rhinitis comprise susceptible groups for O_3-induced adverse health effects.

Although controlled human exposure studies have not found evidence of larger spirometric responses to O_3 in people with COPD relative to healthy subjects, this may be due to the fact that most people with COPD are older adults who would not be expected to be as responsive based on their age. However, in section 8.7.1, the 2006 Criteria Document notes that new epidemiological evidence indicates that people with COPD may be more likely to experience other effects, including emergency room visits, hospital admissions, or premature mortality. For example, results from an analysis of five European cities indicated strong and consistent O_3 effects on unscheduled respiratory hospital admissions, including COPD (Anderson *et al.,* 1997). Also, an analysis of a 9-year data set for the whole population of the Netherlands provided risk estimates for more specific causes of mortality, including COPD (Hoek *et al.,* 2000, 2001; reanalysis Hoek, 2003); a positive, but nonsignificant, excess risk of COPD-related mortality was found to be associated with short-term O_3 concentrations. Moreover, as indicated by Gong *et al.* (1998), the effects of O_3 exposure on alveolar-arterial oxygen gradients may be more pronounced in patients with preexisting obstructive lung diseases. Relative to healthy elderly subjects, COPD patients have reduced gas exchange and low SaO_2. Any inflammatory or edematous responses due to O_3 delivered to the well-ventilated regions of the lung in COPD subjects could further inhibit gas exchange and reduce oxygen saturation. In addition, O_3-induced vasoconstriction could also acutely induce pulmonary hypertension. Inducing pulmonary vasoconstriction and hypertension in these patients would perhaps worsen their condition, especially if their right ventricular function was already compromised (EPA, 2006a, section 6.10). These controlled human exposure and epidemiological studies indicate that people with pre-existing lung diseases other than asthma are also at greater risk from O_3 exposure than people without lung disease.

iii. Children and Older Adults

Supporting evidence exists for heterogeneity in the effects of O_3 by age. As discussed in section 6.5.1 of the 2006 Criteria Document, children, adolescents, and young adults (<18 yrs of age) appear, on average, to have nearly equivalent spirometric responses to O_3, but have greater responses than middle-aged and older adults when exposed to comparable O_3 doses. Symptomatic responses to O_3 exposure, however, do not appear to occur in healthy children, but are observed in asthmatic children, particularly those who use maintenance medications. For adults (>17 yrs of age) symptoms gradually decrease with increasing age. In contrast to young adults, the diminished symptomatic responses in children and the diminished symptomatic and spirometric responses in older adults increases the likelihood that these groups continue outdoor activities leading to greater O_3 exposure and dose.

As described in the section 7.6.7.2 of the 2006 Criteria Document, many epidemiological field studies focused on the effect of O_3 on the respiratory health of school children. In general, children experienced decrements in lung function parameters, including PEF, FEV_1, and FVC. Increases in respiratory symptoms and asthma medication use were also observed in asthmatic children. In one German study, children with and without asthma were found to be particularly susceptible to O_3 effects on lung function. Approximately 20 percent of the children, both with and without asthma, experienced a greater than 10 percent change in FEV_1, compared to only 5 percent of the elderly population and athletes (Höppe *et al.,* 2003).

The American Academy of Pediatrics (2004) notes that children and infants are among the population groups most susceptible to many air pollutants, including O_3. This is in part because their lungs are still developing. For example, eighty percent of alveoli are formed after birth, and changes in lung development continue through adolescence (Dietert *et al.,* 2000). Children are also likely to spend more time outdoors than adults, which results in increased exposure to air pollutants (Wiley *et al.,* 1991a,b). Moreover, children have high minute ventilation rates and high levels of physical activity which also increases their dose (Plunkett *et al.,* 1992).

Several mortality studies have investigated age-related differences in O_3 effects (EPA, 2006a, section 7.6.7.2). Older adults are also often classified as

being particularly susceptible to air pollution. The 2006 Criteria Document (p. 8–60) concludes that the basis for increased O_3 sensitivity among the elderly is not known, but one hypothesis is that it may be related to changes in the respiratory tract lining fluid antioxidant defense network (Kelly *et al.,* 2003). Older adults have lower baseline lung function than younger people, and are also more likely to have preexisting lung and heart disease. Increased susceptibility of older adults to O_3 health effects is most clearly indicated in the newer mortality studies. Among the studies that observed positive associations between O_3 and mortality, a comparison of all age or younger age (≤ 65 years of age) O_3-mortality effect estimates to that of the elderly population (> 65 years) indicates that, in general, the elderly population is more susceptible to O_3 mortality effects. The meta-analysis by Bell *et al.* (2005) found a larger mortality effect estimate for the elderly than for all ages. In the large U.S. 95 communities study (Bell *et al.,* 2004), mortality effect estimates were slightly higher for those aged 65 to 74 years, compared to individuals less than 65 years and 75 years or greater. The absolute effect of O_3 on premature mortality may be substantially greater in the elderly population because of higher rates of preexisting respiratory and cardiac diseases. The 2006 Criteria Document (p. 7–177) concludes that the elderly population (>65 years of age) appear to be at greater risk of O_3-related mortality and hospitalizations compared to all ages or younger populations.

The 2006 Criteria Document notes that, collectively, there is supporting evidence of age-related differences in susceptibility to O_3 lung function effects. The elderly population (> 65 years of age) appear to be at increased risk of O_3-related mortality and hospitalizations, and children (< 18 years of age) experience other potentially adverse respiratory health outcomes with increased O_3 exposure (EPA, 2006a, section 7.6.7.2).

iv. People With Increased Responsiveness to Ozone

New animal toxicology studies using various strains of mice and rats have identified O_3-sensitive and resistant strains and illustrated the importance of genetic background in determining O_3 susceptibility (EPA, 2006a, section 8.7.4). Controlled human exposure studies have also indicated a high degree of variability in some of the pulmonary physiological parameters. The variable effects in individuals have been found to be reproducible, in other words, a person who has a large lung function response after exposure to O_3 will likely have about the same response if exposed again to the same dose of O_3. In controlled human exposure studies, group mean responses are not representative of this segment of the population that has much larger than average responses to O_3. Recent studies of asthmatics by David *et al.* (2003) and Romieu *et al.* (2004) reported a role for genetic polymorphism in observed differences in antioxidant enzymes and genes involved in inflammation to modulate lung function and inflammatory responses to O_3 exposure.[25]

Biochemical and molecular parameters extensively evaluated in these experiments were used to identify specific loci on chromosomes and, in some cases, to relate the differential expression of specific genes to biochemical and physiological differences observed among these species. Utilizing O_3-sensitive and O_3-resistant species, it has been possible to identify the involvement of increased airway reactivity and inflammation processes in O_3 susceptibility. However, most of these studies were carried out using relatively high doses of O_3, making the relevance of these studies questionable in human health effects assessment. The genes and genetic loci identified in these studies may serve as useful biomarkers in the future.

v. Other Population Groups

There is limited, new evidence supporting associations between short-term O_3 exposures and a range of effects on the cardiovascular system. Some but not all, epidemiological studies have reported associations between short-term O_3 exposures and the incidence of heart attacks and more subtle cardiovascular health endpoints, such as changes in HRV and cardiac arrhythmia. Others have reported associations with hospitalization or emergency department visits for cardiovascular diseases, although the results across the studies are not consistent. Studies also report associations between short-term O_3 exposure and mortality from cardiovascular or cardiopulmonary causes. The 2006 Criteria Document (p. 7–65) concludes that current cardiovascular effects evidence from some field studies is rather limited but supportive of a potential effect of short-term O_3 exposure and HRV, cardiac arrhythmia, and heart attack incidence. In the 2006 Criteria Document's evaluation of studies of hospital admissions for cardiovascular disease (EPA 2006a, section 7.3.4), it is concluded that evidence from this growing group of studies is generally inconclusive regarding an association with O_3 in studies conducted during the warm season (EPA 2006a, p. 7–83). This body of evidence suggests that people with heart disease may be at increased risk from short-term exposures to O_3≧ however, more evidence is needed to conclude that people with heart disease are a susceptible population.

Other groups that might have enhanced sensitivity to O_3, but for which there is currently very little evidence, include groups based on race, gender and SES, and those with nutritional deficiencies, which presents factors which modify responsiveness to O_3.

c. Adversity of Effects

In the 2008 rulemaking, in making judgments as to when various O_3-related effects become regarded as adverse to the health of individuals, EPA looked to 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)[26] 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 1997 review, it was concluded that there was evidence of causal associations from controlled human exposure studies for effects in the first of these five ATS-defined categories, evidence of statistically significant associations from epidemiological studies for effects in the second and third categories, and evidence from animal toxicology

[25] Similar to animal toxicology studies referred above, a polymorphism in a specific proinflammatory cytokine gene has been implicated in O_3-induced lung function changes in healthy, mild asthmatics and individuals with rhinitis. These observations suggest a potential role for these markers in the innate susceptibility to O_3, however, the validity of these markers and their relevance in the context of prediction to population studies requires additional research.

[26] 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). Overall, the new guidance does not fundamentally change the approach previously taken to define adversity, nor does it suggest a need at this time to change the structure or content of the tables describing gradation of severity and adversity of effects described below.

studies, which could be extrapolated to humans only with a significant degree of uncertainty, for the last two categories.

For ethical reasons, clear causal evidence from controlled human exposure studies still covers only effects in the first category. However, for this review there are results from epidemiological studies, upon which to base judgments about adversity, for effects in all of the categories. Statistically significant and robust associations have been reported in epidemiology studies falling into the second and third categories. These more serious effects include respiratory events (*e.g.,* triggering asthma attacks) that may require medication (*e.g.,* asthma), but not necessarily hospitalization, as well as respiratory hospital admissions and emergency department 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 have been suggested through evidence from epidemiological and animal toxicology studies, but have not been conclusively demonstrated still fall primarily into the last two categories. In the 1997 review of the O_3 standard, evidence for these more serious effects came from studies of effects in laboratory animals. Evidence from animal studies evaluated in the 2006 Criteria Document strongly suggests that O_3 is capable of damaging the distal airways and proximal alveoli, resulting in lung tissue remodeling leading to apparently irreversible changes. Recent advancements of dosimetry modeling also provide a better basis for extrapolation from animals to humans. Information from epidemiological studies provides supporting, but limited evidence of irreversible respiratory effects in humans than was available in the prior review. Moreover, the findings from single-city and multicity time-series epidemiology studies and meta-analyses of these epidemiological studies are highly suggestive of an association between short-term O_3 exposure and mortality particularly in the warm season.

While O_3 has been associated with effects that are clearly adverse, application of these guidelines, in particular to the least serious category of effects related to ambient O_3 exposures, involves judgments about which medical experts on the CASAC panel and public commenters have expressed diverse views in the past. To help frame such judgments, EPA staff have defined specific ranges of 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 ranges of pulmonary responses and their associated potential impacts are summarized in Tables 3–2 and 3–3 of the 2007 Staff Paper.

For active healthy people, moderate levels of functional responses (*e.g.,* FEV_1 decrements of ≥ 10 percent but < 20 percent, 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 responsive individuals. On the other hand, EPA staff determined that large functional responses (*e.g.,* FEV_1 decrements ≥ 20 percent, 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 responsive individuals. EPA staff determined that these would be considered adverse under ATS guidelines. In the context of standard setting, CASAC indicated that a focus on the mid to upper end of the range of moderate levels of functional responses (*e.g.,* FEV_1 decrements ≥ 15 percent but < 20 percent) is appropriate for estimating potentially adverse lung function decrements in active healthy people. However, for people with lung disease, even moderate functional (*e.g.,* FEV_1 decrements ≥ 10 percent but < 20 percent, 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 more frequent use of medication. For people with lung disease, large functional responses (*e.g.,* FEV_1 decrements ≥ 20 percent, 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. In the context of standard setting, the CASAC indicated (Henderson, 2006c) that a focus on the lower end of the range of moderate levels of functional responses (*e.g.,* FEV_1 decrements ≥ 10 percent) is most appropriate for estimating potentially adverse lung function decrements in people with lung disease.

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.

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 if affected by another agent.

Of the various effects of O_3 exposure that have been studied, many would meet the ATS definition of adversity. Such effects include, for example, any detectible level of permanent lung function loss attributable to air pollution, including both reductions in lung growth or acceleration of the age-related decline of lung function; exacerbations of disease in individuals with chronic cardiopulmonary diseases; reversible loss of lung function in combination with the presence of symptoms; as well as more serious effects such as those requiring medical care including hospitalization and, obviously, mortality.

d. Size of At-Risk Populations

Although O_3-related health risk estimates may appear to be small, their significance from an overall public health perspective is determined by the large numbers of individuals in the population groups potentially at risk for O_3-related health effects discussed above. For example, a population of concern includes people with respiratory disease, which includes approximately 11 percent of U.S. adults and 13 percent of children who have been diagnosed with asthma and 6 percent of adults with chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema) in 2002 and 2003 (Table 8–4 in the 2006 Criteria Document, section 8.7.5.2). More broadly, individuals with preexisting cardiopulmonary disease may constitute an additional population of concern, with potentially tens of millions of people included in each disease category. In addition, populations based on age group also comprise substantial segments of the population that may be potentially at risk for O_3-related health impacts. Based on U.S. census data from 2003, about 26 percent of the U.S. population are under 18 years of age and 12 percent are 65 years of age or older. Hence, large proportions of the U.S. population are included in life stages that are most likely to have increased susceptibility to the health effects of O_3 and/or those with the highest ambient O_3 exposures.

The 2006 Criteria Document (section 8.7.5.2) notes that the health statistics data illustrate what is known as the "pyramid" of effects. At the top of the pyramid, there are approximately 2.5 millions deaths from all causes per year in the U.S. population, with about 100,000 deaths from chronic lower respiratory diseases. For respiratory health diseases, there are nearly 4 million hospital discharges per year, 14 million emergency department visits, 112 million ambulatory care visits, and an estimated 700 million restricted activity days per year due to respiratory conditions from all causes per year. Applying small risk estimates for the O_3-related contribution to such health effects with relatively large baseline levels of health outcomes can result in quite large public health impacts related to ambient O_3 exposure. Thus, even a small percentage reduction in O_3 health impacts on cardiopulmonary diseases would reflect a large number of avoided cases. In considering this information together with the concentration-response relationships that have been observed between exposure to O_3 and various health endpoints, the 2006 Criteria Document (section 8.7.5.2) concludes that exposure to ambient O_3 likely has a significant impact on public health in the U.S.

B. Human Exposure and Health Risk Assessments

To put judgments about health effects that are adverse for individuals into a broader public health context, EPA has developed and applied models to estimate human exposures and health risks. This broader context includes consideration of the size of particular population groups at risk for various effects, the likelihood that exposures of concern will occur for individuals in such groups under varying air quality scenarios, estimates of the number of people likely to experience O_3-related effects, the variability in estimated exposures and risks, and the kind and degree of uncertainties inherent in assessing the exposures and risks involved.

As discussed below there are a number of important uncertainties that affect the exposure and health risk estimates. It is also important to note that there have been significant improvements in both the exposure and health risk model. CASAC expressed the view that the exposure analysis represents a state-of-the-art modeling approach and that the health risk assessment was "well done, balanced and reasonably communicated (Henderson, 2006c). While recognizing and considering the kind and degree of uncertainties in both the exposure and health risk estimates, the 2007 Staff Paper (pp. 6–20 to 6–21) judged that the quality of the estimates is such that they are suitable to be used as an input to the Administrator's decisions on the O_3 primary standard.

In modeling exposures and health risks associated with just meeting the current and alternative O_3 standards, EPA has simulated air quality to represent conditions just meeting these standards based on O_3 air quality patterns in several recent years and on how the shape of the O_3 air quality distribution have changed over time based on historical trends in monitored O_3 air quality data. As described in the 2007 Staff Paper (EPA, 2007b, section 4.5.8) and discussed below, recent O_3 air quality distributions have been statistically adjusted to simulate just meeting the current and selected alternative standards. 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.[27]

As noted in section I.C above, around the time of the release of the final 2007 Staff Paper in January 2007, EPA discovered a small error in the exposure model that when corrected resulted in slight increases in the simulated exposures. Since the exposure estimates are an input to the lung function portion of the health risk assessment, this correction also resulted in slight increases in the lung function risk estimates as well. The exposure and risk estimates discussed in this notice reflect the corrected estimates, and thus are slightly different than the exposure and risk estimates cited in the January 31, 2007 Staff Paper.[28]

1. Exposure Analyses

a. Overview

As part of the 2008 rulemaking, the EPA conducted exposure analyses using a simulation model to estimate O_3 exposures for the general population, school age children (ages 5–18), and school age children with asthma living in 12 U.S. metropolitan areas representing different regions of the country where the then current 8-hour O_3 standard is not met. The emphasis on children reflects the finding of the 1997 O_3 NAAQS review that children are an important at-risk group. The 12 modeled areas combined represent a significant fraction of the U.S. urban population, 89 million people, including 18 million school age children of whom approximately 2.6 million have 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 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, 2007b). The geographic extent of each modeled area consists of the census tracts in the combined statistical area (CSA) as defined by OMB (OMB, 2005).[29]

[27] Modeling that projects whether and how areas might attain alternative standards in a future year is presented in the Regulatory Impact Analysis being prepared in connection with this rulemaking.

[28] EPA made available corrected versions of the final 2007 Staff Paper, and human exposure and health risk assessment technical support documents in July 2007 on the EPA Web site listed in the Availability of Related Information section of this notice.

[29] The 12 CSAs modeled are: Atlanta-Sandy Springs-Gainesville, GA–AL; Boston-Worcester-Manchester, MA–NH; Chicago-Naperville-Michigan City, IL–IN–WI; Cleveland-Akron-Elyria, OH; Detroit-Warren-Flint, MI; Houston-Baytown-Huntsville, TX; Los Angeles-Long Beach-Riverside,

Exposure estimates were developed using a probabilistic exposure model that is designed to explicitly model the numerous sources of variability that affect people's exposures. As discussed below, the model estimates population exposures by simulating human activity patterns, air conditioning prevalence, air exchange rates, and other factors. The modeled exposure estimates were developed for three recent years of ambient O_3 concentrations (2002, 2003, and 2004), as well as for O_3 concentrations adjusted to simulate conditions associated with just meeting the then current NAAQS and various alternative 8-hour standards based on the three year period 2002–2004.[30] This exposure assessment is more fully described and presented in the 2007 Staff Paper and in a technical support document, *Ozone Population Exposure Analysis for Selected Urban Areas* (EPA, 2007c; hereafter Exposure Analysis TSD). The scope and methodology for this exposure assessment were developed over the last few years with considerable input from the CASAC Ozone Panel and the public.[31]

The goals of the O_3 exposure assessment were: (1) To provide estimates of the size of at-risk populations exposed to various levels associated with recent O_3 concentrations, and with just meeting the current O_3 NAAQS and alternative O_3 standards, in specific urban areas; (2) to provide distributions of exposure estimates over the entire range of ambient O_3 concentrations as an important input to the lung function risk assessment summarized below in section II.B.2; (3) to develop a better understanding of the influence of various inputs and assumptions on the exposure estimates; and (4) to gain insight into the distribution of exposures and patterns of exposure reductions associated with meeting alternative O_3 standards.

The EPA recognizes that there are many sources of variability and uncertainty inherent in the inputs to this assessment and that there is uncertainty in the resulting O_3 exposure estimates. With respect to variability, the exposure modeling approach accounts for variability in ambient O_3 levels, demographic characteristics, physiological attributes, activity patterns, and factors affecting microenvironmental (*e.g.,* indoor) concentrations. In EPA's judgment, the most important uncertainties affecting the exposure estimates are related to the modeling of human activity patterns over an O_3 season, the modeling of variations in ambient concentrations near roadways, and the modeling of air exchange rates that affect the amount of O_3 that penetrates indoors. Another important uncertainty that affects the estimation of how many exposures are associated with moderate or greater exertion is the characterization of energy expenditure for children engaged in various activities. As discussed in more detail in the 2007 Staff Paper (EPA, 2007b, section 4.3.4.7), the uncertainty in energy expenditure values carries over to the uncertainty of the modeled breathing rates, which are important since they are used to classify exposures occurring at moderate or greater exertion which are the relevant exposures since O_3-related effects observed in controlled human exposure studies only are observed when individuals are engaged in some form of exercise. The uncertainties in the exposure model inputs and the estimated exposures have been assessed using quantitative uncertainty and sensitivity analyses. Details are discussed in the 2007 Staff Paper (section 4.6) and in a technical memorandum describing the exposure modeling uncertainty analysis (Langstaff, 2007).

b. Scope and Key Components

Population exposures to O_3 are primarily driven by ambient outdoor concentrations, which vary by time of day, location, and peoples' activities. Outdoor O_3 concentration estimates used in the exposure assessment are provided by measurements and statistical adjustments to the measured concentrations. The current exposure analysis allows comparisons of population exposures to O_3 within each urban area, associated with current O_3 levels and with O_3 levels just meeting several potential alternative air quality standards or scenarios. Human exposure, regardless of the pollutant, depends on where individuals are located and what they are doing. Inhalation exposure models are useful in realistically estimating personal exposures to O_3 based on activity-specific breathing rates, particularly when recognizing that large scale population exposure measurement studies have not been conducted that are representative of the overall population or at risk subpopulations.

The model EPA used to simulate O_3 population exposure is the Air Pollutants Exposure Model (APEX), the human inhalation exposure model within the Total Risk Integrated Methodology (TRIM) framework (EPA, 2006c,d). APEX is conceptually based on the probabilistic NAAQS exposure model for O_3 (pNEM/O_3) used in the last O_3 NAAQS review. Since that time the model has been restructured, improved, and expanded to reflect conceptual advances in the science of exposure modeling and newer input data available for the model. Key improvements to algorithms include replacement of the cohort approach with a probabilistic sampling approach focused on individuals, accounting for fatigue and oxygen debt after exercise in the calculation of breathing rates, and a new approach for construction of longitudinal activity patterns for simulated persons. Major improvements to data input to the model include updated air exchange rates, more recent census and commuting data, and a greatly expanded daily time-activities database.

APEX is a probabilistic model designed to explicitly model the numerous sources of variability that affect people's exposures. APEX simulates the movement of individuals through time and space and estimates their exposures to O_3 in indoor, outdoor, and in-vehicle microenvironments. The exposure model takes into account the most significant factors contributing 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 levels within each microenvironment, and the effects of exertion on breathing rate in exposed individuals. A more detailed description of APEX and its application is presented in chapter 4 of the 2007 Staff Paper and associated technical documents (EPA, 2006b,c,d).

Several methods have been used to evaluate the APEX model and to characterize the uncertainty of the model estimates. These include conducting model evaluation, sensitivity analyses, and a detailed uncertainty analysis for one urban area.

CA; New York-Newark-Bridgeport, NY–NJ–CT–PA; Philadelphia-Camden-Vineland, PA–NJ–DE–MD; Sacramento—Arden-Arcade—Truckee, CA–NV; St. Louis-St. Charles-Farmington, MO–IL; Washington-Baltimore-N. Virginia, DC–MD–VA–WV.

[30] All 12 of the CSAs modeled did not meet the 0.084 ppm O_3 NAAQS for the three year period examined.

[31] The general approach used in the human exposure assessment was described in the draft Health Assessment Plan (EPA, 2005d) that was released to the CASAC and general public in April 2005 and was the subject of a consultation with the CASAC O_3 Panel on May 5, 2005. In October 2005, OAQPS released the first draft of the Staff Paper containing a chapter discussing the exposure analyses and first draft of the Exposure Analyses TSD for CASAC consultation and public review on December 8, 2005. In July 2006, OAQPS released the second draft of the Staff Paper and second draft of the Exposure Analyses TSD for CASAC review and public comment which was held by the CASAC O_3 Panel on August 24–25, 2006.

These are discussed fully in the 2007 Staff Paper (section 4.6) and in Langstaff (2007). The uncertainty of model structure was judged to be of lesser importance than the uncertainties of the model inputs and parameters. Model structure refers to the algorithms in APEX designed to simulate the processes that result in people's exposures, for example, the way that APEX models exposures to individuals when they are near roads. The uncertainties in the model input data (*e.g.,* measurement error, ambient concentrations, air exchange rates, and activity pattern data) have been assessed individually, and their impact on the uncertainty in the modeled exposure estimates was assessed in a unified quantitative analysis with results expressed in the form of estimated confidence ranges around the estimated measures of exposure. This uncertainty analysis was conducted for one urban area (Boston) using the observed 2002 O_3 concentrations and 2002 concentrations adjusted to simulate just meeting the current standard, with the expectation that the results would be similar for other cities and years. One significant source of uncertainty, due to limitations in the database used to model peoples' daily activities, was not included in the unified analysis, and was assessed through separate sensitivity analyses. This analysis indicates that the uncertainty of the exposure results is relatively small. For example, 95 percent uncertainty intervals were calculated for the APEX estimates of the percent of children or asthmatic children with exposures above 0.060, 0.070, or 0.080 ppm under moderate exertion, for two air quality scenarios (current 2002 and 2002 adjusted to simulate just meeting the current standard) in Boston (Langstaff, 2007, Tables 26 and 27). The 95 percent uncertainty intervals for this set of 12 exposure estimates indicate the possibility of underpredictions of the exposure estimates ranging from 3 to 25 percent of the modeled estimates, and overpredictions ranging from 4 to 11 percent of the estimates. For example, APEX estimates the percent of asthmatic children with exposures above 0.070 ppm under moderate exertion to be 24 percent, for Boston 2002 O_3 concentrations adjusted to simulate just meeting the current standard. The 95 percent uncertainty interval for this estimate is 23 − 30 percent, or −4 to +25 percent of the estimate. These uncertainty intervals do not include the uncertainty engendered by limitations of the activity database, which is in the range of one to ten percent.

The exposure periods modeled here are the O_3 seasons in 2002, 2003, and 2004. The O_3 season in each area includes the period of the year where elevated O_3 levels tend to be observed and for which routine hourly O_3 monitoring data are available. Typically this period spans from March or April through September or October, or in some areas, spanning the entire year. Three years were modeled to reflect the substantial year-to-year variability that occurs in O_3 levels 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. Nationally, 2002 was a relatively high year with respect to the 4th highest daily maximum 8-hour O_3 levels observed in urban areas across the U.S. (EPA, 2007b, Figure 2–16), with the mean of the distribution of O_3 levels for the urban monitors being in the upper third among the years 1990 through 2006. In contrast, on a national basis, 2004 is the lowest year on record through 2006 for this same air quality statistic, and 8-hour daily maximum O_3 levels observed in most, but not all of the 12 urban areas included in the exposure and risk analyses were relatively low compared to other recent years. The 4th highest daily maximum 8-hour O_3 levels observed in 2003 in the 12 urban areas and nationally generally were between those observed in 2002 and 2004.

Regulatory scenarios examined in the 2008 rulemaking include the then current 0.08 ppm, average of the 4th daily maximum 8-hour averages over a three year period standard; standards with the same form but with alternative levels of 0.080, 0.074, 0.070, and 0.064 ppm; standards specified as the average of the 3rd highest daily maximum 8-hour averages over a three year period with alternative levels of 0.084 and 0.074 ppm; and a standard specified as the average of the 5th highest daily maximum 8-hour averages over a three year period with a level of 0.074 ppm.[32] The then current standard used a rounding convention that allows areas to have an average of the 4th daily maximum 8-hour averages as high as 0.084 ppm and still meet the standard. All alternative standards analyzed were intended to reflect improved precision in the measurement of ambient concentrations (in ppm), where the precision would extend to three instead of two decimal places.

The then current standard and all alternative standards were modeled using a quadratic rollback approach to adjust the hourly concentrations observed in 2002–2004 to yield a design value[33] corresponding to the standard being analyzed. The quadratic rollback technique reduces higher concentrations more than lower concentrations near ambient background levels.[34] This procedure was considered in a sensitivity analysis in the 1997 review of the O_3 standard and has been shown to be more realistic than a linear, proportional rollback method, where all of the ambient concentrations are reduced by the same factor.

c. Exposure Estimates and Key Observations

The exposure assessment, which provides estimates of the number of people exposed to different levels of ambient O_3 while at specified exertion levels,[35] serve two purposes. 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. Second, estimates of personal exposures to ambient O_3 concentrations at and above specific benchmark levels provide some perspective on the public

[32] The 8-hour O_3 standard established in 1997 was 0.08 ppm, but the rounding convention specified that the average of the 4th daily maximum 8-hour average concentrations over a three-year period must be at 0.084 ppm or lower to be in attainment of this standard. When EPA staff selected alternative standards to analyze, it was presumed that the same type of rounding convention would be used, and thus alternative standards of 0.084, 0.074, 0.064 ppm were chosen.

[33] A design value is a statistic that describes the air quality status of a given area relative to the level of the NAAQS. Design values are often based on multiple years of data, consistent with specification of the NAAQS in Part 50 of the CFR. For the 8-hour O_3 NAAQS, the 3-year average of the annual 4th-highest daily maximum 8-hour average concentrations, based on the monitor within (or downwind of) an urban area yielding the highest 3-year average, is the design value.

[34] The quadratic rollback approach and evaluation of this approach are described by Johnson (1997), Duff *et al.* (1998) and Rizzo (2005, 2006).

[35] As discussed above in Section II.A, O_3 health responses observed in controlled human exposure studies are associated with exposures while engaged in moderate or greater exertion and, therefore, these are the exposure measures of interest. The level of exertion of individuals engaged in particular activities is measured by an equivalent ventilation rate (EVR), ventilation normalized by body surface area (BSA, in m^2), which is calculated as VE/BSA, where VE is the ventilation rate (liters/minute). Moderate and greater exertion levels were defined as EVR > 13 liters/min-m^2 (Whitfield *et al.,* 1996) to correspond to the exertion levels measured in most subjects studied in the controlled human exposure studies that reported health effects associated with 6.6 hour O_3 exposures.

health impacts of health effects that cannot currently be evaluated in quantitative risk assessments that may occur at current air quality levels, and the extent to which such impacts might be reduced by meeting the current and alternative standards. This is especially true when there are exposure levels at which it is known or can reasonably be inferred that specific O_3-related health effects are occurring. In this notice, exposures at and above these benchmark concentrations are referred to as "exposures of concern."

It is important to note that although the analysis of "exposures of concern" was conducted using three discrete benchmark levels (*i.e.,* 0.080, 0.070, and 0.060 ppm), 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. The EPA recognizes that there is no sharp breakpoint within the continuum ranging from at and above 0.080 ppm down to 0.060 ppm. In considering the concept of exposures of concern, 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 at lower O_3 levels.

Within the context of this continuum, estimates of exposures of concern at discrete benchmark levels 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 cannot be evaluated in quantitative risk assessments, such as lung inflammation, increased airway responsiveness, and changes in host defenses. They also help in understanding the extent to which such impacts have the potential to be reduced by meeting the current and alternative standards. In the selection of specific benchmark concentrations for this analysis, staff first considered the exposure level of 0.080 ppm, at which there is a substantial amount of controlled human exposure evidence demonstrating a range of O_3-related health effects including lung inflammation and airway responsiveness in healthy individuals. Thus, as in the 1997 review, this level was selected as a benchmark level for this assessment of exposures of concern. Evidence newly available in this review is the basis for identifying additional, lower benchmark levels of 0.070 and 0.060 ppm for this assessment.

More specifically, as discussed above in section II.A.2, evidence available from controlled human exposure and epidemiological studies indicates that people with asthma have larger and more serious effects than healthy individuals, including lung function, respiratory symptoms, increased airway responsiveness, and pulmonary inflammation, which has been shown to be a more sensitive marker than lung function responses. Further, a substantial new body of evidence from epidemiological studies shows associations with serious respiratory morbidity and cardiopulmonary mortality effects at O_3 levels that extend below 0.080 ppm. Additional, but very limited new evidence from controlled human exposure studies shows lung function decrements and respiratory symptoms in healthy subjects at an O_3 exposure level of 0.060 ppm. The selected benchmark level of 0.070 ppm reflects the new information that asthmatics have larger and more serious effects than healthy people and therefore controlled human exposure studies done with healthy subjects may underestimate effects in this group, as well as the substantial body of epidemiological evidence of associations with O_3 levels below 0.080 ppm. The selected benchmark level of 0.060 ppm additionally reflects the very limited new evidence from controlled human exposure studies that show lung function decrements and respiratory symptoms in some healthy subjects at the 0.060 ppm exposure level, recognizing that asthmatics are likely to have more serious responses and that lung function is not likely to be as sensitive a marker for O_3 effects as is lung inflammation.

The estimates of exposures of concern were reported in terms of both "people exposed" (the number and percent of people who experience a given level of O_3 concentrations, or higher, at least one time during the O_3 season in a given year) and "occurrences of exposure" (the number of times a given level of pollution is experienced by the population of interest, expressed in terms of person-days of occurrences). Estimating exposures of concern is important because it provides some indication of the potential public health impacts of a range of O_3-related health outcomes, such as lung inflammation, increased airway responsiveness, and changes in host defenses. These particular health effects have been demonstrated in controlled human exposure studies of healthy individuals to occur at levels as low as 0.080 ppm O_3, but have not been evaluated at lower levels in controlled human exposure studies. The EPA did not include these effects in the quantitative risk assessment due to a lack of adequate information on the exposure-response relationships.

The 1997 O_3 NAAQS review estimated exposures associated with 1-hour heavy exertion, 1-hour moderate exertion, and 8-hour moderate exertion for children, outdoor workers, and the general population. The EPA's analysis in the 1997 Staff Paper showed that exposure estimates based on the 8-hour moderate exertion scenario for children yielded the largest number of children experiencing exposures at or above exposures of concern. Consequently, EPA chose to focus on the 8-hour moderate and greater exertion exposures in all and asthmatic school age children in the current exposure assessment. While outdoor workers and other adults who engage in moderate or greater exertion for prolonged durations while outdoors during the day in areas experiencing elevated O_3 concentrations also are at risk for experiencing exposures associated with O_3-related health effects, EPA did not focus on quantitative estimates for these populations due to the lack of information about the number of individuals who regularly work or exercise outdoors. Thus, the exposure estimates presented here and in the 2007 Staff Paper are most useful for making relative comparisons across alternative air quality scenarios and do not represent the total exposures in all children or other groups within the general population associated with the air quality scenarios.

Population exposures to O_3 were estimated in 12 urban areas for 2002, 2003, and 2004 air quality, and also using O_3 concentrations adjusted to just meet the then current and several alternative standards. The estimates of 8-hour exposures of concern at and above benchmark levels of 0.080, 0.070, and 0.060 ppm aggregated across all 12 areas are shown in Table 1 for air quality scenarios just meeting the current and four alternative 8-hour average standards.[36] Table 1 provides estimates of the number and percent of school age children and asthmatic school age children exposed, with daily 8-hour maximum exposures at or above each O_3 benchmark level of exposures of concern, while at intermittent moderate or greater exertion and based on O_3 concentrations observed in 2002 and

[36] The full range of quantitative exposure estimates associated with just meeting the 0.084 ppm and alternative O_3 standards are presented in chapter 4 and Appendix 4A of the 2007 Staff Paper.

2004. Table 1 summarizes estimates for 2002 and 2004 because these years reflect years that bracket relatively higher and lower O_3 levels, with year 2003 generally containing O_3 levels in between when considering the 12 urban areas modeled. This table also reports the percent change in the number of persons exposed when a given alternative standard is compared with the then current standard.

Key observations important in comparing exposure estimates associated with just meeting the current NAAQS and alternative standards under consideration include:

(1) As shown in Table 6–1 of the 2007 Staff Paper, the patterns of exposure in terms of percentages of the population exceeding a given exposure level are very similar for the general population and for asthmatic and all school age (5–18) children, although children are about twice as likely to be exposed, based on the percent of the population exposed, at any given level.

(2) As shown in Table 1 below, the number and percentage of asthmatic and all school-age children aggregated across the 12 urban areas estimated to experience one or more exposures of concern decline from simulations of just meeting the then current 0.084 ppm standard to simulations of alternative 8-hour standards by varying amounts depending on the benchmark level, the population subgroup considered, and the year chosen. For example, the estimated percentage of school age children experiencing one or more exposures ≥ 0.070 ppm, while engaged in moderate or greater exertion, during an O_3 season is about 18 percent of this population when the 0.084 ppm standard is met using the 2002 simulation; this is reduced to about 12, 4, 1, and 0.2 percent of children upon meeting alternative standards of 0.080, 0.074, 0.070, and 0.064 ppm, respectively (all specified in terms of the 4th highest daily maximum 8-hour average), using the 2002 simulation.

TABLE 1—NUMBER AND PERCENT OF ALL AND ASTHMATIC SCHOOL AGE CHILDREN IN 12 URBAN AREAS ESTIMATED TO EXPERIENCE 8-HOUR OZONE EXPOSURES ABOVE 0.080, 0.070, AND 0.060 PPM WHILE AT MODERATE OR GREATER EXERTION, ONE OR MORE TIMES PER SEASON, AND THE NUMBER OF OCCURRENCES ASSOCIATED WITH JUST MEETING ALTERNATIVE 8-HOUR STANDARDS BASED ON ADJUSTING 2002 AND 2004 AIR QUALITY DATA[1] [2]

Benchmark levels of exposures of concern (ppm)	8–Hour air quality standards[3] (ppm)	All children, ages 5–18 Aggregate for 12 urban areas Number of children exposed (% of all) [% reduction from 0.084 ppm standard]		Asthmatic children, ages 5–18 Aggregate for 12 urban areas Number of children exposed (% of group) [% reduction from 0.084 ppm standard]	
		2002	2004	2002	2004
0.080	0.084	700,000 (4%)	30,000 (0%)	110,000 (4%)	0 (0%)
	0.080	290,000 (2%) [70%]	10,000 (0%) [67%]	50,000 (2%) [54%]	0 (0%)
	0.074	60,000 (0%) [91%]	0 (0%) [100%]	10,000 (0%) [91%]	0 (0%)
	0.070	10,000 (0%) [98%]	0 (0%) [100%]	0 (0%) [100%]	0 (0%)
	0.064	0 (0%) [100%]	0 (0%) [100%]	0 (0%) [100%]	0 (0%)
0.070	0.084	3,340,000 (18%)	260,000 (1%)	520,000 (20%)	40,000 (1%)
	0.080	2,160,000 (12%) [35%]	100,000 (1%) [62%]	330,000 (13%) [36%]	10,000 (0%) [75%]
	0.074	770,000 (4%) [77%]	20,000 (0%) [92%]	120,000 (5%) [77%]	0 (0%) [100%]
	0.070	270,000 (1%) [92%]	0 (0%) [100%]	50,000 (2%) [90%]	0 (0%) [100%]
	0.064	30,000 (0.2%) [99%]	0 (0%) [100%]	10,000 (0.2%) [98%]	0 (0%) [100%]
0.060	0.084	7,970,000 (44%)	1,800,000 (10%)	1,210,000 (47%)	270,000 (11%)
	0.080	6,730,000 (37%) [16%]	1,050,000 (6%) [42%]	1,020,000 (40%) [16%]	150,000 (6%) [44%]
	0.074	4,550,000 (25%) [43%]	350,000 (2%) [80%]	700,000 (27%) [42%]	50,000 (2%) [81%]
	0.070	3,000,000 (16%) [62%]	110,000 (1%) [94%]	460,000 (18%) [62%]	10,000 (1%) [96%]
	0.064	950,000 (5%) [88%]	10,000 (0%) [99%]	150,000 (6%) [88%]	0 (0%) [100%]

[1] Moderate or greater exertion is defined as having an 8-hour average equivalent ventilation rate ≥ 13 l-min/m^2.

[2] Estimates are the aggregate results based on 12 combined statistical areas (Atlanta, Boston, Chicago, Cleveland, Detroit, Houston, Los Angeles, New York, Philadelphia, Sacramento, St. Louis, and Washington, DC). Estimates are for the ozone season which is all year in Houston, Los Angeles and Sacramento and March or April to September or October for the remaining urban areas.

[3] All standards summarized here have the same form as the 8-hour standard established in 1997 which is specified as the 3-year average of the annual 4th highest daily maximum 8-hour average concentrations must be at or below the concentration level specified. As described in the 2007 Staff Paper (EPA, 2007b, section 4.5.8), recent O_3 air quality distributions have been statistically adjusted to simulate just meeting the 0.084 ppm standard and selected alternative standards. These simulations do not represent predictions of when, whether, or how areas might meet the specified standards.

(3) Substantial year-to-year variability in exposure estimates is observed over the three-year modeling period. For example, the estimated number of school age children experiencing one or more exposures ≥ 0.070 ppm during an O_3 season when a 0.084 ppm standard is met in the 12 urban areas included in the analysis is 3.3, 1.0, or 0.3 million for the 2002, 2003, and 2004 simulations, respectively.

(4) There is substantial variability observed across the 12 urban areas in the percent of the population subgroups estimated to experience exposures of concern. For example, when 2002 O_3 concentrations are simulated to just meet a 0.084 ppm standard, the aggregate 12 urban area estimate is 18 percent of all school age children are estimated to experience O_3 exposures ≥ 0.070 ppm (Table 1 below), while the range of exposure estimates in the 12 urban areas considered separately for all children range from 1 to 38 percent (EPA, 2007b, p. 4–48, Exhibit 2). There was also variability in exposure estimates among the modeled areas when using the 2004 air quality simulation for the same scenario; however it was reduced and ranged from 0 to 7 percent in the 12 urban areas (EPA, 2007b, p. 4–60, Exhibit 8).

(5) Of particular note, as discussed above in section II.A of this notice, high inter-individual variability in responsiveness means that only a subset of individuals in these groups who are exposed at and above a given benchmark level would actually be expected to experience such adverse health effects.

(6) In considering these observations, it is important to take into account the variability, uncertainties, and limitations associated with this assessment, including the degree of uncertainty associated with a number of model inputs and uncertainty in the model itself, as discussed above.

2. Quantitative Health Risk Assessment

This section discusses the approach used to develop quantitative health risk estimates associated with exposures to O_3 building upon a more limited risk assessment that was conducted during the last review.[37] As part of the 1997 review, EPA conducted a health risk assessment that produced risk estimates for the number and percent of children and outdoor workers experiencing lung function and respiratory symptoms associated with O_3 exposures for 9 urban areas.[38] The risk assessment for the 1997 review also included risk estimates for excess respiratory-related hospital admissions related to O_3 concentrations for New York City. In the last review, the risk estimates played a significant role in both the staff recommendations and in the proposed and final decisions to revise the O_3 standards. The health risk assessment conducted for the current review builds upon the methodology and lessons learned from the prior review.

a. Overview

The updated health risk assessment conducted as part of the 2008 rulemaking includes estimates of (1) risks of lung function decrements in all and asthmatic school age children, respiratory symptoms in asthmatic children, respiratory-related hospital admissions, and non-accidental and cardiorespiratory-related mortality associated with recent ambient O_3 levels; (2) risk reductions and remaining risks associated with just meeting the then current 0.084 ppm 8-hour O_3 NAAQS; and (3) risk reductions and remaining risks associated with just meeting various alternative 8-hour O_3 NAAQS in a number of example urban areas. This risk assessment is more fully described and presented in chapter 5 of the 2007 Staff Paper and in a technical support document (TSD), *Ozone Health Risk Assessment for Selected Urban Areas* (Abt Associates, 2007a, hereafter referred to as "Risk Assessment TSD"). The scope and methodology for this risk assessment were developed over the last few years with considerable input from the CASAC O_3 Panel and the public.[39] The information contained in these documents included specific criteria for the selection of health endpoints, studies, and locations to include in the assessment. In a peer review letter sent by CASAC to the Administrator documenting its advice in October 2006 (Henderson, 2006c), the CASAC O_3 Panel concluded that the risk assessment was "well done, balanced, and reasonably communicated" and that the selection of health endpoints for inclusion in the quantitative risk assessment was appropriate.

The goals of the risk assessment are: (1) To provide estimates of the potential magnitude of several morbidity effects and mortality associated with current O_3 levels, and with meeting the then current 0.084 ppm standard and alternative 8-hour O_3 standards in specific urban areas; (2) to develop a better understanding of the influence of various inputs and assumptions on the risk estimates; and (3) to gain insights into the distribution of risks and patterns of risk reductions associated with meeting alternative O_3 standards. The health risk assessment is intended to be dependent on and reflect the overall weight and nature of the health effects evidence discussed above in section II.A and in more detail in the 2006 Criteria Document and 2007 Staff Paper. While not independent of the overall evaluation of the health effects evidence, the quantitative health risk assessment provides additional insights regarding the relative public health implications associated with just meeting a 0.084 ppm standard and several alternative 8-hour standards.

The risk assessment covers a variety of health effects for which there is adequate information to develop quantitative risk estimates. However, as noted by CASAC (Henderson, 2007) and in the 2007 Staff Paper, there are a number of health endpoints (*e.g.,* increased lung inflammation, increased airway responsiveness, impaired host defenses, increased medication usage for asthmatics, increased emergency department visits for respiratory causes, and increased school absences) for which there currently is insufficient information to develop quantitative risk estimates, but which are important to consider in assessing the overall public health impacts associated with exposures to O_3. These additional health endpoints are discussed above in section II.A.2 and are also taken into account in considering the level of exposures of concern in populations particularly at risk, discussed above in this notice.

There are two parts to the health risk assessment: One based on combining information from controlled human exposure studies with modeled population exposure and the other based on combining information from community epidemiological studies with either monitored or adjusted ambient concentrations levels. Both parts of the risk assessment were implemented within a new probabilistic version of TRIM.Risk, the component of EPA's Total Risk Integrated Methodology (TRIM) model framework that estimates human health risks.

The EPA recognizes that there are many sources of uncertainty and variability in the inputs to this assessment and that there is significant variability and uncertainty in the resulting O_3 risk estimates. As discussed in chapters 2, 5, and 6 of the 2007 Staff Paper, there is significant year-to-year and city-to-city variability related to the air quality data that affects both the controlled human exposure studies-based and epidemiological studies-based parts of the risk assessment. There are also uncertainties associated with the air quality adjustment procedure used to simulate just meeting various alternative standards. In the prior review, different statistical approaches using alternative functional forms (*i.e.,* quadratic, proportional, Weibull) were used to reflect how O_3 air quality concentrations have historically changed. Based on sensitivity analyses conducted in the prior review, the choice of alternative air quality adjustment procedures had only a modest impact on the risk estimates (EPA, 2007b, p. 6–20). With respect to uncertainties about estimated background concentrations, as discussed below and in the 2007 Staff Paper (section 5.4.3), alternative assumptions about background levels have a variable impact depending on the location, standard, and health endpoint analyzed.

[37] The methodology, scope, and results from the risk assessment conducted in the last review are described in Chapter 6 of the 1996 Staff Paper (EPA, 1996) and in several technical reports (Whitfield *et al.,* 1996; Whitfield, 1997) and publication (Whitfield *et al.,* 1998).

[38] The 9 urban study areas included in the exposure and risk analyses conducted during the last review were: Chicago, Denver, Houston, Los Angeles, Miami, New York City, Philadelphia, St. Louis, and Washington, DC.

[39] The general approach used in the health risk assessment was described in the draft Health Assessment Plan (EPA, 2005d) that was released to the CASAC and general public in April 2005 and was the subject of a consultation with the CASAC O_3 Panel on May 5, 2005. In October 2005, OAQPS released the first draft of the Staff Paper containing a chapter discussing the risk assessment and first draft of the Risk Assessment TSD for CASAC consultation and public review on December 8, 2005. In July 2006, OAQPS released the second draft of the Staff Paper and second draft of the Risk Assessment TSD for CASAC review and public comment which was held by the CASAC O_3 Panel on August 24–25, 2006.

With respect to the lung function part of the health risk assessment, key uncertainties include uncertainties in the exposure estimates, discussed above, and uncertainties associated with the shape of the exposure-response relationship, especially at levels below 0.08 ppm, 8-hour average, where only very limited data are available down to 0.04 ppm and there is an absence of data below 0.04 ppm (EPA, 2007b, pp. 6–20 to 6–21). Concerning the part of the risk assessment based on effects reported in epidemiological studies, important uncertainties include uncertainties (1) surrounding estimates of the O_3 coefficients for concentration-response relationships used in the assessment, (2) involving the shape of the concentration-response relationship and whether or not a population threshold or non-linear relationship exists within the range of concentrations examined in the studies, (3) related to the extent to which concentration-response relationships derived from studies in a given location and time when O_3 levels were higher or behavior and/or housing conditions were different provide accurate representations of the relationships for the same locations with lower air quality distributions and/or different behavior and/or housing conditions, and (4) concerning the possible role of co-pollutants which also may have varied between the time of the studies and the current assessment period. An important additional uncertainty for the mortality risk estimates is the extent to which the associations reported between O_3 and non-accidental and cardiorespiratory mortality actually reflect causal relationships.

As discussed below, some of these uncertainties have been addressed quantitatively in the form of estimated confidence ranges around central risk estimates; others are addressed through separate sensitivity analyses (*e.g.,* the influence of alternative estimates for policy-relevant background levels) or are characterized qualitatively. For both parts of the health risk assessment, statistical uncertainty due to sampling error has been characterized and is expressed in terms of 95 percent credible intervals. The EPA recognizes that these credible intervals do not reflect all of the uncertainties noted above.

b. Scope and Key Components

The health risk assessment is based on the information evaluated in the 2006 Criteria Document. The risk assessment includes several categories of health effects and estimates risks associated with just meeting a 0.084 ppm standard and alternative 8-hour O_3 NAAQS and with several individual recent years of air quality (*i.e.,* 2002, 2003, and 2004). The risk assessment considers the same alternative air quality scenarios that were examined in the human exposure analyses described above. Risk estimates were developed for up to 12 urban areas selected to illustrate the public health impacts associated with these air quality scenarios.[40] As discussed above in section II.B.1, the selection of urban areas was largely determined by identifying areas in the U.S. which represented a range of geographic areas, population demographics, and climatology; with an emphasis on areas that did not meet the then current 0.084 ppm 8-hour O_3 NAAQS and which included the largest areas with O_3 nonattainment problems. The selection criteria also included whether or not there were acceptable epidemiological studies available that reported concentration-response relationships for the health endpoints selected for inclusion in the assessment.

The short-term exposure related health endpoints selected for inclusion in the quantitative risk assessment include those for which the 2006 Criteria Document or the 2007 Staff Paper concluded that the evidence as a whole supports the general conclusion that O_3, acting alone and/or in combination with other components in the ambient air pollution mix, is either clearly causal or is judged to be likely causal. Some health effects met this criterion of likely causality, but were not included in the risk assessment for other reasons, such as insufficient exposure-response data or lack of baseline incidence data.

As discussed in the section above describing the exposure analysis, in order to estimate the health risks associated with just meeting various alternative 8-hour O_3 NAAQS, it is necessary to estimate the distribution of hourly O_3 concentrations that would occur under any given standard. Since compliance is based on a 3-year average, the amount of control has been applied to each year of data (*i.e.,* 2002 to 2004) to estimate risks for a single O_3 season or single warm O_3 season, depending on the health effect, based on a simulation that adjusted each of these individual years so that the three year period would just meet the specified standard.

Consistent with the risk assessment approach used in the last review, the risk estimates developed for both recent air quality levels and just meeting the then current 0.084 ppm standard and selected alternative 8-hour standards represent risks associated with O_3 levels attributable to anthropogenic sources and activities (*i.e.,* risk associated with concentrations above "policy-relevant background"). Policy-relevant background O_3 concentrations used in the O_3 risk assessment were defined in chapter 2 of the 2007 Staff Paper (pp. 2–48—2–55) as the O_3 concentrations that would be observed in the U.S. in the absence of anthropogenic emissions of precursors (*e.g.,* VOC, NO_X, and CO) in the U.S., Canada, and Mexico. The results of a global tropospheric O_3 model (GEOS–CHEM) have been used to estimate monthly background daily diurnal profiles for each of the 12 urban areas for each month of the O_3 season using meteorology for the year 2001. Based on the results of the GEOS–CHEM model, the Criteria Document indicates that background O_3 concentrations are generally predicted to be in the range of 0.015 to 0.035 ppm in the afternoon, and they are generally lower under conditions conducive to man-made O_3 episodes.[41]

This approach of estimating risks in excess of background is judged to be more relevant to policy decisions regarding ambient air quality standards than risk estimates that include effects potentially attributable to uncontrollable background O_3 concentrations. Sensitivity analyses examining the impact of alternative estimates for background on lung function and mortality risk estimates have been developed and are included in the 2007 Staff Paper and Risk Assessment TSD and key observations are discussed below. Further, CASAC noted the difficulties and complexities associated with available approaches to estimating policy-relevant background concentrations (Henderson, 2007).

In the first part of the risk assessment, lung function decrement, as measured by FEV_1, is the only health response that is based on data from controlled human exposure studies. As discussed above, there is clear evidence of a causal relationship between lung function decrements and O_3 exposures for school age children engaged in moderate

[40] The 12 urban areas are the same urban areas evaluated in the exposure analysis discussed in the prior section. However, for most of the health endpoints based on findings from epidemiological studies, the geographic areas and populations examined in the health risk assessment were limited to those counties included in the original epidemiological studies that served as the basis for the concentration-response relationships.

[41] EPA notes that the estimated level of policy-relevant background O_3 used in the prior risk assessment was a single concentration of 0.04 ppm, which was the midpoint of the range of levels for policy-relevant background that was provided in the 1996 Criteria Document.

exertion based on numerous controlled human exposure and summer camp field studies conducted by various investigators. Risk estimates have been developed for O_3-related lung function decrements (measured as changes in FEV_1) for all school age children (ages 5 to 18) and a subset of this group, asthmatic school age children (ages 5 to 18), whose average exertion over an 8-hour period was moderate or greater. The exposure period and exertion level were chosen to generally match the exposure period and exertion level used in the controlled human exposure studies that were the basis for the exposure-response relationships. A combined data set including individual level data from the Folinsbee *et al.* (1988), Horstman *et al.* (1990), and McDonnell *et al.* (1991) studies, used in the previous risk assessment, and more recent data from Adams (2002, 2003a, 2006) have been used to estimate probabilistic exposure-response relationships for 8-hour exposures under different definitions of lung function response (*i.e.,* ≥ 10, 15, and 20 percent decrements in FEV_1). As discussed in the 2007 Staff Paper (p. 5–27), while these specific controlled human exposure studies only included healthy adults aged 18–35, findings from other controlled human exposure studies and summer camp field studies involving school age children in at least six different locations in the northeastern United States, Canada, and Southern California indicated changes in lung function in healthy children similar to those observed in healthy adults exposed to O_3 under controlled chamber conditions.

Consistent with advice from CASAC (Henderson, 2006c), EPA has considered both linear and logistic functional forms in estimating the probabilistic exposure-response relationships for lung function responses. A Bayesian Markov Chain Monte Carlo approach, described in more detail in the Risk Assessment TSD, has been used that incorporates both model uncertainty and uncertainty due to sample size in the combined data set that served as the basis for the assessment. The EPA has chosen a model reflecting a 90 percent weighting on a logistic form and a 10 percent weighting on a linear form as the base case for the risk assessment. The basis for this choice is that the logistic form provides a very good fit to the combined data set, but a linear model cannot be entirely ruled out since there are only very limited data (*i.e.,* 30 subjects) at the two lowest exposure levels (*i.e.,* 0.040 and 0.060 ppm). The EPA has conducted a sensitivity analysis which examines the impact on the lung function risk estimates of two alternative choices, an 80 percent logistic/20 percent linear split and a 50 percent logistic/50 percent linear split.

As noted above, risk estimates have been developed for three measures of lung function response (*i.e.,* ≥ 10, 15, and 20 percent decrements in FEV_1). However, the 2007 Staff Paper and risk estimates summarized below focus on FEV_1 decrements ≥ 15 percent for all school age children and ≥ 10 percent for asthmatic school age children, consistent with the advice from CASAC (Henderson, 2006c) that these levels of response represent indicators of adverse health effects in these populations. The Risk Assessment TSD and 2007 Staff Paper present the broader range of risk estimates including all three measures of lung function response.

Developing risk estimates for lung function decrements involved combining probabilistic exposure-response relationships based on the combined data set from several controlled human exposure studies with population exposure distributions for all and asthmatic school age children associated with recent air quality and air quality simulated to just meet the then current 0.084 ppm standard and alternative 8-hour O_3 NAAQS based on the results from the exposure analysis described in the previous section. The risk estimates have been developed for 12 large urban areas for the O_3 season.[42] These 12 urban areas include approximately 18.3 million school age children, of which 2.6 million are asthmatic school age children.[43]

In addition to uncertainties arising from sample size considerations, which are quantitatively characterized and presented as 95 percentile credible intervals, there are additional uncertainties and caveats associated with the lung function risk estimates. These include uncertainties about the shape of the exposure-response relationship, particularly at levels below 0.080 ppm, and about policy-relevant background levels, for which sensitivity analyses have been conducted. Additional important caveats and uncertainties concerning the lung function portion of the health risk assessment include: (1) The uncertainties and limitations associated with the exposure estimates discussed above and (2) the inability to account for some factors which are known to affect the exposure-response relationships (*e.g.,* assigning healthy and asthmatic children the same responses as observed in healthy adult subjects and not adjusting response rates to reflect the increase and attenuation of responses that have been observed in studies of lung function responses upon repeated exposures). A more complete discussion of assumptions and uncertainties is contained in chapter 5 of the 2007 Staff Paper and in the Risk Assessment TSD.

The second part of the risk assessment is based on health effects observed in epidemiological studies. Based on a review of the evidence evaluated in the 2006 Criteria Document and 2007 Staff Paper, as well as the criteria discussed in chapter 5 of the 2007 Staff Paper, the following categories of health endpoints associated with short-term exposures to ambient O_3 concentrations were included in the risk assessment: respiratory symptoms in moderate to severe asthmatic children, hospital admissions for respiratory causes, and non-accidental and cardiorespiratory mortality. As discussed above, there is strong evidence of a causal relationship for the respiratory morbidity endpoints included in the risk assessment. With respect to nonaccidental and cardiorespiratory mortality, the 2006 Criteria Document concludes that there is strong evidence which is highly suggestive of a causal relationship between nonaccidental and cardiorespiratory-related mortality and O_3 exposures during the warm O_3 season. As discussed in the 2007 Staff Paper (chapter 5), EPA also recognizes that for some of the effects observed in epidemiological studies, such as increased respiratory-related hospital admissions and nonaccidental and cardiorespiratory mortality, O_3 may be serving as an indicator for reactive oxidant species in the overall photochemical oxidant mix and that these other constituents may be responsible in whole or part for the observed effects.

Risk estimates for each health endpoint category were only developed for areas that were the same or close to the location where at least one concentration-response function for the health endpoint had been estimated.[44]

[42] As discussed above in section II.B.1, the urban areas were defined using the consolidated statistical areas definition and the total population residing in the 12 urban areas was approximately 88.5 million people.

[43] For 9 of the 12 urban areas, the O_3 season is defined as a period running from March or April to September or October. In 3 of the urban areas (Houston, Los Angeles, and Sacramento), the O_3 season is defined as the entire year.

[44] The geographic boundaries for the urban areas included in this portion of the risk assessment were generally matched to the geographic boundaries used in the epidemiological studies that served as the basis for the concentration-response functions. In most cases, the urban areas were defined as

Continued

Thus, for respiratory symptoms in moderate to severe asthmatic children only the Boston urban area was included and four urban areas were included for respiratory-related hospital admissions. Nonaccidental mortality risk estimates were developed for 12 urban areas and 8 urban areas were included for cardiorespiratory mortality.

The concentration-response relationships used in the assessment are based on findings from human epidemiological studies that have relied on fixed-site ambient monitors as a surrogate for actual ambient O_3 exposures. In order to estimate the incidence of a particular health effect associated with recent air quality in a specific county or set of counties attributable to ambient O_3 exposures in excess of background, as well as the change in incidence corresponding to a given change in O_3 levels resulting from just meeting various 8-hour O_3 standards, three elements are required for this part of the risk assessment. These elements are: (1) Air quality information (including recent air quality data for O_3 from ambient monitors for the selected location, estimates of background O_3 concentrations appropriate for that location, and a method for adjusting the recent data to reflect patterns of air quality estimated to occur when the area just meets a given O_3 standard); (2) relative risk-based concentration-response functions that provide an estimate of the relationship between the health endpoints of interest and ambient O_3 concentration; and (3) annual or seasonal baseline health effects incidence rates and population data, which are needed to provide an estimate of the seasonal baseline incidence of health effects in an area before any changes in O_3 air quality.

A key component in the portion of the risk assessment based on epidemiological studies is the set of concentration-response functions which provide estimates of the relationships between each health endpoint of interest and changes in ambient O_3 concentrations. Studies often report more than one estimated concentration-response function for the same location and health endpoint. Sometimes models include different sets of co-pollutants and/or different lag periods between the ambient concentrations and reported health responses. For some health endpoints, there are studies that estimated multicity and single-city O_3 concentration-response functions. While the Risk Assessment TSD and chapter 5 of the 2007 Staff Paper present a more comprehensive set of risk estimates, EPA has focused on estimates based on multicity studies where available. As discussed in chapter 5 of the 2007 Staff Paper, the advantages of relying more heavily on concentration-response functions based on multicity studies include: (1) More precise effect estimates due to larger data sets, reducing the uncertainty around the estimated coefficient; (2) greater consistency in data handling and model specification that can eliminate city-to-city variation due to study design; and (3) less likelihood of publication bias or exclusion of reporting of negative or nonsignificant findings. Where studies reported different effect estimates for varying lag periods, consistent with the 2006 Criteria Document, single day lag periods of 0 to 1 days were used for associations with respiratory hospital admissions and mortality. For mortality associated with exposure to O_3 which may result over a several day period after exposure, distributed lag models, which take into account the contribution to mortality effects over several days, were used where available

One of the most important elements affecting uncertainties in the epidemiological-based portion of the risk assessment is the concentration-response relationships used in the assessment. The uncertainty resulting from the statistical uncertainty associated with the estimate of the O_3 coefficient in the concentration-response function was characterized either by confidence intervals or by Bayesian credible intervals around the corresponding point estimates of risk. Confidence and credible intervals express the range within which the true risk is likely to fall if the only uncertainty surrounding the O_3 coefficient involved sampling error. Other uncertainties, such as differences in study location, time period (*i.e.,* the years in which the study was conducted), and model uncertainties are not represented by the confidence or credible intervals presented, but were addressed by presenting estimates for different urban areas, by including risk estimates based on studies using different time periods and models, where available, and/or are discussed throughout section 5.3 of the 2007 Staff Paper. Because O_3 effects observed in the epidemiological studies have been more clearly and consistently shown for warm season analyses, all analyses for this portion of the risk assessment were carried out for the same time period, April through September.

The 2006 Criteria Document (p. 8–44) finds that no definitive conclusion can be reached with regard to the existence of population thresholds in epidemiological studies. The EPA recognizes, however, the possibility that thresholds for individuals may exist for reported associations at fairly low levels within the range of air quality observed in the studies, but not be detectable as population thresholds in epidemiological analyses. Based on the 2006 Criteria Document's conclusions, EPA judged and CASAC concurred, that there is insufficient evidence to support use of potential population threshold levels in the quantitative risk assessment. However, EPA recognizes that there is increasing uncertainty about the concentration-response relationship at lower concentrations which is not captured by the characterization of the statistical uncertainty due to sampling error. Therefore, the risk estimates for respiratory symptoms in moderate to severe asthmatic children, respiratory-related hospital admissions, and premature mortality associated with exposure to O_3 must be considered in light of uncertainties about whether or not these O_3-related effects occur in these populations at very low O_3 concentrations.

With respect to variability within this portion of the risk assessment, there is variability among concentration-response functions describing the relation between O_3 and both respiratory-related hospital admissions and nonaccidental and cardiorespiratory mortality across urban areas. This variability is likely due to differences in population (*e.g.,* age distribution), population activities that affect exposure to O_3 (*e.g.,* use of air conditioning), levels and composition of co-pollutants, baseline incidence rates, and/or other factors that vary across urban areas. The risk assessment incorporates some of the variability in key inputs to the analysis by using location-specific inputs (*e.g.,* location-specific concentration-response functions, baseline incidence rates, and air quality data). Although spatial variability in these key inputs across all U.S. locations has not been fully characterized, variability across the selected locations is imbedded in the analysis by using, to the extent possible, inputs specific to each urban area.

c. Risk Estimates and Key Observations

The 2007 Staff Paper (chapter 5) and Risk Assessment TSD present risk estimates associated with just meeting the then current 0.084 ppm standard and several alternative 8-hour standards, as well as three recent years of air quality as represented by 2002,

either a single county or a few counties for this portion of the risk assessment.

2003, and 2004 monitoring data. As discussed in the exposure analysis section above, there is considerable city-to-city and year-to-year variability in the O_3 levels during this period, which results in significant variability in both portions of the health risk assessment.

In the 1997 risk assessment, risks for lung function decrements associated with 1-hour heavy exertion, 1-hour moderate exertion, and 8-hour moderate exertion exposures were estimated. Since the 8-hour moderate exertion exposure scenario for children clearly resulted in the greatest health risks in terms of lung function decrements, EPA chose to include only the 8-hour moderate exertion exposures in the risk assessment for this health endpoint. Thus, the risk estimates presented here and in the 2007 Staff Paper are most useful for making relative comparisons across alternative air quality scenarios and do not represent the total risks for lung function decrements in children or other groups within the general population associated with any of the air quality scenarios. Thus, some outdoor workers and adults engaged in moderate exertion over multi-hour periods (*e.g.,* 6–8 hour exposures) also would be expected to experience similar lung function decrements. However, the percentage of each of these other subpopulations expected to experience these effects is expected to be smaller than all school age children who tend to spend more hours outdoors while active based on the exposure analyses conducted during the prior review.

Table 2 presents a summary of the risk estimates for lung function decrements for the 0.084 ppm standard set in 1997 and several alternative 8-hour standard levels with the same form.

TABLE 2—NUMBER AND PERCENT OF ALL AND ASTHMATIC SCHOOL AGE CHILDREN IN SEVERAL URBAN AREAS ESTIMATED TO EXPERIENCE MODERATE OR GREATER LUNG FUNCTION RESPONSES ONE OR MORE TIMES PER SEASON ASSOCIATED WITH 8-HOUR OZONE EXPOSURES ASSOCIATED WITH JUST MEETING ALTERNATIVE 8-HOUR STANDARDS BASED ON ADJUSTING 2002 AND 2004 AIR QUALITY DATA [1] [2]

8-Hour air quality standards [3]	All children, ages 5–18 $FEV_1 \geq 15$ percent Aggregate for 12 urban areas Number of children affected (% of all) [% reduction from 0.084 ppm standard]		Asthmatic Children, ages 5–18 $FEV_1 \geq 10$ percent Aggregate for 5 urban areas Number of children affected (% of group) [% reduction from 0.084 ppm standard]	
	2002	2004	2002	2004
0.084 ppm (Standard set in 1997).	610,000 (3.3%)	230,000 (1.2%)	130,000 (7.8%)	70,000 (4.2%)
0.080 ppm	490,000 (2.7%) [20% reduction]	180,000 (1.0%) [22% reduction]	NA [4]	NA
0.074 ppm	340,000 (1.9%) [44% reduction]	130,000 (0.7%) [43% reduction]	90,000 (5.0%) [31% reduction]	40,000 (2.7%) [43% reduction]
0.070 ppm	260,000 (1.5%) [57% reduction]	100,000 (0.5%) [57% reduction]	NA	NA
0.064 ppm	180,000 (1.0%) [70% reduction]	70,000 (0.4%) [70% reduction]	50,000 (3.0%) [62% reduction]	20,000 (1.5%) [71% reduction]

[1] Associated with exposures while engaged in moderate or greater exertion, which is defined as having an 8-hour average equivalent ventilation rate ≥ 13 l-min/m^2.

[2] Estimates are the aggregate central tendency results based on either 12 urban areas (Atlanta, Boston, Chicago, Cleveland, Detroit, Houston, Los Angeles, New York, Philadelphia, Sacramento, St. Louis, and Washington, DC) or 5 urban areas (Atlanta, Chicago, Houston, Los Angeles, New York). Estimates are for the O_3 season which is all year in Houston, Los Angeles and Sacramento and March or April to September or October for the remaining urban areas.

[3] All standards summarized here have the same form as the 8-hour standard set in 1997, which is specified as the 3-year average of the annual 4th highest daily maximum 8-hour average concentrations. As described in the 2007 Staff Paper (section 4.5.8), recent O_3 air quality distributions have been statistically adjusted to simulate just meeting the 0.084 ppm standard set in 1997 and selected alternative standards. These simulations do not represent predictions of when, whether, or how areas might meet the specified standards

[4] NA (not available) indicates that EPA did not develop risk estimates for these scenarios for the asthmatic school age children population.

The estimates are for the aggregate number and percent of all school age children across 12 urban areas and the aggregate number and percent of asthmatic school age children across 5 urban areas [45] who are estimated to have at least 1 moderate or greater lung function response (defined as $FEV_1 \geq 15$ percent in all children and ≥ 10 percent in asthmatic children) associated with 8-hour exposures to O_3 while engaged in moderate or greater exertion on average over the 8-hour period. The lung function risk estimates summarized in Table 2 illustrate the year-to-year variability in both remaining risk associated with a relatively high year (*i.e.,* based on adjusting 2002 O_3 air quality data) and relatively low year (based on adjusting 2004 O_3 air quality data) as well as the year-to-year variability in the risk reduction estimated to occur associated with various alternative standards relative to just meeting the then current 0.084 ppm standard. For example, it is estimated that about 610,000 school age children (3.2 percent of school age children) would experience 1 or more moderate lung function decrements for the 12 urban areas associated with O_3 levels just meeting a 0.084 ppm standard based on 2002 air quality data compared to 230,000 (1.2 percent of children) associated with just meeting a 0.084 ppm standard based on 2004 air quality data.

As discussed in the 2007 Staff Paper, a child may experience multiple occurrences of a lung function response during the O_3 season. For example, upon meeting a 0.084 ppm 8-hour standard, the median estimates are that about 610,000 children would experience a moderate or greater lung function response 1 or more times for the aggregate of the 12 urban areas over a single O_3 season (based on the 2002 simulation), and that there would be almost 3.2 million total occurrences. Thus, on average it is estimated that there would be about 5 occurrences per O_3 season per responding child for air quality just meeting a 0.084 ppm 8-hour

[45] Due to time constraints, lung function risk estimates for asthmatic school age children were developed for only 5 of the 12 urban areas, and the areas were selected to represent different geographic regions. The 5 areas were: Atlanta, Chicago, Houston, Los Angeles, and New York City.

standard across the 12 urban areas. While the estimated number of occurrences per O_3 season is lower when based on the 2004 simulation than for the 2002 simulation, the estimated number of occurrences per responding child is similar. The EPA recognizes that some children in the population might have only 1 or 2 occurrences while others may have 6 or more occurrences per O_3 season. Risk estimates based on adjusting 2003 air quality to simulate just meeting the a 0.084 ppm standard and alternative 8-hour standards are intermediate to the estimates presented in Table 2 above in this notice and are presented in the 2007 Staff Paper (chapter 5) and Risk Assessment TSD.

For just meeting a 0.084 ppm 8-hour standard, Table 5–8 in the 2007 Staff Paper shows that median estimates across the 12 urban areas for all school age children experiencing 1 or more moderate lung function decrements ranges from 0.9 to 5.4 percent based on the 2002 simulation and from 0.8 to 2.2 percent based on the 2004 simulation. Risk estimates for each urban area included in the assessment, for each of the three years analyzed, and for additional alternative standards are presented in chapter 5 of the 2007 Staff Paper and in the Risk Assessment TSD.

For just meeting a 0.084 ppm 8-hour standard, the median estimates across the 5 urban areas for asthmatic school age children range from 3.4 to 10.9 percent based on the 2002 simulation and from 3.2 to 6.9 percent based on the 2004 simulation.

Key observations important in comparing estimated lung function risks associated with just meeting the 0.084 ppm NAAQS and alternative standards under consideration include:

(1) As discussed above, there is significant year to year variability in the range of median estimates of the number of school age children (ages 5–18) estimated to experience at least one FEV_1 decrement ≥ 15 percent due to 8-hour O_3 exposures across the 12 urban areas analyzed, and similarly across the 5 urban areas analyzed for asthmatic school age children (ages 5–18) estimated to experience at least one FEV_1 decrement ≥ 10 percent, when various 8-hour standards are just met.

(2) For asthmatic school age children, the median estimates of occurrences of FEV_1 decrements ≥ 10% range from 52,000 to nearly 510,000 responses associated with just meeting a 0.084 ppm standard (based on the 2002 simulation) and range from 61,000 to about 240,000 occurrences (based on the 2004 simulation). These risk estimates would be reduced to a range of 14,000 to about 275,000 occurrences (2002 simulation) and to about 18,000 to nearly 125,000 occurrences (2004 simulation) upon just meeting the most stringent alternative 8-hour standard (0.064 ppm, 4th highest). The average number of occurrences per asthmatic child in an O_3 season ranged from about 6 to 11 associated with just meeting a 0.084 ppm standard (2002 simulation). The average number of occurrences per asthmatic child ranged from 4 to 12 upon meeting the most stringent alternative examined (0.064 ppm, 4th-highest) based on the 2002 simulation. The number of occurrences per asthmatic child is similar for the scenarios based on the 2004 simulation.

As discussed above, several epidemiological studies have reported increased respiratory morbidity outcomes (*e.g.,* respiratory symptoms in moderate to severe asthmatic children, respiratory-related hospital admissions) and increased nonaccidental and cardiorespiratory mortality associated with exposure to ambient O_3 concentrations. The results and key observations from this portion of the risk assessment are presented below:

(1) Estimates for increased respiratory symptoms (*i.e.,* chest tightness, shortness of breath, and wheeze) in moderate/severe asthmatic children (ages 0–12) were developed for the Boston urban area only. The median estimated number of days involving chest tightness (using the concentration-response relationship with only O_3 in the model) is about 6,100 (based on the 2002 simulation) and about 4,500 (based on the 2004 simulation) upon meeting a 0.084 ppm 8-hour standard and this is reduced to about 4,600 days (2002 simulation) and 3,100 days (2004 simulation) upon meeting the most stringent alternative examined (0.064 ppm, 4th-highest daily maximum 8-hour average). This corresponds to 11 percent (2002 simulation) and 8 percent (2004 simulation) of total incidence of chest tightness upon meeting a 0.084 ppm 8-hour standard and to about 8 percent (2002 simulation) and 5.5 percent (2004 simulation) of total incidence of chest tightness upon meeting a 0.064 ppm, 4th-highest daily maximum 8-hour average standard. Similar patterns of effects and reductions in effects are observed for each of the respiratory symptoms examined.

(2) The 2007 Staff Paper and Risk Assessment TSD present unscheduled hospital admission risk estimates for respiratory illness and asthma in New York City associated with short-term exposures to O_3 concentrations in excess of background levels from April through September for several recent years (2002, 2003, and 2004) and upon just meeting a 0.084 ppm standard and alternative 8-hour standards based on simulating O_3 levels using 2002–2004 O_3 air quality data. For total respiratory illness, EPA estimates about 6.4 cases per 100,000 relevant population (2002 simulation) and about 4.6 cases per 100,000 relevant population (2004 simulation), which represents 1.5 percent (2002 simulation) and 1.0 percent (2004 simulation) of total incidence or about 510 cases (2002 simulation) and about 370 cases (2004 simulation) upon just meeting a 0.084 ppm 8-hour standard. For asthma-related hospital admissions, which are a subset of total respiratory illness admissions, the estimates are about 5.5 cases per 100,000 relevant population (2002 simulation) and about 3.9 cases per 100,000 relevant population (2004 simulation), which represents about 3.3 percent (2002 simulation) and 2.4 percent (2004 simulation) of total incidence or about 440 cases (2002) and about 310 cases (2004) for this same air quality scenario.

For increasingly more stringent alternative 8-hour standards, there is a gradual reduction in respiratory illness cases per 100,000 relevant population from 6.4 cases per 100,000 upon just meeting a 0.084 ppm 8-hour standard to 4.6 cases per 100,000 under the most stringent 8-hour standard (*i.e.,* 0.064 ppm, average 4th-highest daily maximum) analyzed based on the 2002 simulation. Similarly, based on the 2004 simulation there is a gradual reduction from 4.6 cases per 100,000 relevant population upon just meeting a 0.084 ppm 8-hour standard to 3.0 cases per 100,000 under a 0.064 ppm, average 4th-highest daily maximum standard.

Additional respiratory-related hospital admission estimates for three other locations are provided in the Risk Assessment TSD. The EPA notes that the concentration-response functions for each of these locations examined different outcomes in different age groups (*e.g.,* > age 30 in Los Angeles, > age 64 in Cleveland and Detroit, vs. all ages in New York City), making comparison of the risk estimates across the areas very difficult.

(3) Based on the median estimates for incidence for nonaccidental mortality (based on the Bell *et al.* (2004) 95 cities concentration-response function), meeting the most stringent standard (0.064 ppm) is estimated to reduce mortality by 40 percent of what it would be associated with just meeting a 0.084 ppm standard (based on the 2002 simulation). The patterns for cardiorespiratory mortality are similar.

The aggregate O_3-related cardiorespiratory mortality upon just meeting the most stringent standard shown is estimated to be about 42 percent of what it would be upon just meeting a 0.084 ppm standard, using simulated O_3 concentrations that just meet a 0.084 ppm standard and alternative 8-hour standards based on the 2002 simulation. Using the 2004 simulation, the corresponding reductions show a similar pattern but are somewhat greater.

(4) Much of the contribution to the risk estimates for non-accidental and cardiorespiratory mortality upon just meeting a 0.084 ppm 8-hour standard is associated with 24-hour O_3 concentrations between background and 0.040 ppm. Based on examining relationships between 24-hour concentrations averaged across the monitors within an urban area and 8-hour daily maximum concentrations, 8-hour daily maximum levels at the highest monitor in an urban area associated with these averaged 24-hour levels are generally about twice as high as the 24-hour levels. Thus, most O_3-related nonaccidental mortality is estimated to occur when O_3 concentrations are between background and when the highest monitor in the urban area is at or below 0.080 ppm, 8-hour average concentration.

The discussion below highlights additional observations and insights from the O_3 risk assessment, together with important uncertainties and limitations.

(1) As discussed in the 2007 Staff Paper (section 5.4.5), EPA has greater confidence in relative comparisons in risk estimates between alternative standards than in the absolute magnitude of risk estimates associated with any particular standard.

(2) Significant year-to-year variability in O_3 concentrations combined with the use of a 3-year design value to determine the amount of air quality adjustment to be applied to each year analyzed, results in significant year-to-year variability in the annual health risk estimates upon just meeting various 8-hour standards.

(3) There is noticeable city-to-city variability in estimated O_3-related incidence of morbidity and mortality across the 12 urban areas analyzed for both recent years of air quality and for air quality adjusted to simulate just meeting a 0.084 ppm standard and selected potential alternative standards. This variability is likely due to differences in air quality distributions, differences in exposure related to many factors including varying activity patterns and air exchange rates, differences in baseline incidence rates, and differences in susceptible populations and age distributions across the 12 urban areas.

(4) With respect to the uncertainties about estimated policy-relevant background concentrations, as discussed in the 2007 Staff Paper (section 5.4.3), alternative assumptions about background levels had a variable impact depending on the health effect considered and the location and standard analyzed in terms of the absolute magnitude and relative changes in the risk estimates. There was relatively little impact on either absolute magnitude or relative changes in lung function risk estimates due to alternative assumptions about background levels. With respect to O_3-related non-accidental mortality, while notable differences (*i.e.,* greater than 50 percent) [46] were observed for nonaccidental mortality in some areas, particularly for more stringent standards, the overall pattern of estimated reductions, expressed in terms of percentage reduction relative to the 0.084 ppm standard, was significantly less impacted.

C. Reconsideration of the Level of the Primary Standard

1. Evidence and Exposure/Risk-Based Considerations

The approach used in the 2007 Staff Paper as a basis for staff recommendations on standard levels builds upon and broadens the general approach used by EPA in the 1997 review. This approach reflects the more extensive and stronger body of evidence available for the 2008 rulemaking on a broader range of health effects associated with exposure to O_3, including: (1) Additional respiratory-related endpoints; (2) new information about the mechanisms underlying respiratory morbidity effects supporting a judgment that the link between O_3 exposure and these effects is causal; (3) newly identified cardiovascular-related health endpoints from animal toxicology and controlled human exposures studies that are highly suggestive that O_3 can directly or indirectly contribute to cardiovascular morbidity, and (4) new U.S. multicity time series studies, single city studies, and several meta-analyses of these studies that provide relatively strong evidence for associations between short-term O_3 exposures and all-cause (nonaccidental) mortality, at levels below the current primary standard: As well as (5) a substantial body of new evidence of increased susceptibility in people with asthma and other lung diseases. In evaluating evidence-based and exposure/risk-based considerations, the 2007 Staff Paper considered: (1) The ranges of levels of alternative standards that are supported by the evidence, and the uncertainties and limitations in that evidence and (2) the extent to which specific levels of alternative standards reduce the estimated exposures of concern and risks attributable to O_3 and other photochemical oxidants, and the uncertainties associated with the estimated exposure and risk reductions.

a. Evidence-Based Considerations

In taking into account evidence-based considerations, the 2007 Staff Paper evaluated available evidence from controlled human exposure studies and epidemiological studies, as well as the uncertainties and limitations in that evidence. In particular, it focused on the extent to which controlled human exposure studies provide evidence of lowest-observed-effects levels and the extent to which epidemiological studies provide evidence of associations that extend down to the lower levels of O_3 concentrations observed in the studies or some indication of potential effect thresholds in terms of 8-hour average O_3 concentrations.

The most certain evidence of adverse health effects from exposure to O_3 comes from the controlled human exposure studies, as discussed above in section II.A.2, and the large bulk of this evidence derives from studies of exposures at levels of 0.080 ppm and above. At those levels, there is consistent evidence of lung function decrements and respiratory symptoms in healthy young adults, as well as evidence of inflammation and other medically significant airway responses.

Two studies by Adams (2002, 2006), newly available for consideration in the 2008 rulemaking, are the only available controlled human exposure studies that examine respiratory effects associated with prolonged O_3 exposures at levels below 0.080 ppm, which was the lowest exposure level that had been examined in the 1997 review. As discussed above in section II.A.2.a.i.(a)(i), the Adams (2006) study investigated a range of exposure levels, including 0.060 and 0.080 ppm O_3, and analyzed hour-by-hour changes in responses, including lung function (measured in term of decrements in FEV_1) and respiratory

[46] For example, assuming lower background levels resulted in increased estimates of non-accidental mortality incidence per 100,000 that were often 50 to 100 percent greater than the base case estimates; assuming higher background levels resulted in decreased estimates of non-accidental mortality incidence per 100,000 that were less than the base case estimates by 50 percent or more in many of the areas.

symptoms, to investigate the effects of different patterns of exposure. At the 0.060 ppm exposure level, the author reported no statistically significant differences for lung function decrements; statistically significant responses were reported for total subjective respiratory symptoms toward the end of the exposure period for one exposure pattern. The EPA's reanalysis (Brown, 2007) of the data from the Adams (2006) study addressed the more fundamental question of whether there were statistically significant changes in lung function from a 6.6-hour exposure to 0.060 ppm O_3 versus filtered air and used a standard statistical method appropriate for a simple paired comparison. This reanalysis found small group mean lung function decrements in healthy adults at the 0.060 ppm exposure level to be statistically significantly different from responses associated with filtered air exposure.

Moreover, the Adams' studies also report a small percentage of subjects (7 to 20 percent) experienced lung function decrements (>10 percent) at the 0.060 ppm exposure level. This is a concern because, for active healthy people, moderate levels of functional responses (*e.g.,* FEV_1 decrements of >10% but <20%) and/or moderate respiratory symptom responses would likely interfere with normal activity for relatively few responsive individuals. However, for people with lung disease, even moderate functional or symptomatic responses would likely interfere with normal activity for many individuals, and would likely result in more frequent use of medication. In the context of standard setting, the CASAC indicated (Henderson, 2006c) that a focus on the lower end of the range of moderate levels of functional responses (*e.g.,* FEV_1 decrements ≥10%) is most appropriate for estimating potentially adverse lung function decrements in people with lung disease. Therefore, the results of the Adams studies which indicate that a small percentage of healthy, non-asthmatic subjects are likely to experience FEV_1 decrements ≥10% when exposed to 0.060 ppm O_3 have implications for setting a standard that protects public health, including the health of sensitive populations such as asthmatics, with an adequate margin of safety.

In considering these most recent controlled human exposure studies, the 2007 Staff Paper concluded that these studies provide evidence of a lowest-observed-effects level of 0.060 ppm for potentially adverse lung function decrements and respiratory symptoms in some healthy adults while at prolonged moderate exertion. It further concluded that since people with asthma, particularly children, have been found to be more sensitive and to experience larger decrements in lung function in response to O_3 exposures than would healthy adults, the 0.060 ppm exposure level also can be interpreted as representing a level likely to cause adverse lung function decrements and respiratory symptoms in children with asthma and more generally in people with respiratory disease.

In considering controlled human exposure studies of pulmonary inflammation, airway responsiveness, and impaired host defense capabilities, discussed above in section II.A.2.a.i, the 2007 Staff Paper noted that these studies provide evidence of a lowest-observed-effects level for such effects in healthy adults at prolonged moderate exertion of 0.080 ppm, the lowest level tested. Moreover there is no evidence that the 0.080 ppm level is a threshold for these effects. Studies reporting inflammatory responses and markers of lung injury have clearly demonstrated that there is significant variation in response of subjects exposed, even to O_3 exposures at 0.080 ppm. One study showed notable interindividual variability in young healthy adult subjects in most of the inflammatory and cellular injury indicators analyzed at 0.080 ppm. This inter-individual variability suggests that some portion of the population would likely experience such effects at exposure levels extending well below 0.080 ppm.

As discussed above, these physiological effects have been linked to aggravation of asthma and increased susceptibility to respiratory infection, potentially leading to increased medication use, increased school and work absences, increased visits to doctors' offices and emergency departments, and increased hospital admissions. Further, pulmonary inflammation is related to increased cellular permeability in the lung, which may be a mechanism by which O_3 exposure can lead to cardiovascular system effects, and to potential chronic effects such as chronic bronchitis or long-term damage to the lungs that can lead to reduced quality of life. These are all indicators of adverse O_3-related morbidity effects, which are consistent with and lend plausibility to the adverse morbidity effects and mortality effects observed in epidemiological studies.

Significant associations between ambient O_3 exposures and a wide variety of respiratory symptoms and other morbidity outcomes (*e.g.,* asthma medication use, school absences, emergency department visits, and hospital admissions) have been reported in epidemiological studies, as discussed above in section II.A.2.a.i. Overall, the 2006 Criteria Document concludes that positive and robust associations were found between ambient O_3 concentrations and various respiratory disease hospitalization outcomes, when focusing particularly on results of warm-season analyses. Recent studies also generally indicate a positive association between O_3 concentrations and emergency department visits for asthma during the warm season. These positive and robust associations are supported by the controlled human exposure, animal toxicological, and epidemiological evidence for lung function decrements, increased respiratory symptoms, airway inflammation, and increased airway responsiveness. Taken together, the overall evidence supports a causal relationship between acute ambient O_3 exposures and increased respiratory morbidity outcomes resulting in increased emergency department visits and hospitalizations during the warm season (EPA, 2006a, p. 8–77).

Moreover, many single- and multicity epidemiological studies observed positive associations of ambient O_3 concentrations with total nonaccidental and cardiopulmonary mortality. As discussed above in section II.A.2.b.i, the 2006 Criteria Document finds that the results from U.S. multicity time-series studies provide the strongest evidence to date for O_3 effects on acute mortality. Recent meta-analyses also indicate positive risk estimates that are unlikely to be confounded by PM; however, future work is needed to better understand the influence of model specifications on the magnitude of risk. The 2006 Criteria Document concludes that the "positive O_3 effects estimates, along with the sensitivity analyses in these three meta-analyses, provide evidence of a robust association between ambient O_3 and mortality" (EPA, 2006a, p. 7–97). In summary, the 2006 Criteria Document (p. 8–78) concludes that these findings are highly suggestive that short-term O_3 exposure directly or indirectly contribute to non-accidental and cardiopulmonary-related mortality, but additional research is needed to more fully establish underlying mechanisms by which such effects occur.

The 2007 Staff Paper considered the epidemiological studies to evaluate evidence related to potential effects thresholds at the population level for morbidity and mortality effects. As discussed above in section II.A.3.a (and more fully in the 2007 Staff Paper in chapter 3 and the 2006 Criteria

Document in chapter 7), a number of time-series studies have used statistical modeling approaches to evaluate potential thresholds at the population level. A few such studies reported some suggestive evidence of possible thresholds for morbidity and mortality outcomes in terms of 24-hour, 8-hour, and 1-hour averaging times. These results, taken together, provide some indication of possible 8-hour average threshold levels from below about 0.025 to 0.035 ppm (within the range of background concentrations) up to approximately 0.050 ppm. Other studies, however, observe linear concentration-response functions suggesting no effect threshold. The 2007 Staff Paper (p.6–60) concluded that the statistically significant associations between ambient O_3 concentrations and lung function decrements, respiratory symptoms, indicators of respiratory morbidity including increase emergency department visits and hospital admissions, and possibly mortality reported in a large number of studies likely extend down to ambient O_3 concentrations that are well below the level of the then current standard (0.084 ppm). These associations also extend well below the level of the standard set in 2008 (0.075 ppm) in that the highest level at which there is any indication of a threshold is approximately 0.050 ppm. Toward the lower end of the range of O_3 concentrations observed in such studies, ranging down to background levels (*i.e.,* 0.035 to 0.015 ppm), however, the 2007 Staff Paper stated that there is increasing uncertainty as to whether the observed associations remain plausibly related to exposures to ambient O_3, rather than to the broader mix of air pollutants present in the ambient atmosphere.

The 2007 Staff Paper also considered studies that did subset analyses, which included only days with ambient O_3 concentrations below the level of the then current standard, or below even lower O_3 concentrations, and continue to report statistically significant associations. Notably, as discussed above, Bell *et al.* (2006) conducted a subset analysis that continued to show statistically significant mortality associations even when only days with a maximum 8-hour average O_3 concentration below a value of approximately 0.061 ppm were included.[47] Also of note is the large multicity NCICAS (Mortimer *et al.,* 2002) that reported statistically significant associations between ambient O_3 concentrations and lung function decrements even when days with 8-hour average O_3 levels greater than 0.080 ppm were excluded (which consisted of less than 5 percent of the days in the eight urban areas in the study).

Further, as discussed above in section II.A.3.a, there are limitations in epidemiological studies that make discerning thresholds in populations difficult, including low data density in the lower concentration ranges, the possible influence of exposure measurement error, and interindividual differences in susceptibility to O_3-related effects in populations. There is the possibility that thresholds for individuals may exist in reported associations at fairly low levels within the range of air quality observed in the studies but not be detectable as population thresholds in epidemiological analyses.

Based on the above considerations, the 2007 Staff Paper recognized that the available evidence neither supports nor refutes the existence of effect thresholds at the population level for morbidity and mortality effects, and that if a population threshold level does exist, it would likely be well below the level of the then current standard and possibly within the range of background levels. Taken together, these considerations also support the conclusion that if a population threshold level does exist, it would likely be well below the level of the 0.075 ppm, 8-hour average, standard set in 2008.

In looking more broadly at evidence from animal toxicological, controlled human exposure, and epidemiological studies, the 2006 Criteria Document found substantial evidence, newly available in the 2008 rulemaking, that people with asthma and other preexisting pulmonary diseases are among those at increased risk from O_3 exposure. Altered physiological, morphological, and biochemical states typical of respiratory diseases like asthma, COPD, and chronic bronchitis may render people sensitive to additional oxidative burden induced by O_3 exposure (EPA, 2006a, section 8.7). Children and adults with asthma are the groups that have been studied most extensively. Evidence from controlled human exposure studies indicates that asthmatics may exhibit larger lung function decrements in response to O_3 exposure than healthy controls. As discussed more fully in section II.A.4 above, asthmatics present a different response profile for cellular, molecular, and biochemical parameters (EPA, 2006a, Figure 8–1) that are altered in response to acute O_3 exposure. They can have larger inflammatory responses, as manifested by larger increases in markers of inflammation such as white bloods cells (*e.g.,* PMNs) or inflammatory cytokines. Asthmatics, and people with allergic rhinitis, are more likely to have an allergic-type response upon exposure to O_3, as manifested by increases in white blood cells associated with allergy (*i.e.,* eosinophils) and related molecules, which increase inflammation in the airways. The increased inflammatory and allergic responses also may be associated with the larger late-phase responses that asthmatics can experience, which can include increased bronchoconstrictor responses to irritant substances or allergens and additional inflammation.

In addition to the experimental evidence of lung function decrements, respiratory symptoms, and other respiratory effects in asthmatic populations, two large U.S. epidemiological studies as well as several smaller U.S. and international studies, have reported fairly robust associations between ambient O_3 concentrations and measures of lung function and daily respiratory symptoms (*e.g.,* chest tightness, wheeze, shortness of breath) in children with moderate to severe asthma and between O_3 and increased asthma medication use (EPA, 2007a, chapter 6). These more serious responses in asthmatics and others with lung disease provide biological plausibility for the respiratory morbidity effects observed in epidemiological studies, such as emergency department visits and hospital admissions.

The body of evidence from controlled human exposure and epidemiological studies, which includes asthmatic as well as non-asthmatic subjects, indicates that controlled human exposure studies of lung function decrements and respiratory symptoms that evaluate only healthy, non-asthmatic subjects likely underestimate the effects of O_3 exposure on asthmatics and other susceptible populations. Therefore, relative to the healthy, non-asthmatic subjects used in most controlled human exposure studies, including the Adams (2002, 2006) studies, a greater proportion of people with asthma may be affected, and those who are affected may have as large or larger lung function and symptomatic responses at ambient exposures to 0.060 ppm O_3. This indicates that the lowest-observed-effects levels demonstrated in controlled human exposure studies that use only healthy subjects may not

[47] Bell *et al.* (2006) referred to this level as being approximately equivalent to 120 $\mu g/m^3$, daily 8-hour maximum, the World Health Organization guideline and European Commission target value for O_3.