

Air Quality Criteria for Ozone and Related Photochemical Oxidants

Volume II of III

Air Quality Criteria for Ozone and Related Photochemical Oxidants

Volume II

National Center for Environmental Assessment-RTP Office
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PREFACE

National Ambient Air Quality Standards (NAAQS) are promulgated by the United States Environmental Protection Agency (EPA) to meet requirements set forth in Sections 108 and 109 of the U.S. Clean Air Act (CAA). Sections 108 and 109 require the EPA Administrator (1) to list widespread air pollutants that reasonably may be expected to endanger public health or welfare; (2) to issue air quality criteria for them that assess the latest available scientific information on nature and effects of ambient exposure to them; (3) to set “primary” NAAQS to protect human health with adequate margin of safety and to set “secondary” NAAQS to protect against welfare effects (e.g., effects on vegetation, ecosystems, visibility, climate, manmade materials, etc); and (5) to periodically review and revise, as appropriate, the criteria and NAAQS for a given listed pollutant or class of pollutants.

In 1971, the U.S. Environmental Protection Agency (EPA) promulgated National Ambient Air Quality Standards (NAAQS) to protect the public health and welfare from adverse effects of photochemical oxidants. The EPA promulgates the NAAQS on the basis of scientific information contained in air quality criteria issued under Section 108 of the Clean Air Act. Following the review of criteria as contained in the EPA document, Air Quality Criteria for Ozone and Other Photochemical Oxidants published in 1978, the chemical designation of the standards was changed from photochemical oxidants to ozone (O₃) in 1979 and a 1-hour O₃ NAAQS was set. The 1978 document focused mainly on the air quality criteria for O₃ and, to a lesser extent, on those for other photochemical oxidants (e.g., hydrogen peroxide and the peroxyacyl nitrates), as have subsequent revised versions of the document.

To meet Clean Air Act requirements noted above for periodic review of criteria and NAAQS, the O₃ criteria document, *Air Quality Criteria for Ozone and Other Photochemical Oxidants*, was next revised and released in August 1986; and a supplement, *Summary of Selected*

New Information on Effects of Ozone on Health and Vegetation, was issued in January 1992. These documents were the basis for a March 1993 decision by EPA that revision of the existing 1-h NAAQS for O₃ was not appropriate at that time. That decision, however, did not take into account newer scientific data that had become available after completion of the 1986 criteria document. Such literature was assessed in the next periodic revision of the O₃ air quality criteria document (O₃ AQCD) which has completed in 1996 and provided scientific bases supporting the setting by EPA in 1997 of the current 8-h O₃ NAAQS.

The purpose of this revised air quality criteria document for O₃ and related photochemical oxidants is to critically evaluate and assess the latest scientific information published since that assessed in the above 1996 O₃ AQCD, with the main focus being on pertinent new information useful in evaluating health and environmental effects data associated with ambient air O₃ exposures. However, other scientific data are also discussed in order to provide a better understanding of the nature, sources, distribution, measurement, and concentrations of O₃ and related photochemical oxidants and their precursors in the environment. The document mainly assesses pertinent literature published through 2004, but also includes assessment of a few additional important studies published or accepted for publication in 2005.

A First External Review Draft of this O₃ AQCD (dated January 2005) was released for public comment and was reviewed by the Clean Air Scientific Advisory Committee (CASAC) in May, 2005 to obtain. Public comments and CASAC recommendations were then taken into account in making revisions to the document for incorporation into a Second External Review Draft (dated August, 2005), which underwent further public comment and CASAC review at a December, 2005 public meeting. Public comments and CASAC advice derived from review of that Second External Review Draft were considered in making revisions incorporated into this final version of the document (dated February, 2006). Evaluations contained in the present document will be drawn on to provide inputs to associated O₃ Staff Paper analyses prepared by EPA's Office of Air Quality Planning and Standards (OAQPS) to pose options for consideration by the EPA Administrator with regard to proposal and, ultimately, promulgation of decisions on potential retention or revision, as appropriate, of the current O₃ NAAQS.

Preparation of this document was coordinated by staff of EPA's National Center for Environmental Assessment in Research Triangle Park (NCEA-RTP). NCEA-RTP scientific staff, together with experts from other EPA/ORD laboratories and academia, contributed to

writing of document chapters. Earlier drafts of document materials were reviewed by non-EPA experts in peer consultation workshops held by EPA. The document describes the nature, sources, distribution, measurement, and concentrations of O₃ in outdoor (ambient) and indoor environments. It also evaluates the latest data on human exposures to ambient O₃ and consequent health effects in exposed human populations, to support decision making regarding the primary, health-related O₃ NAAQS. Lastly, the document also evaluates ambient O₃ environmental effects on vegetation and ecosystems, surface level solar UV radiation flux and global climate change, and man-made materials to support decision making on secondary O₃ NAAQS.

NCEA acknowledges the valuable contributions provided by authors, contributors, and reviewers and the diligence of its staff and contractors in the preparation of this document.

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Authors, Contributors, and Reviewers

CHAPTER 2 ANNEX (ATMOSPHERIC PHYSICS/CHEMISTRY)

Principal Author

Dr. Joseph Pinto—National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Russell Dickerson—Department of Atmospheric and Oceanic Sciences, University of
Maryland, College Park, MD

Contributing Authors

Dr. Brooke Hemming—National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Daniel Jacob—Department of Earth and Planetary Sciences, Harvard University,
Cambridge, MA

Dr. William Keene—Department of Environmental Sciences, University of Virginia,
Charlottesville, VA

Dr. Tadeusz Kleindienst—National Exposure Research Laboratory, U.S. Environmental
Protection Agency, Research Triangle Park, NC

Dr. Jennie Moody—Department of Environmental Sciences, University of Virginia,
Charlottesville, VA

Mr. Charles Piety—Department of Atmospheric and Oceanic Sciences, University of Maryland,
College Park, MD

Dr. Sandy Sillman—Department of Atmospheric, Oceanic, and Space Sciences, University of
Michigan, Ann Arbor, MI

Dr. Jeffrey Stehr—Department of Atmospheric and Oceanic Sciences, University of Maryland,
College Park, MD

Dr. Bret Taubman—Department of Atmospheric Sciences, Pennsylvania State University,
State College, PA

Authors, Contributors, and Reviewers

(cont'd)

Contributors and Reviewers

Dr. Christoph Bruhl—Max Planck Institute for Atmospheric Chemistry, Mainz, Germany

Dr. Mohammed Elshahawy—Department of Meteorology and Astronomy, Cairo University, Giza, Egypt.

Dr. Arlene Fiore—National Oceanic and Atmospheric Administration/Geophysical Fluid Dynamics Laboratory, Princeton, NJ

Mr. Chris Geron—National Risk Management Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. David Golden—Department of Chemistry, Stanford University, Palo Alto, CA

Dr. John Merrill—Graduate School of Oceanography, University of Rhode Island, Kingston, RI

Dr. Sam Oltmans—National Oceanic and Atmospheric Administration/Climate Monitoring and Diagnostic Laboratory, Boulder, CO

Dr. David Parrish—National Oceanic and Atmospheric Administration/Aeronomy Laboratory, Boulder, CO

Dr. Perry Samson—Department of Atmospheric, Ocean, and Space Sciences, University of Michigan, Ann Arbor, MI

Dr. Sandy Sillman—Department of Atmospheric, Ocean, and Space Sciences, University of Michigan, Ann Arbor, MI

Dr. Melvin Shapiro—National Center for Atmospheric Research, Boulder, CO

CHAPTER 3 ANNEX (AIR QUALITY AND EXPOSURE)

Principal Authors

Ms. Beverly Comfort—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Joseph Pinto—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Authors, Contributors, and Reviewers

(cont'd)

Principal Authors

(cont'd)

Dr. Arlene Fiore—National Oceanic and Atmospheric Administration/Geophysical Fluid Dynamics Laboratory, Princeton, NJ

Dr. Daniel Jacob—Department of Earth and Planetary Sciences, Harvard University, Cambridge, MA

Dr. Alan S. Lefohn—ASL & Associates, Helena, MT

Dr. Clifford Weisel—Environmental and Occupational Health Sciences Institute, Rutgers University, New Brunswick, NJ

Contributing Authors

Dr. Jee Young Kim—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Dennis Kotchmar—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Timothy Lewis—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. Thomas McCurdy—National Exposure Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC

Contributors and Reviewers

Dr. Christoph Bruehl—Max Planck Institute for Atmospheric Chemistry, Mainz, Germany

Dr. Russell Dickerson—Department of Atmospheric and Oceanic Sciences, University of Maryland, College Park, MD

Dr. Judith Graham—American Chemistry Council, Washington, D.C.

Dr. Laszlo Horvath—Hungarian Meteorological Service, Budapest, Hungary

Dr. Ted Johnson—TRJ Associates, Durham, NC

Authors, Contributors, and Reviewers
(cont'd)

Contributors and Reviewers

(cont'd)

Dr. John Merrill—Graduate School of Oceanography, University of Rhode Island, Kingston, RI

Dr. Jennie Moody—Department of Environmental Sciences, University of Virginia,
Charlottesville, VA

Dr. Sam Oltmans—National Oceanic and Atmospheric Administration/Climate Monitoring and
Diagnostic Laboratory, Boulder, CO

Dr. Michiel G.M. Roemer—TNO, The Netherlands

Dr. Sandy Sillman—Department of Atmospheric, Ocean, and Space Sciences, University of
Michigan, Ann Arbor, MI

Dr. Tamas Weidinger—Department of Meteorology, University of Budapest, Budapest, Hungary

CHAPTER 4 ANNEX (DOSIMETRY)

Principal Authors

Dr. John Overton—U.S. Environmental Protection Agency, National Health and Environmental
Effects Research Laboratory-Research Triangle Park, NC 27711 (retired)

Dr. James S. Brown—National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Lori White—National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributors and Reviewers

Dr. Gary Hatch—U.S. Environmental Protection Agency, National Health and Environmental
Effects Research Laboratory, NC

Authors, Contributors, and Reviewers
(cont'd)

CHAPTER 5 ANNEX (ANIMAL TOXICOLOGY)

Principal Authors

Dr. Lori White—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. James Raub—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711 (Retired)

Dr. Deepak Bhalla—Department of Occupational and Environmental Health Sciences, Wayne State University, Detroit, MI

Dr. Carroll Cross—School of Medicine, University of California, Davis, CA

Dr. Mitch Cohen—NYU School of Medicine, New York University, New York, NY

Contributors and Reviewers

Dr. Steven Kleeberger—National Institute of Environmental Health Sciences, Research Triangle Park, NC 27711

Dr. George Liekauf—Department of Environmental Health, University of Cincinnati, Cincinnati, OH

Dr. David Basset—Department of Occupational and Environmental Health Sciences, Wayne State University, Detroit, MI

Dr. E.M. Postlethwait—Department of Environmental Health Sciences, University of Texas Medical Branch, Galveston, TX

Dr. Kent Pinkerton—Center for Health and the Environment, University of California, Davis, CA

Dr. Edward Schelegle—Department of Anatomy, Physiology, and Cell Biology, University of California, Davis, CA

Dr. Judith Graham—American Chemical Council, Arlington, VA

Dr. Paul Reinhart—National Center for Environment (B243-03), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Authors, Contributors, and Reviewers
(cont'd)

CHAPTER 6 ANNEX (CONTROLLED HUMAN EXPOSURE)

Principal Authors

Dr. James S. Brown—National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. James Raub—National Center for Environmental Assessment (B243-01), U.S. Environmental
Protection Agency, Research Triangle Park, NC 27711 (Retired)

Dr. William C. Adams—Human Performance Laboratory, University of California, Davis, CA
(retired)

Dr. Milan J. Hazucha—Center for Environmental Medicine, Asthma, and Lung Biology,
University of North Carolina, Chapel Hill, NC

Dr. E. William Spannake—Department of Environmental Health Sciences, Johns Hopkins
University, Baltimore, MD

Contributors and Reviewers

Dr. Edward Avol—Department of Preventive Medicine, University of Southern California,
Los Angeles, CA

Dr. Jane Q. Koenig—Department of Environmental and Occupational Health, University of
Washington, Seattle, WA

Dr. Michael Madden—National Health and Environmental Effects Research Laboratory,
U.S. Environmental Protection Agency, Chapel Hill, NC

Dr. William McDonnell—National Health and Environmental Effects Research Laboratory,
U.S. Environmental Protection Agency, Chapel Hill, NC

Authors, Contributors, and Reviewers
(cont'd)

CHAPTER 7 ANNEX (EPIDEMIOLOGY)

Principal Authors

Dr. Dennis Kotchmar—National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Jee Young Kim—National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. David Svendsgaard—National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Kazuhiko Ito—New York University School of Medicine, Nelson Institute of
Environmental Medicine, Tuxedo, NY

Dr. Patrick Kinney—Columbia University, Mailman School of Public Health, New York, NY

Reviewers

Dr. Richard Burnett—Health Canada, Ottawa, Canada

Dr. Vic Hasselblad—Duke University, Durham, NC

Dr. Lucas Neas—National Health and Environmental Effects Research Laboratory,
U.S. Environmental Protection Agency, Chapel Hill, NC

**U.S. Environmental Protection Agency Project Team
for Development of Air Quality Criteria for Ozone
and Related Photochemical Oxidants**

Executive Direction

Dr. Lester D. Grant (Director)—National Center for Environmental Assessment-RTP Division, (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Scientific Staff

Dr. Lori White(Ozone Team Leader)—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Joseph Pinto—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Beverly Comfort—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Brooke Hemming—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. James S. Brown—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Dennis Kotchmar—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Jee Young Kim—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. David Svendsgaard—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Srikanth Nadadur—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Timothy Lewis—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. William Hogsett—National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Corvallis, OR

**U.S. Environmental Protection Agency Project Team
for Development of Air Quality Criteria for Ozone
and Related Photochemical Oxidants**

(cont'd)

Scientific Staff

(cont'd)

Dr. Christian Andersen—National Health and Environmental Effects Research Laboratory,
U.S. Environmental Protection Agency, Corvallis, OR

Dr. Jay Garner—National Center for Environmental Assessment (B243-01), U.S. Environmental
Protection Agency, Research Triangle Park, NC 27711 (retired)

Mr. Bill Ewald—National Center for Environmental Assessment (B243-01), U.S. Environmental
Protection Agency, Research Triangle Park, NC 27711 (retired)

Mr. James Raub—National Center for Environmental Assessment (B243-01), U.S. Environmental
Protection Agency, Research Triangle Park, NC 27711 (retired)

Technical Support Staff

Ms. Nancy Broom—Information Technology Manager, National Center for Environmental
Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. Douglas B. Fennell—Technical Information Specialist, National Center for Environmental
Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Emily R. Lee—Management Analyst, National Center for Environmental Assessment
(B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Diane H. Ray—Program Specialist, National Center for Environmental Assessment
(B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Donna Wicker—Administrative Officer, National Center for Environmental Assessment
(B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711 (retired)

Mr. Richard Wilson—Clerk, National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

**U.S. Environmental Protection Agency Project Team
for Development of Air Quality Criteria for Ozone
and Related Photochemical Oxidants**

(cont'd)

Document Production Staff

Ms. Carolyn T. Perry—Manager, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

Mr. John A. Bennett—Technical Information Specialist, Library Associates of Maryland, 11820 Parklawn Drive, Suite 400, Rockville, MD 20852

Mr. William Ellis—Records Management Technician, InfoPro, Inc., 8200 Greensboro Drive, Suite 1450, McLean, VA 22102

Ms. Sandra L. Hughey—Technical Information Specialist, Library Associates of Maryland, 11820 Parklawn Drive, Suite 400, Rockville, MD 20852

Mr. Matthew Kirk—Graphic Artist, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

Dr. Barbara Liljequist—Technical Editor, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

Ms. Rosemary Procko—Senior Word Processor, TekSystems, 1201 Edwards Mill Road, Suite 201, Raleigh, NC 27607

Ms. Faye Silliman—Publication/Graphics Specialist, InfoPro, Inc., 8200 Greensboro Drive, Suite 1450, McLean, VA 22102

Mr. Carlton Witherspoon—Graphic Artist, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

**U.S. Environmental Protection Agency Science Advisory Board (SAB)
Staff Office Clean Air Scientific Advisory Committee (CASAC)
Ozone Review Panel**

Chair

Dr. Rogene Henderson*, Scientist Emeritus, Lovelace Respiratory Research Institute, 2425 Ridgecrest Drive SE, Albuquerque, NM, 87108, Phone: 505-348-9464, Fax: 505-348-8541, (rhenders@lrri.org) (FedEx: Dr. Rogene Henderson, Lovelace Respiratory Research Institute, 2425 Ridgecrest Drive SE, Albuquerque, NM, 87108, Phone: 505-348-9464)

Members

Dr. John Balmes, Professor, Department of Medicine, University of California San Francisco, University of California - San Francisco, San Francisco, California, 94143, Phone: 415-206-8953, Fax: 415-206-8949, (jbalmes@itsa.ucsf.edu)

Dr. Ellis Cowling*, University Distinguished Professor-at-Large, North Carolina State University, Colleges of Natural Resources and Agriculture and Life Sciences, North Carolina State University, 1509 Varsity Drive, Raleigh, NC, 27695-7632, Phone: 919-515-7564 , Fax: 919-515-1700, (ellis_cowling@ncsu.edu)

Dr. James D. Crapo*, Professor, Department of Medicine, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO, 80206, Phone: 303-398-1436, Fax: 303- 270-2243, (crapoj@njc.org)

Dr. William (Jim) Gauderman, Associate Professor, Preventive Medicine, University of Southern California, 1540 Alcazar #220, Los Angeles, CA, 91016, Phone: 323-442-1567, Fax: 323-442-2349, (jimg@usc.edu)

Dr. Henry Gong, Professor of Medicine and Preventive Medicine, Medicine and Preventive Medicine, Keck School of Medicine, University of Southern California, Environmental Health Service, MSB 51, Rancho Los Amigos NRC, 7601 East Imperial Highway, Downey, CA, 90242, Phone: 562-401-7561, Fax: 562-803-6883, (hgong@ladhs.org)

Dr. Paul J. Hanson, Senior Research and Development Scientist , Environmental Sciences Division, Oak Ridge National Laboratory (ORNL), Bethel Valley Road, Building 1062, Oak Ridge, TN, 37831-6422, Phone: 865-574-5361, Fax: 865-576-9939, (hansonpz@comcast.net)

Dr. Jack Harkema, Professor, Department of Pathobiology, College of Veterinary Medicine, Michigan State University, 212 Food Safety & Toxicology Center, East Lansing, MI, 48824, Phone: 517-353-8627, Fax: 517-353-9902, (harkemaj@msu.edu)

U.S. Environmental Protection Agency Science Advisory Board (SAB)
Staff Office Clean Air Scientific Advisory Committee (CASAC)
Ozone Review Panel
(cont'd)

Members

(cont'd)

Dr. Philip Hopke, Bayard D. Clarkson Distinguished Professor, Department of Chemical Engineering, Clarkson University, Box 5708, Potsdam, NY, 13699-5708, Phone: 315-268-3861, Fax: 315-268-4410, (hopkep@clarkson.edu) (FedEx: 8 Clarkson Avenue, Potsdam, NY 136995708)

Dr. Michael T. Kleinman, Professor, Department of Community & Environmental Medicine, 100 FRF, University of California - Irvine, Irvine, CA, 92697-1825, Phone: 949-824-4765, Fax: 949-824-2070, (mtkleinm@uci.edu)

Dr. Allan Legge, President, Biosphere Solutions, 1601 11th Avenue NW, Calgary, Alberta, CANADA, T2N 1H1, Phone: 403-282-4479, Fax: 403-282-4479, (allan.legge@shaw.ca)

Dr. Morton Lippmann, Professor, Nelson Institute of Environmental Medicine, New York University School of Medicine, 57 Old Forge Road, Tuxedo, NY, 10987, Phone: 845-731-3558, Fax: 845-351-5472, (lippmann@env.med.nyu.edu)

Dr. Frederick J. Miller*, Consultant, 911 Queensferry Road, Cary, NC, 27511, Phone: 919-467-3194, (fjmill@nc.rr.com)

Dr. Maria Morandi, Assistant Professor of Environmental Science & Occupational Health, Department of Environmental Sciences, School of Public Health, University of Texas - Houston Health Science Center, 1200 Herman Pressler Street, Houston, TX, 77030, Phone: 713-500-9288, Fax: 713-500-9249, (mmorandi@sph.uth.tmc.edu) (FedEx: 1200 Herman Pressler, Suite 624)

Dr. Charles Plopper, Professor, Department of Anatomy, Physiology and Cell Biology, School of Veterinary Medicine, University of California - Davis, Davis, California, 95616, Phone: 530-752-7065, (cgplopper@ucdavis.edu)

Mr. Richard L. Poirot*, Environmental Analyst, Air Pollution Control Division, Department of Environmental Conservation, Vermont Agency of Natural Resources, Bldg. 3 South, 103 South Main Street, Waterbury, VT, 05671-0402, Phone: 802-241-3807, Fax: 802-241-2590, (rich.poirot@state.vt.us)

Dr. Armistead (Ted) Russell, Georgia Power Distinguished Professor of Environmental Engineering, Environmental Engineering Group, School of Civil and Environmental Engineering, Georgia Institute of Technology, 311 Ferst Drive, Room 3310, Atlanta, GA, 30332-0512, Phone: 404-894-3079, Fax: 404-894-8266, (trussell@ce.gatech.edu)

U.S. Environmental Protection Agency Science Advisory Board (SAB)
Staff Office Clean Air Scientific Advisory Committee (CASAC)
Ozone Review Panel
(cont'd)

Members

(cont'd)

Dr. Elizabeth A. (Lianne) Sheppard, Research Associate Professor, Biostatistics and Environmental & Occupational Health Sciences, Public Health and Community Medicine, University of Washington, Box 357232, Seattle, WA, 98195-7232, Phone: 206-616-2722, Fax: 206 616-2724, (sheppard@u.washington.edu)

Dr. Frank Speizer*, Edward Kass Professor of Medicine, Channing Laboratory, Harvard Medical School, 181 Longwood Avenue, Boston, MA, 02115-5804, Phone: 617-525-2275, Fax: 617-525-2066, (frank.speizer@channing.harvard.edu)

Dr. James Ultman, Professor, Chemical Engineering, Bioengineering program, Pennsylvania State University, 106 Fenske Lab, University Park, PA, 16802, Phone: 814-863-4802, Fax: 814-865-7846, (jsu@psu.edu)

Dr. Sverre Vedal, Professor of Medicine, Department of Environmental and Occupational Health Sciences, School of Public Health and Community Medicine, University of Washington, 4225 Roosevelt Way NE, Suite 100, Seattle, WA, 98105-6099, Phone: 206-616-8285, Fax: 206-685-4696, (svedal@u.washington.edu)

Dr. James (Jim) Zidek, Professor, Statistics, Science, University of British Columbia, 6856 Agriculture Rd., Vancouver, BC, Canada, V6T 1Z2, Phone: 604-822-4302, Fax: 604-822-6960, (jim@stat.ubc.ca)

Dr. Barbara Zielinska*, Research Professor, Division of Atmospheric Science, Desert Research Institute, 2215 Raggio Parkway, Reno, NV, 89512-1095, Phone: 775-674-7066, Fax: 775-674-7008, (barbz@dri.edu)

Science Advisory Board Staff

Mr. Fred Butterfield, CASAC Designated Federal Officer, 1200 Pennsylvania Avenue, N.W., Washington, DC, 20460, Phone: 202-343-9994, Fax: 202-233-0643 (butterfield.fred@epa.gov) (Physical/Courier/FedEx Address: Fred A. Butterfield, III, EPA Science Advisory Board Staff Office (Mail Code 1400F), Woodies Building, 1025 F Street, N.W., Room 3604, Washington, DC 20004, Telephone: 202-343-9994)

*Members of the statutory Clean Air Scientific Advisory Committee (CASAC) appointed by the EPA Administrator

ABBREVIATIONS AND ACRONYMS

AA	arachidonic acid
AA	ascorbic acid
a1-AT	a1-antitrypsin
AC	air conditioning
ACh	acetylcholine
ADSS	aged and diluted sidestream cigarette smoke
AED	aerodynamic diameter
AER	air exchange rate
AEROCE	Atmospheric/Ocean Chemistry Experiment
AF	adsorbed fraction
AGL	above ground level
AH ₂	ascorbic acid
AHCs	aromatic hydrocarbons
AHR	airway hyperreactivity
AirPEX	Air Pollution Exposure (model)
AirQUIS	Air Quality Information System (model)
AIRS	Aerometric Information Retrieval System
ALI	air-liquid interface
AM	alveolar macrophage
ANOVA	analysis of variance
AP	alkaline phosphatase
AP-CIMS	Atmospheric Pressure Chemical Ionization Mass Spectrometer
APEX	Air Pollutants Exposure (model)
APHEA	Air Pollution on Health: European Approach (study)
AQCD	Air Quality Criteria Document
AQS	Air Quality System
ASC	ascorbate
ASTM	American Society for Testing and Materials
ATLAS	atmospheric model (by Kurucz)

A/V	surface-to-volume ratio
β	log relative risk
β_2 -AR	beta-2-adrenergic receptor
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
BALT	bronchus-associated lymphoid tissue
B[a]P	benzo[a]pyrene
BC	black carbon
BEIS	Biogenic Emission Inventory System
BERLIOZ	Berlin Ozone Experiment
BF	black female
BHC	biogenic hydrocarbons
BM	black male
BME	Bayesian Maxim Entropy
BMZ	basement membrane zone
BP	blood pressure
bpm	breaths per minute
BrdU	bromodeoxyuridine
BS	black smoke
BSA	body surface area
BSA	bovine serum albumin
B_{scatter}	back scatter
C	concentration
C3a	complement protein fragment
CAAA	Clean Air Act Amendments of 1990
CADS	Cincinnati Activity Diary Study
CAPMoN	Canadian Air and Precipitation Monitoring Network
CAPs	concentrated ambient particles
CAR	centriacinar region
CARB	California Air Resources Board

CASTNet, CASTNET	Clean Air Status and Trends Network
CAT	catalase
CB	carbon black
CBL	convective boundary layer
CBU	cumulative breath units
% C/C	percent carbon of total carbon
CC16	Clara cell secretory protein
CCh	carbachol
CCSP	Clara cell secretory protein
C_{dyn}	dynamic lung compliance
CE	continuous exercise
CEPEX	Central Equatorial Pacific Experiment
CFD	computational fluid dynamics
CFR	Code of Federal Regulations
CG	cloud-to-ground (flash)
CH_3	ammonia
CH_4	methane
C_2H_4	ethene
C_5H_8	isoprene
C_6H_6	benzene
CHAD	Consolidated Human Activities Database
$\text{CH}_2=\text{C}(\text{CH}_3)\text{-CHO}$	methacrolein
$\text{CH}_3\text{-CCl}_3$	methyl chloroform
$\text{C}_6\text{H}_5\text{CH}_3$	toluene
$\text{CH}_3\text{-CHO}$	acetaldehyde
$\text{CH}_3\text{CH}(\text{ONO}_2)\text{CHO}$	2-nitratopropanol
CHCl_3	chloroform
CH_3CN	acetonitrile
$\text{CH}_3\text{-CO}$	acetyl
$\text{CH}_3\text{-C}(\text{O})\text{-CH=CH}_2$	methyl vinyl ketone

$\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{ONO}_2$	1-nitratopropanone
$\text{CH}_3\text{-C}(\text{O})\text{O}_2$, $\text{CH}_3\text{-C}(\text{O})\text{OO}$	acetyl peroxy, peroxyacetyl
CHO	Chinese hamster ovary (cells)
CH_3O	methoxy
CH_3O_2	methyl peroxy
CH_3OH	methanol
$\text{CH}_3\text{-O}(\text{O})\text{CH}_3$	acetone
CH_3OOH	methyl hydroperoxide
CI	confidence interval
CIMS	Chemical Ionization Mass Spectroscopy
CINC	cytokine-induced neutrophil chemoattractant
CIU	cumulative inhalation units
CL	chemiluminescence
CMAQ	Community Model for Air Quality
CMBO	chloromethylbutenone
CMD	count mean diameter
CMSA	consolidated metropolitan statistical area
CN	condensation nuclei
CO	carbon monoxide
CO_2	carbon dioxide
COD	coefficient of divergence
ConA	concanavalin A
COPD	chronic obstructive pulmonary disease
CSA	consolidated statistical area
CTM	chemistry transport model
CV	coefficient of variation
CYP	cytochrome P-450
cyt.	cytochrome
Δ	delta; change in a variable
2-D	two-dimensional

DA	dopamine
DA	dry airstream
DD	doubling dose
DHBA	2,3-dihydroxybenzoic acid
DI	dry intrusion
DIAL	differential absorption lidar (system)
DNA	deoxyribonucleic acid
DOAS	differential optical absorption spectroscopy
DOC	dissolved organic carbon
DOE	Department of Energy
DOPAC	3,4-dihydroxyphenylacetic acid
DPPC	dipalmitoylglycero-3-phosphocholine
DR	disulfide reductase
DTPA	diethylenetriaminepentaacetic acid
EBC	exhaled breath condensate (fluid)
EC	elemental carbon
EC _{0.05%}	0.05% excess risk in mortality
ECG	electrocardiographic
EC-SOD	extracellular superoxide dismutase
EDMAS	Exposure and Dose Modeling and Analysis System
EE	energy expenditure
eGPx	extracellular glutathione peroxidase
ELF	epithelial lining fluid
EM	electron microscopy
ENA-78	epithelial cell-derived neutrophil-activating peptide 78
eNOS	endothelial nitric oxide synthase
EOFs	empirical orthogonal functions
EPA	U.S. Environmental Protection Agency
EPeM	Event Probability Exposure Model
EPR	electron paramagnetic resonance (spectroscopy)

EPRI	Electric Power Research Institute
ER	emergency room
ERAQS	Eastern Regional Air Quality Study
ESR	electron spin resonance (spectroscopy)
ET	endotracheal
ETS	environmental tobacco smoke
EVR	equivalent ventilation rate
F	female
f, f, f_b	frequency of breathing
F344	Fischer 344 (rat)
FA	filtered air
FA	fractional absorption; absorbed fraction
FAA	Federal Aviation Administration
FEF	forced expiratory flow
$FEF_{25-75}, FEF_{25\%-75\%}$	forced expiratory flow between 25 and 75% of vital capacity
FEF_x	forced expiratory flow after X% vital capacity (e.g., after 25, 50, or 75% vital capacity)
FEV_1	forced expiratory volume in 1 second
FGFR	fibroblast growth factor receptor
FIVC	forced inspiratory vital capacity
F_n	fibronectin
FP	fluticasone propionate
FRC	functional residual capacity
FS	field stimulation
FTIR	Fourier Transform Infrared Spectroscopy
FVC	forced vital capacity
GAM	General Additive Model
GCE	Goddard Cumulus Ensemble (model)
GC-FID	gas chromatography-flame ionization detection
GCM	general circulation model
GC/MS	gas chromatography-mass spectrometry

GDT	glutathione-disulfide transhydrogenase
GEE	Generalized Estimating Equations
GEOS-CHEM	three-dimensional model of atmospheric composition driven by assimilated Goddard Earth Orbiting System observations
GEOS-1 DAS	NASA Goddard Earth Orbiting System Data Assimilation System
GM-CSF	granulocyte-macrophage colony stimulating factor
GMT	Greenwich mean time
G6PD	glucose-6-phosphate dehydrogenase
GSH	glutathione; reduced glutathione
GSHPx, GPx	glutathione peroxidase
GSSG	glutathione disulfide
GSTM1	glutathione <i>S</i> -transferase μ -1 (genotype)
GSTM1null	glutathione <i>S</i> -transferase μ -1 null (genotype)
H ⁺	hydrogen ion; symbol for acid
³ H	radiolabeled hydrogen
HCO	formyl
H ₂ CO, HCHO	formaldehyde
HDMA	house dust mite allergen
HF	Howland Forest site
H ₂ O ₂	hydrogen peroxide
H ₂ SO ₄	sulfuric acid
HCs	hydrocarbons
HHP-C9	1-hydroxy-1-hydroperoxynonane
5-HIAA	5-hydroxyindolacetic acid
HIST	histamine
HLA	human leukocyte antigen
HNE	4-hydroxynonenal
HNO ₂	nitrous acid
HNO ₃	nitric acid
HNO ₄	pernitric acid
HO	hydroxy

HO ₂	hydroperoxy
H ₂ O ₂	hydrogen peroxide
H ₃ O ⁺	protonated water
HOCH ₂ OOH	hydroxymethylhydroperoxide
HONO	nitrous acid
HOONO	pernitrous acid
HO ₂ NO ₂	peroxynitric acid
HO _x	hydrogen oxides
HPLC	high-pressure liquid chromatography
HR	heart rate
HR _{max}	maximum heart rate
HRV	heart rate variability
5-HT	5-hydroxytryptamine
hν	solar ultraviolet photon
HVAC	heating, ventilation, and air conditioning
IAS	interalveolar septum
IBM	individual-based model or modeling
IC	inspiratory capacity
IC	intracloud (flash)
ICAM	intracellular adhesion molecule
ICEM	Indoor Chemistry and Exposure Model
ICS	inhaled steroids
ID#	identification number
IE	intermittent exercise
IFN	interferon
Ig	immunoglobulin (e.g., IgA, IgE, IgG, IgM)
IL	interleukin (e.g., IL-1, IL-6, IL-8)
IN	intranasal
INF	interferon
inh	inhalation

iNOS	inducible nitric oxide synthase
I/O	indoor-to-outdoor ratio
ip	intraperitoneal
IPCC	Intergovernmental Panel on Climate Change
IPMMI	International Photolysis Frequency Measurement and Modeling Intercomparison
IQR	interquartile range
ISCCP	International Satellite Cloud Climatology Project
IT	intratracheal
IU	International Units
iv	intravenous
$j(\text{NO}_2)$	photolysis rate coefficient for O_3 to NO_2
$j(\text{O}_3)$	photolysis rate coefficient for O_3 to $\text{O}(^1\text{D})$
K_a	intrinsic mass transfer coefficient/parameter
KM	particle optical reflectance
KO	knockout
K_{TB}	tracheobronchial region overall mass transfer coefficient
LDH	lactate dehydrogenase
LFHFR	low frequency/high frequency (ratio)
LFT	lower free troposphere
LI	labeling index
LIDAR	LIght Detection And Ranging
LIF	laser-induced fluorescence
LIS	lateral intercellular space
LLJ	low-level jet
LM	light microscopy
LOESS	locally estimated smoothing splines
LPS	lipopolysaccharide
LST	local standard time
LT	leukotriene (e.g., LTB_4 , LTC_4 , LTD_4 , LTE_4)
LT	local time

LTA	lymphotoxin-alpha
LWC	liquid water content
M	air molecule
M	male
MAQSIP	Multiscale Air Quality Simulation Platform
MBL	marine boundary layer
NBTH	3-methyl-2-benzothiazolinone acetone azine
MCCP	Mountain Cloud Chemistry Program
MCh	methacholine
MCM	master chemical mechanism
MCP	monocyte chemotactic protein
MEF ₅₀	maximal expiratory flow at 50% of vital capacity
MENTOR	Modeling Environment for Total Risk Studies
MET	metabolic equivalent of work
MHC	major histocompatibility
MI	myocardial infarction
MIESR	matrix isolation electron spin resonance (spectroscopy)
MIP	macrophage inflammatory protein
MLN	mediastinal lymph node
MM	Mt. Mitchell site
MM5	National Center for Atmospheric Research/Penn State Mesoscale Model
MMAD	mass median aerodynamic diameter
MMEF	maximal midexpiratory flow
MMMD	mean maximum mixing height depth
MoO _x	molybdenum oxides
MOZAIC	Measurement of Ozone and Water Vapor by Airbus In-Service Aircraft
MPAN	methacryloylperoxynitrate; peroxy-methacrylic nitric anhydride
mRNA	messenger ribonucleic acid
MS	mass spectrometry

MS	Mt. Moosilauke site
MSA	metropolitan statistical area
MS/MS	tandem mass spectrometry
MT, Mt	metallothionein
Mtn	mountain
MW	molecular weight
n, N	number
N100	number of hours ≥ 0.10 ppm
NA	noradrenaline
NA, N/A	not available
NAAQS	National Ambient Air Quality Standards
NADH	reduced nicotinamide adenine dinucleotide
NADP	National Atmospheric Deposition Program
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NADPH-CR	reduced nicotinamide adenine dinucleotide phosphate-cytochrome c reductase
NAMS/SLAMS	National Ambient Monitoring Stations and State and Local Air Monitoring Stations
NAPBN	National Air Pollution Background Network
NARE	North Atlantic Regional Experiment
NASA	National Aeronautics and Space Administration
NBS	National Bureau of Standards
NCICAS	National Cooperative Inner-City Asthma Study
NCLAN	National Crop Loss Assessment Network
ND	not detectable
NEM	National Ambient Air Quality Standards Exposure Model
NESCAUM	Northeast States for Coordinated Air Use Management
NF	national forest
NF- κ B	nuclear factor kappa B
NH ₃	ammonia
NH ₄ ⁺	ammonium ion

NHAPS	National Human Activity Pattern Survey
NHBE	cultured human bronchial epithelial (cells)
$(\text{NH}_4)_2\text{SO}_4$	ammonium sulfate
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NK	natural killer (cells)
NL	nasal lavage
NLF	nasal lavage fluid
NM	national monument
NMHCs	nonmethane hydrocarbons
NMMAPS	National Morbidity, Mortality and Air Pollution Study
NMOCs	nonmethane organic compounds
NMVOCs	nonmethane volatile organic compounds
NNK	4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
NO_2	nitrogen dioxide
NO_3	nitrate (radical)
NO_3^-	nitrate (ion)
N_2O_5	dinitrogen pentoxide
NOAA	National Oceanic and Atmospheric Administration
NOAEL	non-observable-adverse-effect level
NOS	nitric oxide synthase
NO_x	nitrogen oxides
NO_y	total reactive nitrogen; sum of NO_x and NO_z ; odd nitrogen species
NO_z	nitrogen-containing species, the sum of the products of the oxidation of NO_x
NP	national park
NQO1	NAD(P)H-quinone oxidoreductase (genotype)
NQO1wt	NAD(P)H-quinone oxidoreductase wild type (genotype)
NR	not reported

NRC	National Research Council
NS	national seashore
NS	nonsignificant
NS	nonsmoker
NSAID	non-steroidal anti-inflammatory agent
NSBR	nonspecific bronchial responsiveness
NTE	nasal turbinates epithelial (cells)
NTRMs	NIST Traceable Reference Materials
NWR	national wildlife refuge
NZW	New Zealand white (rabbit)
O ₂	molecular oxygen
O ₂ ⁻	superoxide
O ₃	ozone
¹⁸ O	radiolabeled oxygen atom
OC	organic carbon
OAQPS	Office of Air Quality Planning and Standards
OBM _s	observationally based methods
O(¹ D)	electronically excited oxygen atom
OH	hydroxy
8-OHdG	8-hydroxy-2'-deoxyguanosine
OLS	ordinary least squares
O(³ P)	ground-state oxygen atom
OPE	ozone production efficiency
OVA	ovalbumin
O _x	odd oxygen species; total oxidants
p	probability
P ₉₀	values of the 90th percentile absolute difference in concentrations
PAF	platelet-activating factor
PAHs	polycyclic aromatic hydrocarbons
PAMS, PAMs	Photochemical Aerometric Monitoring System

PAN	peroxyacetyl nitrate
P _a O ₂	partial pressure of arterial oxygen
PAR	proximal alveolar region
<i>p</i> -ATP	<i>para</i> -acetamidophenol
PBL	peripheral blood lymphocytes
PBL	planetary boundary layer
PBM	population-based model or modeling
PBN	C-phenyl N-tert-butyl nitron
PBPK	physiologically based pharmacokinetic (approach)
PC ₂₀	provocative concentration that produces a 20% decrease in forced expiratory volume in 1 second
PC ₅₀	provocative concentration that produces a 50% decrease in forced expiratory volume in 1 second
PCA	principal component analysis
PC-ALF	1-palmitoyl-2-(9-oxonononoyl)- <i>sn</i> -glycero-3-phosphocholine
pCNEM	Canadian version of National Ambient Air Quality Standards Exposure Model
pCO ₂	partial pressure of carbon dioxide
PD ₂₀ , PD ₂₀ FEV ₁	provocative dose that produces a 20% decrease in FEV ₁
PC ₂₀ FEV ₁	provocative concentration that produces a 20% decrease in FEV ₁
PD ₁₀₀ SRaw	provocative dose that produces a 100% increase in SRaw
PE	postexposure
PEF	peak expiratory flow
PEF _{0.75}	peak expiratory flow in 0.75 second
PEFR	peak expiratory flow rate
PEG-CAT	polyethylene glycol-catalase
PEG-SOD	polyethylene glycol-superoxide dismutase
PEM	personal exposure monitor
PG	prostaglandin (e.g., PGD ₂ , PGE, PGE ₁ , PGE ₂ , PGF _{1α} , PGF _{2α})
6PGD	6-phosphogluconate dehydrogenase
PGHS-2	prostaglandin endoperoxide G/H synthase 2

PHA	phytohemagglutinin
PIF	peak inspiratory flow
PK	pharmacokinetics
PM	particulate matter
Pm _{0.1}	pressure at mouth at 0.1 second of inspiration against a transiently occluded mouthpiece (an index of inspiratory drive)
PM _{2.5}	fine particulate matter (mass median aerodynamic diameter ≤2.5 μm)
PM ₁₀	combination of coarse and fine particulate matter (mass median aerodynamic diameter ≤10 μm)
PM _{10-2.5}	coarse particulate matter (mass median aerodynamic diameter between 10 and 2.5 μm)
PM ₁₅	combination of coarse and fine particulate matter (mass median aerodynamic diameter ≤15 μm)
PM-CAMx	Particulate Matter Comprehensive Air Quality Model with Extensions
PMNs	polymorphonuclear leukocytes; neutrophils
PMT	photomultiplier tube
PND	postnatal day
pNEM	Probabilistic National Ambient Air Quality Standard Exposure Model
PNN ₅₀	proportion of adjacent N-N intervals differing by more than 50 ms
POC	particulate organic carbon
polyADPR	poly(adenosinediphosphate-ribose)
ppb	parts per billion
ppbv	parts per billion by volume
pphm	parts per hundred million
ppm	parts per million
ppmv	parts per million by volume
PPN	peroxypropionyl nitrate
PPPs	power plant plumes
pptv	parts per trillion by volume
PRB	policy relevant background

PTR-MS	proton-transfer-reaction mass spectroscopy
PU, PUL	pulmonary
PUFAs	polyunsaturated fatty acids
PV	potential vorticity
PVOCs	photochemical volatile organic compounds
PWM	pokeweed mitogen
R	intraclass correlation coefficient
r	correlation coefficient
R ²	multiple correlation coefficient
r ²	correlation coefficient
RACM	Regional Air Chemistry Mechanism
RADM	Regional Acid Deposition Model
rALP	recombinant antileukoprotease
RAMS	Regional Atmospheric Modeling System
RANTES	regulated on activation, normal T cell-expressed and -secreted (cells)
R _{aw} , Raw	airway resistance
RB	respiratory bronchiole
RBC	red blood cell
RDBMS	Relational Database Management Systems
REHEX	Regional Human Exposure Model
RER	rough endoplasmic reticulum
RH	relative humidity
RIOPA	Relationship of Indoor, Outdoor, and Personal Air (study)
R _L	total pulmonary resistance
RMR	resting metabolic rate
rMSSD	square root of the mean of the squared difference between adjacent normal R-R intervals
RO ₂	organic peroxy
ROI	reactive oxygen intermediate/superoxide anion
RONO ₂	organic nitrate
ROONO ₂ , RO ₂ NO ₂	peroxy nitrate

ROS	reactive oxygen species
RR	relative risk
RRMS	relatively remote monitoring sites
RT	respiratory tract
R_T	transepithelial resistance
σ_g	sigma-g; geometric standard deviation
S	smoker
SAC	<i>Staphylococcus aureus</i> Cowan 1 strain
SAI	Systems Applications International
S_aO_2	oxygen saturation of arterial blood
SAPRC	Statewide Air Pollution Research Center, University of California, Riverside
SAROAD	Storage and Retrieval of Aerometric Data (U.S. Environmental Protection Agency centralized database; superseded by Aerometric Information Retrieval System [AIRS])
SAW_{grp}	small airway function group
SC	stratum corneum
sc	subcutaneous
SCAQS	Southern California Air Quality Study
SD	Sprague-Dawley
SD	standard deviation
SDNN	standard deviation of normal R-R intervals
SE	standard error
SEM	standard error of the mean
SES	socioeconomic status
SGaw	specific airway conductance
SH	Shenandoah National Park site
SHEDS	Simulation of Human Exposure and Dose System
sICAM	soluble intracellular adhesion molecule
SO ₂	sulfur dioxide
SO ₄ ²⁻	sulfate

SOA	secondary organic aerosol
SOD	superoxide dismutase
SOS	Southern Oxidant Study
SO _x	sulfur oxides
SP	substance P
SP	surfactant protein (e.g., SP-A, SP-D)
SRaw, sRaw	specific airway resistance
SRBC	sheep red blood cell
SRM	standard reference material
STE	stratospheric-tropospheric exchange
STEP	Stratospheric-Tropospheric-Exchange Project
STPD	standard temperature and pressure, dry
STRF	Spatio-Temporal Random Field
SUM06	seasonal sum of all hourly average concentrations ≥ 0.06 ppm
SUM07	seasonal sum of all hourly average concentrations ≥ 0.07 ppm
SUM08	seasonal sum of all hourly average concentrations ≥ 0.08 ppm
SURE	Sulfate Regional Experiment Program
τ	tau; atmospheric lifetime
T	time (duration of exposure)
t	<i>t</i> -test statistical value; <i>t</i> statistic
T ₃	triiodothyronine
T ₄	thyroxine
TAR	Third Assessment Report
TB	terminal bronchiole
TB	tracheobronchial (region)
TBA	thiobarbituric acid
TBARS	thiobarbituric acid reactive substances
^{99m} Tc-DTPA	radiolabeled diethylenetriaminepentaacetic acid
T _{CO}	core temperature
TDLAS	tunable-diode laser absorption spectroscopy

T _e	expiratory time
TEM	transmission electron microscopy
Tg	teragram
TGFβ1	transforming growth factor-beta 1
T _i	inspiratory time
TLC	total lung capacity
TLR	Toll-like receptor
TNF	tumor necrosis factor
TOMS	Total Ozone Mapping Satellite; total ozone mapping spectrometer
TOPSE	Tropospheric Ozone Production About the Spring Equinox
TRIM	Total Risk Integrated Methodology (model)
TRIM.EXPO	Total Risk Integrated Methodology Exposure Event (model)
TPLIF	two-photon laser-induced fluorescence
TSH	thyroid-stimulating hormone
TSP	total suspended particulate
TTFMS	two-tone frequency-modulated spectroscopy
TVA	Tennessee Valley Authority
TWA	time-weighted average
TX	thromboxane (e.g., TXA ₂ , TXB ₂)
UA	uric acid
UAM	Urban Airshed Model
ULLI	unit length labeling index
URT	upper respiratory tract
UT	Universal Time
UTC	Coordinated Universal Time
UV	ultraviolet
UV-A	ultraviolet radiation of wavelengths 320 to 400 nm
UV-B	ultraviolet radiation of wavelengths 280 to 320 nm
UV-DIAL	Ultraviolet Differential Absorption Lidar
VC	vital capacity
VCAM	vascular cell adhesion molecule

V_D	anatomic dead space
V_D	deposition velocity
\dot{V}_E	minute ventilation; expired volume per minute
$\dot{V}_{E_{max}}$	maximum minute ventilation
$\dot{V}_{max25\%}$	maximum expiratory flow at 25% of the vital capacity
$\dot{V}_{max50\%}$	maximum expiratory flow at 50% of the vital capacity
$\dot{V}_{max75\%}$	maximum expiratory flow at 75% of the vital capacity
VMD	volume median diameter
$\dot{V}O_2$	oxygen consumption
$\dot{V}O_{2max}$	maximal oxygen uptake (maximal aerobic capacity)
VOCs	volatile organic compounds
V_T	tidal volume
V_{TB}	tracheobronchial region volume
V_{Tmax}	maximum tidal volume
W126	cumulative integrated exposure index with a sigmoidal weighting function
WBGT	wet bulb globe temperature
WCB	warm conveyor belt
WF	white female
WF, WFM	White Face Mountain site
WM	white male
WT	White Top Mountain site
WT	wild type

ANNEX AX2. PHYSICS AND CHEMISTRY OF OZONE IN THE ATMOSPHERE

AX2.1 INTRODUCTION

This annex (Annex AX2) provides detailed supporting information for Chapter 2 on the physics and chemistry of ozone (O_3) in the atmosphere. The organization of the material in this annex follows that used in prior Air Quality Criteria Documents, i.e., material is presented in sections and subsections. This annex provides material supporting Chapter 2 of the current draft Air Quality Criteria Document for Ozone.

Section AX2.2 focuses on the chemistry of O_3 formation. A very brief overview of atmospheric structure is presented in Section AX2.2.1. An overview of O_3 chemistry is given in Section AX2.2.2. Information about reactive chemical species that initiate the oxidation of VOCs is given in Section AX2.2.3. The chemistry of nitrogen oxides is then discussed briefly in Section AX2.2.4. The oxidation of methane, the simplest hydrocarbon is outlined in Section AX2.2.5.

The photochemical cycles leading to O_3 production are best understood by considering the oxidation of methane, structurally the simplest VOC. The CH_4 oxidation cycle serves as a model which can be viewed as representing the chemistry of the relatively clean or unpolluted troposphere (although this is a simplification because vegetation releases large quantities of complex VOCs, such as isoprene, into the atmosphere). Although the chemistry of the VOCs emitted from anthropogenic and biogenic sources in polluted urban and rural areas is more complex, a knowledge of the CH_4 oxidation reactions aids in understanding the chemical processes occurring in the polluted atmosphere because the underlying chemical principles are the same. The oxidation of more complex hydrocarbons (alkanes, alkenes, and aromatic compounds) is discussed in Sections AX2.2.6, AX2.2.7, and AX2.2.8, respectively. The chemistry of oxygenated species is addressed in Section AX2.2.9. Greater emphasis is placed on the oxidation of aromatic hydrocarbons in this section because of the large amount of new information available since the last Air Quality Criteria for Ozone document (AQCD 96) was published (U.S. Environmental Protection Agency, 1996) and because of their importance in O_3 formation in polluted areas. Multiphase chemical processes influencing O_3 are discussed in

Section AX2.2.10. Meteorological processes that control the formation of O₃ and other oxidants and that govern their transport and dispersion, and the sensitivity of O₃ to atmospheric parameters are given in Section AX2.3. Greater emphasis is placed on those processes for which a large amount of new information has become available since AQCD 96. The role of stratospheric-tropospheric exchange in determining O₃ in the troposphere is presented in Section AX2.3.1. The importance of deep convection in redistributing O₃ and its precursors and other oxidants throughout the troposphere is given in Section AX2.3.2. The possible importance of nocturnal low-level jets in transporting O₃ and other pollutants is presented in Section AX2.3.3. Information about the mechanisms responsible for the intercontinental transport of pollutants and for the interactions between stratospheric-tropospheric exchange and convection is given in Section AX2.3.4. Much of the material in this section is based on results of field programs examining atmospheric chemistry over the North Atlantic ocean. The sensitivity of O₃ to solar ultraviolet radiation and temperature is given in Section AX2.3.5. The relations of O₃ to its precursors and to other oxidants based on field and modeling studies are discussed in Section AX2.4. Methods used to calculate relations between O₃ its precursors and other oxidants are given in Section AX2.5. Chemistry-transport models are discussed in Section AX2.5.1. Emissions of O₃ precursors are presented in Section AX2.5.2. Issues related to the evaluation of chemistry-transport models and emissions inventories are presented in Section AX2.5.3. Measurement methods are summarized in Section AX2.6. Methods used to monitor ground-level O₃ are given in Section AX2.6.1, NO and NO₂ in Section AX2.6.2, HNO₃ in Section AX2.6.3 and some important VOCs in Section AX2.6.4.

AX2.2 TROPOSPHERIC OZONE CHEMISTRY

AX2.2.1 Atmospheric Structure

The atmosphere can be divided into several distinct vertical layers, based primarily on the major mechanism by which that portion of the atmosphere is heated or cooled. The lowest major layer is the troposphere, which extends from the earth's surface to about 8 km above polar regions and to about 16 km above tropical regions. The troposphere is heated by convective transport from the surface, and by the absorption of infrared radiation emitted by the surface, principally by water vapor and CO₂. The planetary boundary layer (PBL) is the sublayer of the

troposphere that mixes with surface air on time scales of a few hours or less. It typically extends to 1-2 km altitude and is often capped by a temperature inversion. The sublayer of the troposphere above the PBL is called the free troposphere. Ventilation of the PBL with free tropospheric air takes place on a time scale of a week. Vertical mixing of the whole troposphere takes place on a time scale of a month or two. The stratosphere extends from the tropopause, or the top of the troposphere, to about 50 km in altitude. The upper stratosphere is heated by the absorption of solar ultraviolet radiation by O₃, while dissipation of wave energy transported upwards from the troposphere is a primary heating mechanism in the lower stratosphere. Heating of the stratosphere is balanced by radiative cooling due to infrared emissions to space by CO₂, H₂O, and O₃. As a result of heating of the upper stratosphere, temperatures increase with height, inhibiting vertical mixing. A schematic overview of the major chemical cycles involved in O₃ formation and destruction in the stratosphere and troposphere is shown in Figure AX2-1. The figure emphasizes gas phase processes, but the importance of multiphase processes is becoming apparent. The sequences of reactions shown in the lower right quadrant of the figure will be discussed in Section AX2.2. The reader is referred to any of the large number of texts on atmospheric chemistry, such as Wayne (2000) or Seinfeld and Pandis (1998), for an introduction to stratospheric photochemistry, including the impact of O₃-destroying compounds.

AX2.2.2 Overview of Ozone Chemistry

Ozone is found not only in polluted urban atmospheres but throughout the troposphere, including remote areas of the globe. Even without ground-level production, some O₃ would be found in the troposphere due to downward transport from the stratosphere. Tropospheric photochemistry leading to the formation of O₃ and other photochemical air pollutants is complex, involving thousands of chemical reactions and thousands of stable and reactive intermediate products. Other photochemical oxidants, such as peroxyacetyl nitrate (PAN), are among the reactive products. Ozone can be photolyzed in the presence of water to form hydroxyl radical (OH), which is responsible for the oxidation of NO_x and SO_x to form nitric (HNO₃) and sulfuric acid (H₂SO₄), respectively. Ozone participates directly in the oxidation of unsaturated hydrocarbons, via the ozonolysis mechanism, yielding secondary organic compounds that contribute to aerosol formation and mass, as well as formaldehyde (H₂CO) and other carbonyl compounds, such as aldehydes and ketones.

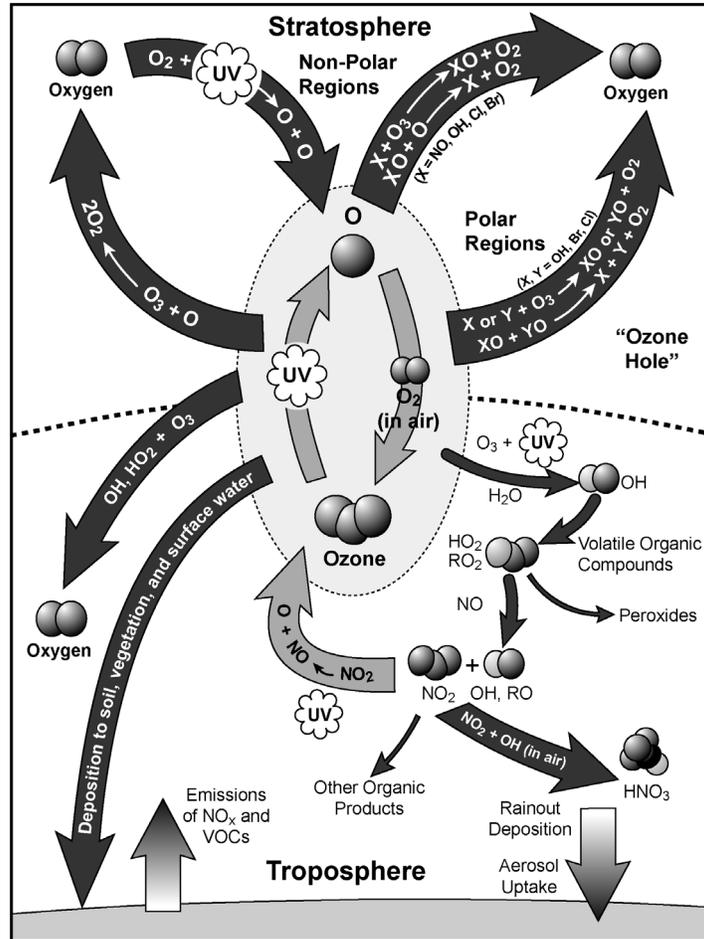
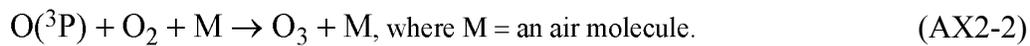


Figure AX2-1. Schematic overview of O₃ photochemistry in the stratosphere and troposphere.

There is a rapid photochemical cycle in the troposphere that involves the photolysis of nitrogen dioxide (NO₂) by solar UV-A radiation to yield nitric oxide (NO) and a ground-state oxygen atom, O(³P),



O(³P) then reacts with molecular oxygen to form O₃: A molecule from the surrounding air collides with the newly-formed O₃ molecule, removing excess energy to allow it to stabilize.



Reaction AX2-2 is the only significant reaction forming O₃ in the troposphere.

NO and O₃ react to reform NO₂:



This reaction is responsible for O₃ decreases found near sources of NO (e.g., highways) especially at night. The oxidation of reactive VOCs leads to the formation of reactive radical species that allow the conversion of NO to NO₂ without the participation of O₃ (as in reaction AX2-3).



O₃ can, therefore, accumulate as NO₂ photolyzes as in reaction AX2-1 followed by reaction AX2-2.

It is often convenient to speak about families of chemical species that are defined in terms of members which interconvert rapidly among themselves on time scales that are shorter than that for formation or destruction of the family as a whole. For example, an “odd oxygen” (O_x) family can be defined as $\sum (\text{O}({}^3\text{P}) + \text{O}({}^1\text{D}) + \text{O}_3 + \text{NO}_2)$ in much the same way as the NO_x (NO + NO₂) family is defined. We can then see that production of O_x occurs by the schematic reaction AX2-4, and that the sequence of reactions given by reactions AX2-1 through AX2-3 represents no net production of O_x. Definitions of species families and methods for constructing families are discussed in Jacobson (1999) and references therein. Other families that include nitrogen containing species, and will be referred to later in this chapter, are NO_z, which is the sum of the products of the oxidation of NO_x = $\sum (\text{HNO}_3 + \text{PAN} (\text{CH}_3\text{CHO-OO-NO}_2) + \text{HNO}_4 + \text{other organic nitrates} + \text{particulate nitrate})$; and NO_y, which is the sum of NO_x and NO_z.

AX2.2.3 Initiation of the Oxidation of VOCs

The key reactive species in the troposphere is the OH radical. OH radicals are responsible for initiating the photochemical oxidation of CO and most anthropogenic and biogenic VOCs, including those responsible for depleting stratospheric O₃ (e.g., CH₃Br, hydrochlorofluorocarbons), and those which contribute to the greenhouse effect (e.g., CH₄). Because of their role in removing so many potentially damaging species, OH radicals have sometimes been referred to as the atmosphere's detergent. In the presence of NO, reactions of OH with VOCs lead to the formation of O₃. In addition to OH radicals, there are several other atmospheric species such as NO₃, Cl, and Br radicals and O₃ that are capable of initiating VOC oxidation. Rate coefficients and estimated atmospheric lifetimes (the e-folding time) for reactions of a number of alkanes, alkenes and dienes involved in O₃ formation with these oxidants at concentrations characteristic of the relatively unpolluted planetary boundary layer are given in Table AX2-1. As can be seen from Table AX2-1, there is a wide range of lifetimes calculated for the different species. However, under certain conditions the relative importance of these oxidants can change from those shown in the table. For hydrocarbons whose atmospheric lifetime is much longer than a day, diurnally averaged concentrations of oxidant concentrations can be used, but for those whose lifetime is much shorter than a day it is more appropriate to use either daytime or nighttime averages depending on when the oxidant is at highest concentrations. During these periods, these averages are of the order of twice the values used in Table AX2-1.

The main source of OH radicals is the photolysis of O₃ by solar ultraviolet radiation at wavelengths < 340 nm (solar radiation at wavelengths < 320 nm is also referred to as UV-B) to generate electronically excited O(¹D) atoms (Jet Propulsion Laboratory, 2003),



The O(¹D) atoms can either be deactivated to the ground state O(³P) atom by collisions with N₂ and O₂, or they react with water vapor to form two OH radicals:



Table AX2-1. Comparison of the Atmospheric Lifetimes (τ) of Low Molecular Weight Hydrocarbons Due to Reaction with OH, NO₃, Cl, Br, and O₃

Hydrocarbon	$k, \text{cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$									
	OH		NO ₃		Cl		Br		O ₃	
	$k \times 10^{12}$	τ	$k \times 10^{12}$	τ	$k \times 10^{10}$	τ	$k \times 10^{12}$	τ	$k \times 10^{18}$	τ
<i>Alkanes</i>										
Ethane	0.24	48 d	$< 1.0 \times 10^{-5}$	$> 13 \text{ y}$	0.57	6.7 mo	3.1×10^{-7}	$1.0 \times 10^6 \text{ y}^2$	< 0.01	$> 3.2 \text{ y}$
Propane	1.1	11 d	0.00021	> 0.60	1.3	90 d	0	$6.5 \times 10^3 \text{ y}^2$	< 0.01	$> 3.2 \text{ y}$
2-Methylpropane	2.1	5.6 d	< 0.00007	$> 18 \text{ y}$	1.3	90 d	$< 1.0 \times$	$> 3.2 \times 10^7 \text{ y}^2$	< 0.01	$> 3.2 \text{ y}$
<i>n</i> -Butane	2.3	5.2 d	0.000046	2.8 y	2.3	50 d	$< 1.0 \times$	$> 3.2 \times 10^7 \text{ y}^2$	< 0.01	$> 3.2 \text{ y}$
2-Methylbutane	4	2.9 d	0.00016	0.79 y	2	60 d	NA	NA	NA	NA
<i>n</i> -Pentane	3.8	3.0 d	0.000081	1.6 y	2.5	46 d	NA	NA	NA	NA
2,2-Dimethylbutane	2.7	4.3 d	NA	NA	NA	NA	NA	NA	NA	NA
2,3-Dimethylbutane	6.4	1.8d	0.00041	110 d	2	60 d	0.0064	50 y	NA	NA
2-Methylpentane	5.6	2.1 d	0.000017	7.5 y	2.5	47 d	NA	NA	NA	NA
3-Methylpentane	5.8	2.0 d	0.00002	6.3 y	2.5	46d	NA	NA	NA	NA
<i>n</i> -Hexane	5.2	2.2 d	0.00011	1.2 y	3.1	38 d	NA	NA	NA	NA
2,2,4-Trimethylpentane	3.8	3.0 d	0.000075	1.7 y	2.3	50 d	0.0068	47 y	NA	NA

Table AX2-1 (cont'd). Comparison of the Atmospheric Lifetimes (τ) of Low Molecular Weight Hydrocarbons Due to Reaction with OH, NO₃, Cl, Br and O₃

Hydrocarbon	$k, \text{cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$									
	OH		NO ₃		Cl		Br		O ₃	
	$k \times 10^{12}$	τ	$k \times 10^{12}$	τ	$k \times 10^{10}$	τ	$k \times 10^{12}$	τ	$k \times 10^{18}$	τ
<i>Alkenes</i>										
Ethene	8.5	33 h	0	230 d	0.99	3.8 m	0.18	1.8 y	1.6	7.2 d
Propene	26	11 h	0.01	4.9 d	2.3	50 d	5.3	22 d	10	1.2 d
2-Methylpropene	51	5.4 h	0.34	3.3 h	0.42	9.0 m	NA	NA	11	1.1 d
1-Butene	31	9.0 h	0.013	3.6 d	1.4	65 d	3.4	34 d	9.6	1.2 d
<i>trans</i> -2-Butene	64	4.3 h	0.39	2.8 h	NA	NA	0.23	1.4 y	190	1.5 h
<i>cis</i> -2-Butene	56	5.0 h	0.35	3.2 h	NA	NA	6.3	18 d	125	2.3 h
1,3-Butadiene	67	4.1 h	0.1	11 h	4.2	28 d	57	2.0 d	6.3	1.8 d
Isoprene	100	2.8 h	0.68	1.6 h	5.1	23 d	74	1.6 d	13	21 h
2-Methyl-2-butene	87	3.2 h	9.4	0.12 h	NA	NA	19	6.1 d	400	0.69 h
1-Pentene	31	9.0 h	0.7	1.6 h	NA	NA	NA	NA	11	1.1 d
<i>trans</i> -2-Pentene	67	4.1 h	1.6	0.69 h	NA	NA	NA	NA	320	0.86 h
<i>cis</i> -2-Pentene	65	4.3 h	1.4	0.79 h	NA	NA	NA	NA	210	1.3 h
2,4,4-Trimethyl-1-pentene	65	4.3 h	0.51	2.2 h	NA	NA	NA	NA	NA	NA

Notes: NA = Reaction rate coefficient not available. Rate coefficients were calculated at 298k and 1 atmosphere. y = year. d = day.

OH = $1 \times 10^6/\text{cm}^3$; NO₃ = $2.5 \times 10^8/\text{cm}^3$; Cl = $1 \times 10^3/\text{cm}^3$; Br = $1 \times 10^5/\text{cm}^3$; O₃ = $1 \times 10^{12}/\text{cm}^3$. Value for Br calculated based on equilibrium with BrO = 1 ppt.

¹ Rate Coefficients were Obtained from the NIST Online Kinetics Database for Reactions of Alkanes and for all Cl and Br Reactions.

All Other Rate Coefficients were Obtained from the Evaluation of Calvert et al. (2000).

² Lifetimes should be regarded as lower limits.

Sources: NIST online kinetics database (<http://kinetics.nist.gov/index.php>).

The O(³P) atoms formed directly in the photolysis of O₃ in the Huggins and Chappuis bands or formed from deactivation of O(¹D) atoms reform O₃ through reaction AX2-2. Hydroxyl radicals produced by reactions AX2-5 and AX2-6 can react further with species such as carbon monoxide and with many hydrocarbons (for example, CH₄) to produce HO₂ radicals.

Measurements of OH radical concentrations in the troposphere (Poppe et al., 1995; Eisele et al., 1997; Brune et al., 1999; Martinez et al., 2003; Ren et al., 2003) show that, as expected, the OH radical concentrations are highly variable in space and time, with daytime maximum concentrations of $> 3 \times 10^6$ molecules /cm³ in urban areas. A global, mass-weighted mean tropospheric OH radical concentration also can be derived from the estimated emissions and measured atmospheric concentrations of methylchloroform (CH₃CCl₃) and the rate constant for the reaction of the OH radical with CH₃CCl₃. Krol et al. (1998) derived a global average OH concentration of 1.07×10^6 molecules /cm³ for 1993 along with an upward trend of about 0.5%/yr between 1978 and 1993. Using an integrated data set of observed O₃, H₂O, NO_y, CO, VOCs, temperature and cloud optical depth, Spivakovsky et al. (2000) calculated a global annual mean OH concentration of 1.16×10^6 molecules cm⁻³, consistent to within 10% of the value obtained by Krol et al. (1998).

HO₂ radicals do not initiate the oxidation of hydrocarbons, but serve to recycle OH mainly by way of reaction with NO, O₃, and itself (the latter produces H₂O₂, which can photolyze to yield OH). The HO₂ radicals also react with organo-peroxy radicals produced during the oxidation of VOCs to form organo-peroxides (cf., Section AX2.2.5, reaction AX2-20). Organo-peroxides undergo wet or dry deposition (Wesely and Hicks, 2000) or degrade further by photolysis and reaction with OH (Jet Propulsion Laboratory, 2003).

At night, NO₃ assumes the role of primary oxidant (Wayne et al., 1991). Although it is generally less reactive than OH, its high abundance in the polluted atmosphere compensates for its lower reactivity. For several VOCs, however, including dimethylsulfide, isoprene, some terpenes (α -pinene, limonene, linalool) and some phenolic compounds (phenol, *o*-cresol), oxidation by NO₃ at night is competitive with oxidation by OH during the day, making it an important atmospheric removal mechanism for these compounds (Wayne et al., 1991) (see Table AX2-1). The role of NO₃ radicals in the chemistry of the remote marine boundary layer has been examined recently by Allen et al., (2000) and in the polluted continental boundary layer by Geyer and Platt (2002).

Cl atoms, derived from products of multiphase processes can initiate the oxidation of most of the same VOCs as OH radicals, however, the rate coefficients for the reactions of alkanes with Cl atoms are usually much higher. Cl will also oxidize alkenes and aromatic compounds, but with a significantly lower rate constant than for OH reactions. Following the initial reaction with Cl, the degradation of the hydrocarbon proceeds as with OH and NO₃, generating an enhanced supply of odd hydrogen radicals leading to O₃ production in the presence of sufficient NO_x. The corresponding reactions of Br with hydrocarbons proceed in a similar manner, but with rate coefficients that can be substantially lower or higher.

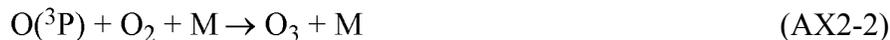
Chlorine and bromine radicals will also react directly with O₃ to form ClO and BrO radicals, providing a sink for odd oxygen if they do not react with NO to form NO₂ (e.g., Pszenny et al., 1993). As with other oxidants present in the atmosphere, Cl chemistry provides a modest net sink for O₃ when NO_x is less than 20 pptv, and is a net source at higher NO_x. Kasting and Singh (1986) estimated that as much as 25% of the loss of nonmethane hydrocarbons in the nonurban atmosphere can occur by reaction with Cl atoms, based on the production of Cl atoms from gas phase photochemical reactions involving chlorine containing molecules (HCl, CH₃Cl, CHCl₃, etc.). Elevated concentrations of atomic Cl and other halogen radicals can be found in polluted coastal cities where precursors are emitted directly from industrial sources and/or are produced via acid-catalyzed reactions involving sea-salt particles (Tanaka et al., 2000; Spicer et al., 2001).

Substantial chlorine-VOC chemistry has been observed in the cities of Houston and Beaumont/Port Arthur, Texas (Tanaka et al., 2000; Chang et al., 2002; Tanaka et al., 2003). Industrial production activities in those areas frequently result in large releases of chlorine gas (Tanaka et al., 2000). Chloromethylbutenone (CMBO), the product of the oxidation of isoprene by atomic Cl and a unique marker for chlorine radical chemistry in the atmosphere (Nordmeyer et al., 1997), has been found at significant mixing ratios (up to 145 pptv) in ambient Houston air (Riemer and Apel, 2001). However, except for situations in which there are strong local sources such as these, the evidence for the importance of Cl as an oxidizing agent is mixed. Parrish et al. (1992, 1993) argued that ratios of selected hydrocarbons measured at Pt. Arena, CA were consistent with loss by reaction with OH radicals and that any deviations could be attributed to mixing processes. Finlayson-Pitts (1993), on the other hand had suggested that these deviations could have been the result of Cl reactions. McKeen et al. (1996) suggested that hydrocarbon

ratios measured downwind of anthropogenic source regions affecting the western Pacific Basin are consistent with loss by reaction with OH radicals only. Rudolph et al. (1997), based on data for several pairs of hydrocarbons collected during a cruise in the western Mediterranean Sea, the eastern mid- and North Atlantic Ocean and the North Sea during April and May of 1991, also found that ratios of hydrocarbons to each other are consistent with their loss given mainly by reaction with OH radicals without substantial contributions from reactions with Cl. Their best estimate, for their sampling conditions was a ratio of Cl to OH of about 10^{-3} , implying a concentration of Cl of about $10^3/\text{cm}^3$ using the globally averaged OH concentration of about $10^6/\text{cm}^3$ given above. In contrast Wingenter et al. (1996) and Singh et al. (1996a) inferred significantly higher concentrations of atomic Cl (10^4 to 10^5 cm^{-3}) based on relative concentration changes in VOCs measured over the eastern North Atlantic and Pacific Oceans, respectively. Similar approaches employed over the high-latitude southern ocean yielded lower estimates of Cl concentrations (10^3 cm^{-3} ; Wingenter et al., 1999). Taken at face value, these observations indicate substantial variability in Cl concentrations and uncertainty in “typical” values.

AX2.2.4 Chemistry of Nitrogen Oxides in the Troposphere

In the troposphere, NO, NO₂, and O₃ are interrelated by the following reactions:



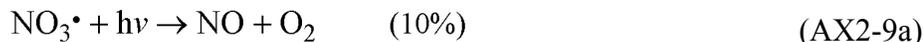
The reaction of NO₂ with O₃ leads to the formation of the nitrate (NO₃) radical,



which in the lower troposphere is nearly in equilibrium with dinitrogen pentoxide (N₂O₅):



However, because the NO_3 radical photolyzes rapidly (with a lifetime of ≈ 5 s for an overhead sun [Atkinson et al., 1992]),



its concentration remains low during daylight hours, but can increase after sunset to nighttime concentrations of $< 5 \times 10^7$ to 1×10^{10} molecules cm^{-3} (< 2 to 430 ppt) over continental areas influenced by anthropogenic emissions of NO_x (Atkinson et al., 1986). This leads to an increase of N_2O_5 concentrations during the night by reaction (AX2-8).

The tropospheric chemical removal processes for NO_x involve the reaction of NO_2 with the OH radical and the hydrolysis of N_2O_5 in aqueous aerosol solutions to produce HNO_3 .



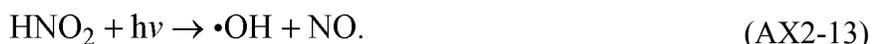
The gas-phase reaction of the OH radical with NO_2 initiates the major and ultimate removal process for NO_x in the troposphere. This reaction removes radicals (OH and NO_2) and competes with hydrocarbons for OH radicals in areas characterized by high NO_x concentrations, such as urban centers (see Section AX2.4). In addition to gas-phase nitric acid, Golden and Smith (2000) have concluded that, pernitrous acid (HOONO) is also produced by the reaction of NO_2 and OH radicals on the basis of theoretical studies. However, a recent assessment (Jet Propulsion Laboratory, 2003) has concluded that this channel represents a minor yield (approximately 15% at the surface). HOONO will thermally decompose or photolyze. Gas-phase HNO_3 formed from reaction AX2-10 undergoes wet and dry deposition to the surface and uptake by ambient aerosol particles. The tropospheric lifetime of NO_x due to reaction AX2-10 ranges from a few hours to a few days. Geyer and Platt (2002) concluded that reaction AX2-11 constituted about 10% of the removal of NO_x at a site near Berlin, Germany during

spring and summer. However, during winter the relative importance of reaction AX2-11 could be much higher because of the much lower concentration of OH radicals and the enhanced stability of N₂O₅ due to lower temperatures and intensity of sunlight. Note that reaction AX2-11 surely proceeds as a heterogeneous reaction.

OH radicals also can react with NO to produce nitrous acid (HNO₂):



In the daytime, HNO₂ is rapidly photolyzed back to the original reactants:



At night, HNO₂ can be formed by heterogeneous reactions of NO₂ in aerosols or at the earth's surface (Lammel and Cape, 1996; Jacob, 2000; Sakamaki et al., 1983; Pitts et al., 1984; Svensson et al., 1987; Jenkin et al., 1988; Lammel and Perner, 1988; Notholt et al., 1992a,b). This results in accumulation of HNO₂ during nighttime. Modeling studies suggest that photolysis of this HNO₂ following sunrise, could provide an important early-morning source of OH radicals to drive O₃ formation (Harris et al., 1982).

Another important process controlling NO_x concentrations is the formation of organic nitrates. Oxidation of VOCs produces organic peroxy radicals (RO₂), as discussed in the hydrocarbon chemistry subsections to follow. Reaction of these RO₂ radicals with NO and NO₂ produces organic nitrates (RONO₂) and peroxy nitrates (RO₂NO₂):



Reaction (AX2-14) is a minor branch for the reaction of RO₂ with NO (the major branch produces RO and NO₂, as discussed in the next section). The organic nitrate yield increases with carbon number (Atkinson, 2000).

The organic nitrates may react further, depending on the functionality of the R group, but they will typically not return NO_x and can therefore be viewed as a permanent sink for NO_x . This sink is usually small compared to HNO_3 formation, but the formation of isoprene nitrates may be a significant sink for NO_x in the United States in summer (Liang et al., 1998).

The peroxy nitrates produced by (AX2-15) are thermally unstable and most have very short lifetimes (less than a few minutes) against thermal decomposition to the original reactants. They are thus not effective sinks of NO_x . Important exceptions are the peroxyacetyl nitrates (PANs) arising from the peroxyacetyl radicals RC(O)OO produced by oxidation and photolysis of carbonyl compounds. PANs have lifetimes ranging from ~1 hour at room temperature to several weeks at 250K. They can thus provide an effective sink of NO_x at cold temperatures, but also a reservoir allowing eventual release of NO_x as air masses warm, in particular by subsidence. By far the most important of these PANs compounds is peroxyacetyl nitrate (PAN), with formula $\text{CH}_3\text{C(O)OONO}_2$. PAN is a significant product in the oxidation of most VOCs. It is now well established that PAN decomposition provides a major source of NO_x in the remote troposphere (Staudt et al., 2003). PAN decomposition in subsiding Asian air masses over the eastern Pacific could make an important contribution to O_3 enhancement in the U.S. from Asian pollution (Hudman et al., 2004).

AX2.2.5 The Methane Oxidation Cycle

The photochemical cycles leading to O_3 production are best understood by considering the oxidation of methane, structurally the simplest VOC. The CH_4 oxidation cycle serves as a model which describes the chemistry of the relatively clean or unpolluted troposphere (although this is a simplification because vegetation releases large quantities of complex VOCs into the atmosphere). Although the chemistry of the VOCs emitted from anthropogenic and biogenic sources in polluted urban and rural areas is more complex, a knowledge of the CH_4 oxidation reactions aids in understanding the chemical processes occurring in the polluted atmosphere because the underlying chemical principles are the same.

Methane is emitted into the atmosphere as the result of anaerobic microbial activity in wetlands, rice paddies, the guts of ruminants, landfills, and from mining and combustion of fossil fuels (Intergovernmental Panel on Climate Change, 2001). The major tropospheric removal process for CH_4 is by reaction with the OH radical,



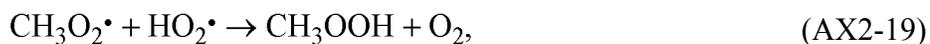
In the troposphere, the methyl radical reacts solely with O_2 to yield the methyl peroxy ($\text{CH}_3\text{O}_2\cdot$) radical (Atkinson et al., 1992):



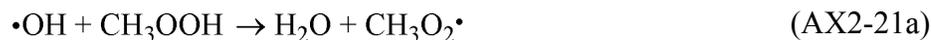
In the troposphere, the methyl peroxy radical can react with NO , NO_2 , HO_2 radicals, and other organic peroxy (RO_2) radicals, with the reactions with NO and HO_2 radicals being the most important (see, for example, World Meteorological Organization, 1990). The reaction with NO leads to the formation of the methoxy ($\text{CH}_3\dot{\text{O}}$) radical,



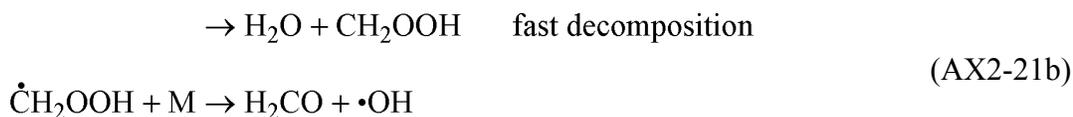
The reaction with the HO_2 radical leads to the formation of methyl hydroperoxide (CH_3OOH),



which can photolyze or react with the OH radical (Atkinson et al., 1992):



or



Methyl hydroperoxide is much less soluble than hydrogen peroxide (H_2O_2), and so wet deposition after incorporation into cloud droplets is much less important as a removal process than it is for H_2O_2 . CH_3OOH can also be removed by dry deposition to the surface or transported by convection to the upper troposphere. The lifetime of CH_3OOH in the troposphere due to photolysis and reaction with the OH radical is estimated to be ≈ 2 days. Methyl hydroperoxide is then a temporary sink of radicals, with its wet or dry deposition representing a loss process for tropospheric radicals.

The only important reaction for the methoxy radical ($\text{CH}_3\dot{\text{O}}$) is



The HO_2 radicals produced in (AX2-22) can react with NO, O_3 , or other HO_2 radicals according to,



Formaldehyde (H_2CO) produced in reaction AX2-22 can be photolyzed:



Formaldehyde also reacts with the OH radical,



The H atom and HĊO (formyl) radical produced in these reactions react solely with O₂ to form the HO₂ radical:



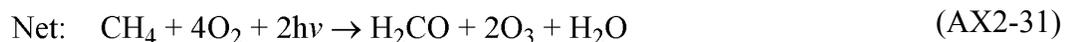
The lifetimes of H₂CO due to photolysis and reaction with OH radicals are ≈4 h and 1.5 days, respectively, leading to an overall lifetime of slightly less than 4 hours for H₂CO for overhead sun conditions (Rogers, 1990).

The final step in the oxidation of CH₄ involves the oxidation of CO by reaction with the OH radical to form CO₂:



The lifetime of CO in the lower troposphere is ≈2 months at midlatitudes.

NO and HO₂ radicals compete for reaction with CH₃O₂ and HO₂ radicals, and the reaction route depends on the rate constants for these two reactions and the tropospheric concentrations of HO₂ and NO. The rate constants for the reaction of the CH₃O₂· radicals with NO (reaction AX2-18) and HO₂ radicals (reaction AX2-19) are of comparable magnitude (e.g., Jet Propulsion Laboratory, 2003). Based on expected HO₂ radical concentrations in the troposphere, Logan et al. (1981) calculated that the reaction of the CH₃O₂· radical with NO dominates for NO mixing ratios of >30 ppt. For NO mixing ratios <30 ppt, the reaction of the CH₃O₂· radical with HO₂ dominates. The overall effects of methane oxidation on O₃ formation for the case when NO >30 ppt can be written as:



Further O₃ formation occurs, based on the subsequent reactions of H₂CO, e.g.,



Reactions in the above sequence lead to the production of two OH radicals which can further react with atmospheric constituents (e.g., Crutzen, 1973). There is also a less important pathway:



These reaction sequences are important for tropospheric chemistry because formaldehyde is an intermediate product of the oxidation of most VOCs. The reaction of O_3 and HO_2 radicals leads to the net destruction of tropospheric O_3 :



Using the rate constants reported for reactions AX2-23 and AX2-24 (Atkinson et al., 1992) and the background tropospheric O_3 mixing ratios given above, the reaction of HO_2 radicals with NO dominates over reaction with O_3 for NO mixing ratios >10 ppt. The rate constant for reaction AX2-25 is such that an NO mixing ratio of this magnitude also means that the HO_2 radical reaction with NO will be favored over the self-reaction of HO_2 radicals.

Consequently, there are two regimes in the “relatively clean” troposphere, depending on the local NO concentration: (1) a “very low- NO_x ” regime in which HO_2 and CH_3O_2 radicals combine (reaction AX2-19), and HO_2 radicals undergo self-reaction (to form H_2O_2) and react with O_3 (reactions AX2-25 and AX2-24), leading to net destruction of O_3 and inefficient OH radical regeneration (see also Ehhalt et al., 1991; Ayers et al., 1992); and (2) a “low- NO_x ” regime (by comparison with much higher NO_x concentrations found in polluted areas) in which HO_2 and CH_3O_2 radicals react with NO to convert NO to NO_2 , regenerate the OH radical,

and, through the photolysis of NO_2 , produce O_3 . In the “low NO_x ” regime there still may be significant competition from peroxy-peroxy reactions, depending on the local NO concentration.

Nitric oxide mixing ratios are sufficiently low in the remote marine boundary layer relatively unaffected by transport of NO_x from polluted continental areas (< 15 ppt) that oxidation of CH_4 will lead to net destruction of O_3 , as discussed by Carroll et al. (1990) and Ayers et al. (1992). In continental and marine areas affected by transport of NO_x from combustion sources, NO mixing ratios are high enough (of the order of ~one to a few hundred ppt) for the oxidation of CH_4 , nonmethane hydrocarbons (NMHCs) and CO to lead to net O_3 formation (e.g., Carroll et al., 1990; Dickerson et al., 1995). Generally, NO mixing ratios increase with altitude and can be of the order of fifty to a few hundred ppt in the upper troposphere depending on location. The oxidation of peroxides, carbon monoxide and acetone transported upward by convection, in the presence of this NO , can lead to local O_3 formation (e.g., Singh et al., 1995; McKeen et al., 1997; Wennberg et al., 1998; Brühl et al., 2000).

AX2.2.6 The Atmospheric Chemistry of Alkanes

The same basic processes by which CH_4 is oxidized occur in the oxidation of other, even more reactive and more complex VOCs. As in the CH_4 oxidation cycle, the conversion of NO to NO_2 during the oxidation of VOCs results in the production of O_3 and the efficient regeneration of the OH radical, which in turn can react with other VOCs (Figure AX2-2). The chemistry of the major classes of VOCs important for O_3 formation such as alkanes, alkenes (including alkenes from biogenic sources), and aromatic hydrocarbons will be summarized in turn.

Reaction with OH radicals represents the main loss process for alkanes and as also mentioned earlier, reaction with nitrate and chlorine radicals are additional sinks for alkanes. For alkanes having carbon-chain lengths of four or less, the chemistry is well understood and the reaction rates are slow in comparison to alkenes and other VOCs of similar structure and molecular weight. See Table AX2-1 for a comparison of reaction rate constants for several small alkanes and their alkene and diene homologues. For alkanes larger than C_5 , the situation is more complex because the products generated during the degradation of these compounds are usually not well characterized. Branched alkanes have rates of reaction that are highly

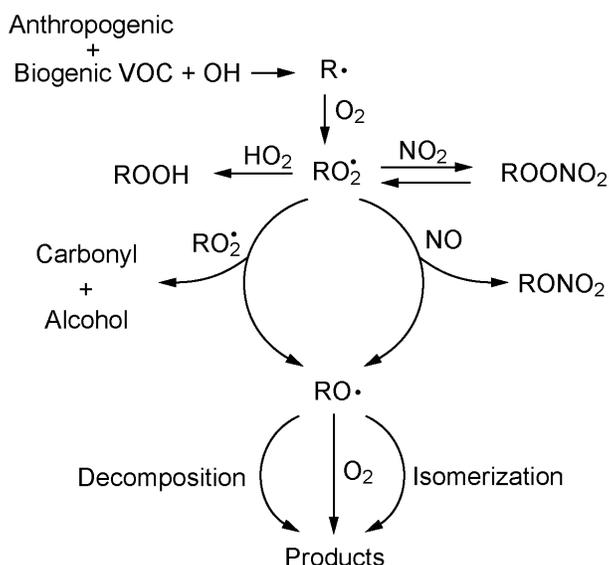


Figure AX2-2. General chemical mechanism for the oxidative degradation of VOCs.

Source: Atkinson (2000).

dependent on carbon backbone structure. Stable products of alkane photooxidation are known to include carbonyl compounds, alkyl nitrates, and hydroxycarbonyls.

Alkyl nitrates form primarily as an alternate product of reaction AX2-34 (below). Several modeling studies have predicted that large fractions of NO_y exist as alkyl and hydroxy alkyl nitrates (Calvert and Madronich, 1987; Atherton and Penner, 1988; Trainer et al., 1991). In NO_x- and VOC-rich urban atmospheres, 100 different alkyl and 74 different hydroxy alkyl nitrate compounds have been predicted and identified (Calvert and Madronich, 1987; Schneider and Ballschmiter, 1999; Schneider et al., 1998). Uncertainties in the atmospheric chemistry of the alkanes include the branching ratio of reaction AX2-34, i.e., the extent to which alkyl nitrates form versus RO and NO₂. These uncertainties affect modeling predictions of NO_x concentrations, NO-to-NO₂ conversion and O₃ formation during photochemical degradation of the VOCs. Discrepancies between observations and theory have been found in aircraft measurements of NO_y (Singh et al., 1996b). Recent field studies conducted by Day et al. (2003) have shown that large fractions of organic nitrates, which may be associated with isoprene

oxidation products, are present in urban and rural atmosphere that have not been previously measured and considered in NO_y calculations to date.

Alcohols and ethers in ambient air react almost exclusively with the OH radical, with the reaction proceeding primarily via H-atom abstraction from the C–H bonds adjacent to the oxygen-containing function group in these compounds (Atkinson and Arey, 2003).

The following list of general reactions, analogous to those described for methane, summarizes the role of alkane oxidation in tropospheric O_3 formation.



The oxidation of alkanes can also be initiated by other oxidizing agents such as NO_3 and Cl radicals. In this case, there is net production of an OH radical which can reinitiate the oxidation sequence. The reaction of OH radicals with aldehydes forms acyl ($\text{R}'\text{CO}$) radicals, and acyl peroxy radicals ($\text{R}'\text{C}(\text{O})\text{O}_2$) are formed by the addition of O_2 . As an example, the oxidation of ethane ($\text{C}_2\text{H}_5\text{-H}$) yields acetaldehyde ($\text{CH}_3\text{-CHO}$). Acetyl ($\text{CH}_3\text{-CO}$) and acetylperoxy ($\text{CH}_3\text{-C}(\text{O})\text{O}_2$) radicals can then be formed. Acetylperoxy radicals can combine with NO_2 to form peroxyacetyl nitrate (PAN) via:



PAN can act as a temporary reservoir for NO_2 . Upon the decomposition of PAN, either locally or elsewhere, NO_2 is released to participate in the O_3 formation process again. During the oxidation of propane, the relatively long-lived intermediate acetone ($\text{CH}_3\text{-C(O)CH}_3$) is formed, as shown in Figure AX2-3. The photolysis of acetone can be an important source of OH radicals, especially in the upper troposphere (e.g., Singh et al., 1995). Examples of oxidation mechanisms of more complex alkanes and other classes of hydrocarbons can be found in comprehensive texts such as Seinfeld and Pandis (1998).

AX2.2.7 The Atmospheric Chemistry of Alkenes

As shown in Figure AX2-3, the presence of a double carbon-carbon bond, i.e., $> \text{C} = \text{C} <$, in a VOC can greatly increase the range of potential reaction intermediates and products, complicating the prediction of O_3 production. The alkenes emitted from anthropogenic sources are mainly ethene, propene, and the butenes, with lesser amounts of the $\geq \text{C}_5$ alkenes. The major biogenic alkenes emitted from vegetation are isoprene (2-methyl-1,3-butadiene) and $\text{C}_{10}\text{H}_{16}$ monoterpenes (Atkinson and Arey, 2003), and their tropospheric chemistry is currently the focus of much attention (Zhang et al., 2002; Sauer et al., 1999; Geiger et al., 2003; Sprengnether et al., 2002; Witter et al., 2002; Bonn and Moortgat, 2003; Berndt et al., 2003; Fick et al., 2003; Kavouras et al., 1999; Atkinson and Arey, 2003).

Alkenes react in ambient air with OH and NO_3 radicals and with O_3 . The mechanisms involved in their oxidation have been discussed in detail by Calvert et al. (2000). All three processes are important atmospheric transformation processes, and all proceed by initial addition to the $> \text{C} = \text{C} <$ bonds or, to a much lesser extent, by H atom extraction. Products of alkene photooxidation include carbonyl compounds, hydroxy alkyl nitrates and nitratocarbonyls, and decomposition products from the high energy biradicals formed in alkene- O_3 reactions. Table AX2-2 provides estimated atmospheric lifetimes for biogenic alkenes with respect to oxidation by OH, NO_3 and O_3 . The structures of most of the compounds given in Table AX2-2 are shown in Figure AX2-4.

Uncertainties in the atmospheric chemistry of the alkenes concern the products and mechanisms of their reactions with O_3 , especially the yields of OH radicals, H_2O_2 , and secondary organic aerosol in both outdoor and indoor environments. However, many product analyses of important biogenic and anthropogenic alkenes in recent years have aided in the narrowing of

Table AX2-2. Calculated Atmospheric Lifetimes of Biogenic Volatile Organic Compounds (adapted from Atkinson and Arey, 2003) ^a

Biogenic VOC	Lifetime for Reaction with		
	OH ^b	O ₃ ^c	NO ₃ ^d
Isoprene	1.4 h	0.92 d	1.6 h
<i>Monoterpenes</i>			
Camphene	2.6 h	13 d	1.7 h
2-Carene	1.7 h	1.2 h	4 min
3-Carene	16 h	8.0 h	7 min
Limonene	49 min	1.4 h	5 min
Myrcene	39 min	35 min	6 min
<i>cis-/trans</i> -Ocimene	33 min	31 min	3 min
α -Phellandrene	27 min	5.6 min	0.9 min
β -Phellandrene	50 min	5.9 h	8 min
α -Pinene	2.6 h	3.2 h	11 min
β -Pinene	1.8 h	0.77 d	27 min
Sabinene	1.2 h	3.4 h	7 min
α -Terpinene	23 min	0.7 min	0.5 min
γ -Terpinene	47 min	2.0 h	2 min
Terpinolene	37 min	9.1 min	0.7 min
<i>Sesquiterpenes</i>			
β -Caryophyllene	42 min	1.4 min	3 min
α -Cedrene	2.1 h	9.8 h	8 min
α -Copaene	1.5 h	1.8 h	4 min
α -Humulene	28 min	1.4 min	2 min
Longifolene	2.9 h	> 23 d	1.6 h
<i>Oxygenates</i>			
Acetone ^e	61 d ^f	> 3.2 y ^g	> 8 y ^f
Camphor	2.5 d ^h	> 165 d ^h	> 300 d ^h
1,8-Cineole	1.0 d ⁱ	> 77 d ^j	1.5 y ⁱ
<i>cis</i> -3-Hexen-1-ol	1.3 h ^k	4.3 h ^k	4.1 h ^k
<i>cis</i> -3-Hexenyl acetate	18 h ^k	5.1 h ^k	4.5 h ^k
Linalool	52 min ^k	39 min ^k	6 min ^k

Table AX2-2 (cont'd). Calculated Atmospheric Lifetimes of Biogenic Volatile Organic Compounds (adapted from Atkinson and Arey, 2003)^a

Biogenic VOC	Lifetime for Reaction with		
	OH ^b	O ₃ ^c	NO ₃ ^d
<i>Oxygenates</i> (cont'd)			
Methanol	12 d ^f	> 3.2 y ^g	2.0 y ^f
2-Methyl-3-buten-2-ol	2.4 h ^l	1.2 d ^m	7.7 d ⁿ
6-Methyl-5-hepten-2-one	53 min ^o	0.7 h ^o	9 min ^o

^a Rate coefficients from Calvert et al. (2000) unless noted otherwise.

^b Assumed OH radical concentration: 1.0×10^6 molecule cm⁻³.

^c Assumed O₃ concentration: 1×10^{12} molecule cm⁻³, 24-h average.

^d Assumed NO₃ radical concentration: 2.5×10^8 molecule cm⁻³, 12-h nighttime average.

^e Photolysis will also occur with a calculated photolysis lifetime of ~60 day for the lower troposphere, July, 40° N (Meyrahn et al., 1986).

^f Atkinson et al. (1999).

^g Estimated.

^h Reissell et al. (2001).

ⁱ Corchnoy and Atkinson (1990).

^j Atkinson et al. (1990).

^k Atkinson et al. (1995).

^l Papagni et al. (2001).

^m Grosjean and Grosjean (1994).

ⁿ Rudich et al. (1996).

^o Smith et al. (1996).

these uncertainties. The reader is referred to extensive reviews by Calvert et al. (2000) and Atkinson and Arey (2003) for detailed discussions of these products and mechanisms.

Oxidation by OH

As noted above, the OH radical reactions with the alkenes proceed mainly by OH radical addition to the > C = C < bonds. As shown in Figure AX2-3, for example, the OH radical reaction with propene leads to the formation of two OH-containing radicals. The subsequent reactions of these radicals are similar to those of the alkyl radicals formed by H-atom abstraction from the alkanes. Under high NO conditions, CH₃CHCH₂OH continues to react — producing several smaller, “second generation,” reactive VOCs.

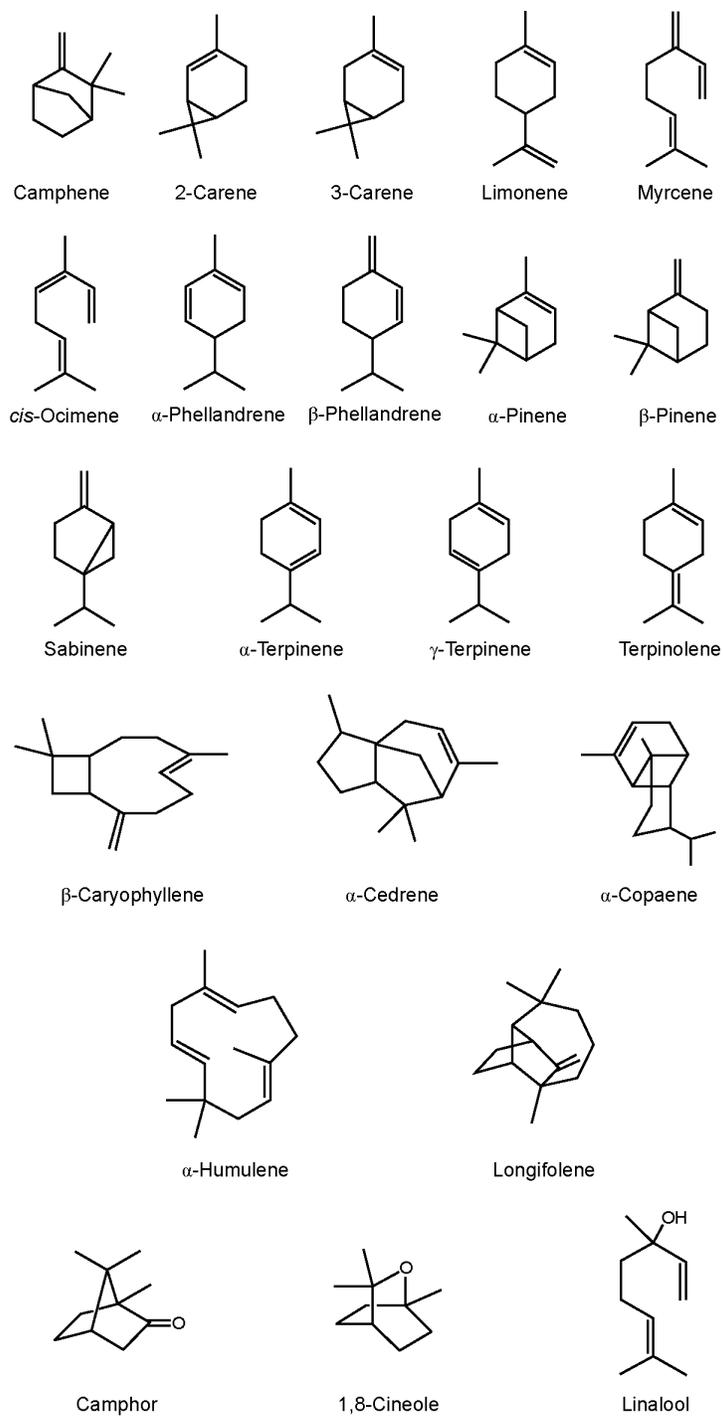


Figure AX2-4. Structures of a selected number of terpene and sesquiterpene compounds.

Source: Atkinson and Arey (2003).

For the simple $\leq C_4$ alkenes, the intermediate OH-containing radicals appear to undergo mainly decomposition at room temperature and atmospheric pressure. Hence, for propene, the “first-generation” products of the OH radical reaction in the presence of NO are HCHO and CH_3CHO , irrespective of which OH-containing radical is formed.

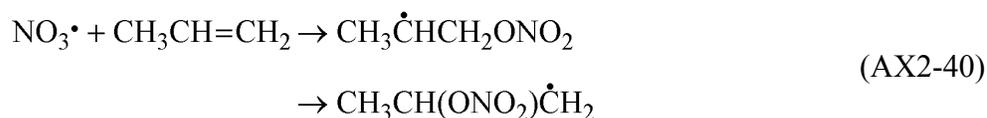
For the more complex alkenes of biogenic origin, multiple products may be possible from the initial oxidation step. Each product will further react, following a distinct degradation pathway. Formaldehyde (HCHO), methacrolein ($CH_2 = C(CH_3)-CHO$) and methyl vinyl ketone ($CH_3-C(O)-CH=CH_2$) have been identified as the major products of the OH-isoprene reaction. These products also react with OH radicals and undergo photolysis. Yields of these products (and others) are sensitive to the concentration of NO_x used in laboratory experiments. For $NO_x \sim 100$ ppt, methacrolein, methyl vinyl ketone and formaldehyde are formed with yields of roughly 20%, 16%, and 33% and yields of other carbonyl compounds are about 17%, based on the results of Ruppert and Becker (2000) and references therein. Ruppert and Becker also observed much lower yields of C5-unsaturated diols (2 to 5%), methanol and methyl hydroperoxide indicating the presence of peroxy radical interactions. For $NO_x \sim 1$ ppb, the yields of methacrolein are similar to those for $NO_x \sim 100$ ppb, but the yields of methyl vinyl ketone ($\sim 33\%$), formaldehyde ($\sim 60\%$) are much higher and the diols, methanol and methyl hydroperoxide were not observed. Orlando et al. (1999) found that the major products of the oxidation of methacrolein were CO, CO_2 , hydroxyacetone, formaldehyde and methacryloylperoxynitrate (MPAN) in their experiment. Horowitz et al. (1998) suggested that isoprene may be the principal precursor of PAN over the United States in summer. Hydroperoxy and organic peroxy radicals formed during the oxidation of isoprene and its products can oxidize NO to NO_2 , initiating photochemical O_3 formation. It should be noted that only about two-thirds of the carbon in isoprene can be accounted for on a carbon atom basis for $NO_x \geq 1$ ppb. The values are much lower for lower NO_x concentrations. The situation is much better for methacrolein. Observed products can account for more than 90% of the reacted carbon.

The rates of formation of condensable, oxidation products of biogenic compounds that may contribute to secondary organic aerosol formation is an important matter for the prediction of ambient aerosol concentrations. Claeys et al. (2004a,b) found that 2-methyltetrols are formed from the oxidation of isoprene in yields of about 0.2% on a molar basis, or 0.4% on a mass basis.

These are semivolatile compounds that can condense on existing particles. On the other hand, pinene oxidation leads to substantial organic aerosol formation.

Oxidation by Nitrate Radical

NO₃ radical reacts with alkenes mainly by addition to the double bond to form a β-nitrooxyalkyl radical (Atkinson 1991, 1994, 1997). The abstraction pathway may account for up to 20% of the reaction. For propene, the initial reaction is followed by a series of reactions



that (Atkinson, 1991) to lead to the formation of, among others, carbonyls and nitrate-carbonyls including formaldehyde (HCHO), acetaldehyde (CH₃CHO), 2-nitratopropanal (CH₃CH(ONO₂)CHO), and 1-nitratopropanone (CH₃C(O)CH₂ONO₂). By analogy to OH, conjugated dienes like butadiene and isoprene will react with NO₃ to form β-nitrooxyalkyl radicals (Atkinson, 2000). If NO₃ is available for reaction in the atmosphere, then NO concentrations will be low, owing to the rapid reaction between NO₃ and NO. Consequently, nitrooxyalkyl peroxy radicals are expected to react primarily with NO₂, yielding thermally unstable peroxy nitrates, NO₃, HO₂, and organoperoxy radicals (Atkinson, 2000).

Several studies have undertaken the quantification of the products of NO₃⁻ initiated degradation of several of the important biogenic alkenes in O₃ and secondary organic aerosol formation, including isoprene, α- and β-pinene, 3-carene, limonene, linalool, and 2-methyl-3-buten-2-ol. See Figure AX2-4 for the chemical structures of these and other biogenic compounds. The results of these studies have been tabulated by Atkinson and Arey (2003).

Oxidation by Ozone

Unlike other organic compounds in the atmosphere, alkenes react at significant rates with O₃. Ozone initiates the oxidation of alkenes by addition across carbon-carbon double bonds, at rates that are competitive with reaction with OH (see Table AX2-1). The addition

of O₃ across the double bond yields an unstable ozonide, a 5-member ring including a single carbon-carbon bond linked to the three oxygen atoms, each singly bound. The ozonide rearranges spontaneously and then fragments to form an aldehyde or ketone, depending on the original position of the double bond, and a high energy Criegee biradical. Collisional energy transfer may stabilize the radical, preventing it from decomposing. Low pressure studies of the decomposition of the Criegee biradical have shown high yields of the OH radical. At atmospheric pressures, the rates of OH production have not been reliably established, due to complications arising from subsequent reactions of the OH produced with the ozonide fragments (Calvert et al., 2000).

The ozonolysis of larger biogenic alkenes yields high molecular weight oxidation products with sufficiently low vapor pressures to allow condensation into the particle phase. Many oxidation products of larger biogenic alkenes have been identified in ambient aerosol, eliminating their further participation in O₃ production. Figure AX2-5 shows the chemical structures of the oxidation products of α-pinene and illustrates the complexity of the products. Carbonyl containing compounds are especially prevalent. A summary of the results of product yield studies for several biogenic alkenes can be found in Atkinson and Arey (2003).

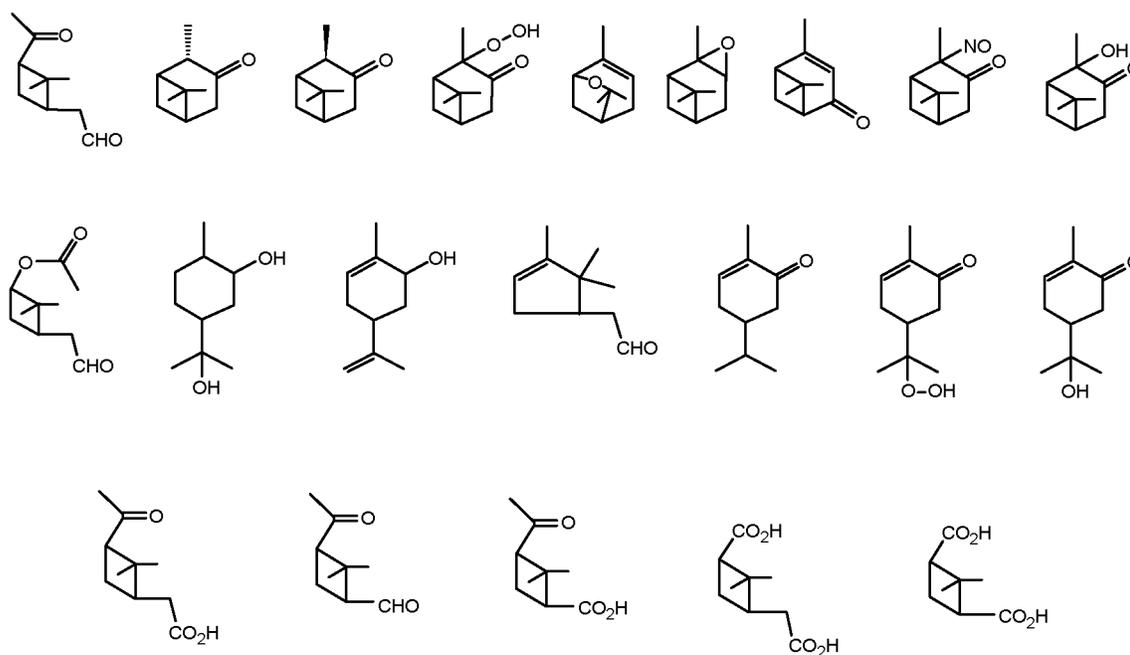


Figure AX2-5. Products from the reaction of terpenes with O₃.

Source: Atkinson and Arey (2003).

NO₂ also participates to a very small degree in the oxidation of alkenes by addition to double bonds in a manner similar to O₃. Rate constants for reactions of this type range from 10⁻¹⁸ to 10⁻²⁴ for dienes and monoalkenes (King et al., 2002). It should also be noted that O₃ reacts with terpenoid compounds released from household products such as air fresheners and cleaning agents in indoor air to produce ultrafine particles (Wainman et al., 2000; Sarwar et al., 2002)

AX2.2.8 The Atmospheric Chemistry of Aromatic Hydrocarbons

Aromatic hydrocarbons represent a major class of compounds found in gasoline and other liquid fuels. Upon vaporization, most of these compounds react rapidly in the atmosphere (Davis et al., 1975) and following a series of complex processes, involving molecular oxygen and oxides of nitrogen, produce O₃. Reaction with OH radicals serves as the major atmospheric loss process of aromatic hydrocarbons. Atmospheric losses of alkyl aromatic compounds by O₃ and nitrate radicals have been found to be minor processes for most monocyclic aromatic hydrocarbons. (However, the reaction with of the nitrate radical with substituted hydroxybenzenes, such as phenol or *o*-, *m*-, *p*-cresol, can be an important atmospheric loss process for these compounds.) Much of the early work in this field focused on the temperature dependence of the OH reactions (Perry et al., 1977; Tully et al., 1981) using absolute rate techniques. Typically two temperature regions were observed for a large number of aromatic compounds and the complex temperature profile suggested that two mechanisms were operative. In the high temperature region, hydrogen (H)-atom abstraction from the aromatic ring dominates, and in the temperature regime less than 320K, OH addition to the aromatic ring is the dominant process. Thus, at normal temperatures and pressures in the lower troposphere, ring addition is the most important reactive process followed by H-atom abstraction from any alkyl substituents. The kinetics of monocyclic aromatic compounds are generally well understood and there is generally broad consensus regarding the atmospheric lifetimes for these compounds. By contrast, there is generally a wide range of experimental results from product studies of these reactions. This leads to a major problem in model development due to a general lack of understanding of the product identities and yields for even the simplest aromatic compounds, which is due to the complex reaction paths following initial reaction with OH, primarily by the addition pathway.

Two comprehensive reviews, which provide a detailed understanding of the current state-of-science of aromatic hydrocarbons have been written in the past five years. Atkinson (2000) reviewed the atmospheric chemistry of volatile organic compounds, of which aromatic hydrocarbons are included in one section of the review. More recently Calvert et al. (2002) conducted a highly comprehensive examination of the reaction rates, chemical mechanisms, aerosol formation, and contributions to O₃ formation for monocyclic and polycyclic aromatic hydrocarbons.

AX2.2.8.1 Chemical Kinetics and Atmospheric Lifetimes of Aromatic Hydrocarbons

Rate constants for the reaction of species in the atmosphere with aromatic hydrocarbons vary widely depending on the number of aromatic rings and substituent groups. Reactions of O₃ with aromatic hydrocarbons (AHCs) are generally slow except for monocyclic aromatic hydrocarbons having unsaturated substituent groups. For example, indene and styrene have atmospheric lifetimes of 3.3 h and 23 h with respect to reaction with O₃, which are much longer than that due to reactive loss with either OH or NO₃. Thus, the atmospheric lifetimes and reaction products of O₃ and aromatic hydrocarbons will be ignored in this discussion. In addition to chemical reaction, some organic compounds photolyze in the lower atmosphere. Virtually all aromatic precursors are not subject to photolysis, although many of the ring fragmentation products having multiple carbonyl groups can photolyze in the troposphere.

The reaction rates and atmospheric lifetimes of monocyclic aromatic compounds due to reaction with OH radicals are generally dependent on the number and types of substituent groups associated with the ring. These reaction rates have been found to be highly temperature and pressure dependent. The temperature regimes are governed by the processes involved and show a quite complex appearance. At room temperature (~300 K), both addition to the aromatic ring and H-atom abstraction occur with the addition reaction being dominant. For the two smallest monocyclic aromatic hydrocarbons, the initial addition adduct is not completely stabilized at total pressures below 100 torr.

Numerous studies have been conducted to measure the OH + benzene rate constant over a wide range of temperatures and pressures. An analysis of absolute rate data taken at approximately 100 torr argon and not at the high pressure limit yielded a value of $1.2 \times 10^{-12} \text{ cm}^3$

$\text{molec}^{-1} \text{s}^{-1}$. Atkinson (1989) recommended a value of $1.4 \times 10^{-12} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$ at room temperature and atmospheric pressure. This recommendation has been refined only slightly and is reflected in the recent value recommended by Calvert et al. (2002) which is given as $1.39 \times 10^{-12} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$. This recommended value for the reaction of OH + benzene together with values for other monocyclic aromatic hydrocarbons is given in Table AX2-3.

In general, it is observed that the OH rate constants with monocyclic alkyl aromatic hydrocarbons are strongly influenced by the number of substituent groups found on the aromatic ring. (That is, the identity of the alkyl substituent groups has little influence on the overall reactions rate constant.) Single substituent single-ring aromatic compounds which include toluene, ethyl benzene, n-propylbenzene, isopropylbenzene, and t-butylbenzene have average OH reaction rate constants ranging from 4.5 to $7.0 \times 10^{-12} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$ at room temperature and atmospheric pressure. These rate constants lead to atmospheric lifetimes (see below) that are still greater than 1 day. Rate constants for monocyclic aromatic compounds with greater than 10 carbon atoms or more are generally not available.

The dominant monocyclic aromatic compounds with two substituents are *m*-, *o*-, and *p*-xylene. Their recommended OH rate constants range from 1.4 to $2.4 \times 10^{-11} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$. Similarly, the three isomers of ethyltoluene have recommended OH rate constants ranging from 1.2 to $1.9 \times 10^{-11} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$. The only other two substituent single-ring aromatic compound for which the OH rate constant has been measured is *p*-cymene (*para*-isopropyltoluene), giving a value of $1.5 \times 10^{-11} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$.

OH rate constants for the C₉ trimethyl substituted aromatic hydrocarbons (1,2,3-; 1,2,4-; 1,3,5-trimethylbenzene) are higher by a factor of approximately 2.6 over the di-substituted compounds. Rate constants for the three isomers range from 3.3 to $5.7 \times 10^{-11} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$. While concentrations for numerous other trisubstituted benzene compounds have been reported (e.g., 1,2-dimethyl-4-ethylbenzene), OH rate constants for trimethylbenzene isomers are the only trisubstituted aromatic compounds that have been reported.

Aromatic hydrocarbons having substituent groups with unsaturated carbon groups have much higher OH rate constants than their saturated analogues. The smallest compound in this group is the C₈ AHC, styrene. This compound reacts rapidly with OH and has a recommended rate constant of $5.8 \times 10^{-11} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$ (Calvert, 2002). Other methyl substituted styrene-

Table AX2-3. Hydroxyl Rate Constants and Atmospheric Lifetimes of Mono- and Di-cyclic Aromatic Hydrocarbons (adapted from Atkinson 2000)

Compound	OH Rate Constant ($\times 10^{12}$)	τ_{OH} (as indicated)
Benzene	1.4	8.3 d*
Toluene	5.6	2.1 d
Ethylbenzene	7	1.7 d
<i>n</i> -Propylbenzene	5.8	2.0 d
Isopropylbenzene	6.3	1.8 d
<i>t</i> -Butylbenzene	4.5	2.6 d
<i>o</i> -Xylene	14	20 h
<i>m</i> -Xylene	23	12 h
<i>p</i> -Xylene	14	19 h
<i>o</i> -Ethyltoluene	12	23 h
<i>m</i> -Ethyltoluene	19	15 h
<i>p</i> -Ethyltoluene	12	24 h
<i>p</i> -Cymene	14	19 h
1,2,3-Trimethylbenzene	33	8.4 h
1,2,4-Trimethylbenzene	33	8.6 h
1,3,5-Trimethylbenzene	57	4.8 h
Indan	19	15 h
Styrene ³	58	4.8 h
α -Methylstyrene	51	5.4 h
Napthalene	23	12 h
1-Methylnapthalene	53	4.8 h
2-Methylnapthalene	52	8.8 h

¹ Rate coefficients given as $\text{cm}^3/\text{molec}\cdot\text{sec}$.

² Lifetime for zero and single alkyl substituted aromatic based on OH concentration of $1 \times 10^6 \text{ molec cm}^{-3}$.

³ Lifetime for reaction of styrene with NO_3 is estimated to be 44 min based on a nighttime NO_3 concentration of $2.5 \times 10^8 \text{ molec cm}^{-3}$ and a rate coefficient of $1.5 \times 10^{-12} \text{ cm}^3/\text{molec}\cdot\text{sec}$.

type compounds (e.g., α -methylstyrene) have OH rate constants within a factor of two of that with styrene. However, for unsaturated monocyclic aromatic hydrocarbons other processes including atmospheric removal by NO₃ radicals can also be important, particularly at night when photolysis does not substantially reduce the NO₃ radical concentration (see below).

Polycyclic aromatic hydrocarbons are found to a much lesser degree in the atmosphere than are the monocyclic aromatic hydrocarbons. For example, measurements made in Boston during 1995 (Fujita et al., 1997) showed that a single PAH (naphthalene) was detected in the ambient morning air at levels of approximately 1% (C/C) of the total monocyclic aromatic hydrocarbons. 1-methyl and 2-methylnaphthalene have sufficient volatility to be present in the gas phase. Other higher molecular weight PAHs (≤ 3 aromatic rings), if present, are expected to exist in the gas phase at much lower concentrations than naphthalene and are not considered here. OH rate constants for naphthalene and the two methyl substituted naphthalene compounds have been reviewed by Calvert et al. (2002). The values recommended (or listed) by Calvert et al. (2002) are given in Table AX2-3. As seen in the monocyclic aromatic hydrocarbons, the substitution of methyl groups on the aromatic ring increases the OH rate constant, in this case by a factor of 2.3.

Some data is available for the reaction of OH with aromatic oxidation products. (In this context, aromatic oxidation products refer to those products which retain the aromatic ring structure.) These include the aromatic carbonyl compound, benzaldehyde, 2,4-; 2,5-; and 3,4-dimethyl-benzaldehyde, and t-cinnamaldehyde. Room temperature rate constants for these compounds range from $1.3 \times 10^{-11} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$ (benzaldehyde) to $4.8 \times 10^{-11} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$ (t-cinnamaldehyde). While the yields for these compounds are typically between 2 to 6%, they can contribute to the aromatic reactivity for aldehydes having high precursor concentration (e.g., toluene, 1,2,4-trimethylbenzene). OH also reacts rapidly with phenolic compounds. OH reaction rates with phenols and *o*-, *m*-, and *p*-cresol are typically rapid (2.7 to $6.8 \times 10^{-11} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$) at room temperature. Five dimethylphenols and two trimethylphenols have OH reaction rates ranging between 6.6×10^{-11} and $1.25 \times 10^{-10} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$. Finally, unlike the aromatic aldehydes and phenols, reaction rates for OH + nitrobenzene and OH + *m*-nitrotoluene are much lower than the parent molecules, given their electron withdrawing behavior from the aromatic ring. The room temperature rate constants are 1.4×10^{-13} and 1.2×10^{-12} , respectively.

The NO_3 radical is also known to react with selected AHCs and aromatic photooxidation products. Reaction can either occur by hydrogen atom abstraction or addition to the aromatic ring. However, these reactions are typically slow for alkyl aromatic hydrocarbons and the atmospheric removal due to this process is considered negligible. For AHCs having substituent groups with double bonds (e.g., styrene, α -methylstyrene), the reaction is much more rapid, due to the addition of NO_3 to the double bond. For these compounds, NO_3 rate constants are on the order of $10^{-12} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$. This leads to atmospheric lifetimes on the order of about 1 h for typical night time atmospheric NO_3 levels of $2.5 \times 10^8 \text{ molec cm}^{-3}$ (Atkinson, 2000).

The most important reactions of NO_3 with AHCs are those which involve phenol and methyl, dimethyl, and trimethyl analogs. These reactions can be of importance due to the high yields of phenol for the atmospheric benzene oxidation and *o*-, *m*-, *p*-cresol from toluene oxidation. The $\text{NO}_3 + \text{phenol}$ rate has been given as $3.8 \times 10^{-12} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$. Similarly, the cresol isomers each has an extremely rapid reaction rate with NO_3 ranging from 1.1 to $1.4 \times 10^{-11} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$. As a result, these compounds, particularly the cresol isomers, can show rapid nighttime losses due to reaction with NO_3 with nighttime lifetimes on the order of a few minutes. There is little data for the reaction of NO_3 with dimethylphenols or trimethylphenols which have been found as products of the reaction of $\text{OH} + m$ -, *p*-xylene and $\text{OH} + 1,2,4$ -, $1,3,5$ -trimethylbenzene.

AX2.2.8.2 Reaction Products and Mechanisms of Aromatic Hydrocarbon Oxidation

An understanding of the mechanism of the oxidation of AHCs is important if O_3 is to be accurately predicted in urban atmospheres through modeling studies. As noted above, most monocyclic aromatic hydrocarbons are removed from the atmosphere through reaction with OH . Thus, product studies of the $\text{OH} + \text{AHC}$ should provide the greatest information regarding the AHC oxidation products. However, the effort to study these reactions has been intractable over the past two decades due to a number of difficulties inherent in the OH -aromatic reaction system. There are several reasons for the slow progress in understanding these mechanisms. (1) Product yields for OH -aromatic systems are poorly understood; for the most studied system, OH -toluene, approximately 50% of the reaction products have been identified under conditions where NO_2 reactions do not dominate the removal of the OH -aromatic adduct. (2) As noted, the reaction mechanism can change as the ratio of NO_2 to O_2 changes in the system (Atkinson and

Aschmann, 1994). Thus, reaction product distributions that may be measured in the laboratory at high NO_2 (or NO_x) concentrations may not be applicable to atmospheric conditions. This also limits the usefulness of models to predict O_3 formation to the extent that secondary aromatic reactions are not completely parameterized in the system. (3) Aromatic reactions produce highly polar compounds for which there are few calibration standards available. In most cases, surrogate compounds have to be used in GC/MS calibrations. Moreover, it is not at all clear whether the present sampling techniques or analytical instruments are appropriate to measure the highly polar products produced in these systems. (4) Finally for benzene and toluene in particular, reaction rates of the products are substantially faster than that of the parent compounds. Thus, it is difficult to measure yields accurately without substantial interferences due to secondary reactions. Even given these difficulties, over the past decade a body of knowledge has been developed whereby the initial steps in the OH-initiated photooxidation have been established and a wide range of primary products from each of the major reaction systems have been catalogued.

Benzene is one of the most important aromatic hydrocarbons released into the atmosphere and is a recognized carcinogen. However, its reaction with OH is extremely slow and its contribution to urban O_3 formation is generally recognized to be negligible (Carter, 1994). As a result, relatively few studies have been conducted on the OH reaction mechanism of benzene. Major products of the oxidation of benzene have been found to be phenol and glyoxal (Berndt et al., 1999; Tuazon et al., 1986).

Most of the product analysis and mechanistic work on alkyl aromatic compounds in the gas phase has focused on examining OH reactions with toluene. The primary reaction of OH with toluene follows either of two paths, the first being an abstraction reaction from the methyl group and the second being addition to the ring. It has previously been found that H-atom abstraction from the aromatic ring is of minor importance (Tully et al., 1981). A number of studies have examined yields of the benzyl radical formed following OH abstraction from the methyl group. This radical forms the benzyl peroxy radical, which reacts with nitric oxide (NO) leading to the stable products benzaldehyde, with an average yield of 0.06, and benzyl nitrate, with an average yield less than 0.01 (Calvert et al., 2002). Thus, the overall yield for the abstraction channel is less than approximately 7%.

It is now generally recognized that addition of OH to the aromatic ring is the major process removing toluene from the atmosphere and appears to account for more than 90% of the reaction yield for OH + toluene. The addition of OH to the ring leads to an intermediate OH-toluene adduct that can be stabilized or can redissociate to the reactant compounds. For toluene, OH addition can occur at any of the three possible positions on the ring (ortho, meta, or para) to form the adduct. Addition of OH to the toluene has been shown to occur predominately at the ortho position (yield of 0.81) with lesser amounts at the meta (0.05) and para (0.14) positions (Kenley et al., 1981). The initial steps for both the abstraction and addition pathways in toluene have been shown in Figure AX2-6; only the path to form the ortho-adduct is shown, viz. reaction (2).

The OH-toluene adduct formed is an energy-rich intermediate that must be stabilized by third bodies in the system to undergo further reaction. Stabilization has been found to occur at pressures above 100 Torr for most third bodies (Perry et al., 1977; Tully et al., 1981). Therefore, at atmospheric pressure, the adduct will not substantially decompose back to its reactants as indicated by reaction (-2). The stabilized adduct (I) is removed by one of three processes: H-atom abstraction by O₂ to give a cresol, as in reaction (5); an addition reaction with O₂, as in reaction (6); or reaction with NO₂ to give *m*-nitrotoluene as in reaction (7).

The simplest fate for the adduct (I) is reaction with O₂ to form *o*-cresol. Data from a number of studies (e.g., Kenley et al., 1981; Atkinson et al., 1980; Smith et al., 1998; Klotz et al., 1998; summarized by Calvert et al., 2002) over a wide range of NO₂ concentrations (generally above 1 ppmv) show an average yield of approximately 0.15 for *o*-cresol. Most of the measurements suggest the *o*-cresol yield is independent of total pressure, identity of the third body, and NO₂ concentration (Atkinson and Aschmann, 1994; Moschonas et al., 1999), but the data tend to be scattered. This finding suggests that the addition of NO₂ to the hydroxy methylcyclo-hexadienyl radical does not contribute to the formation of phenolic-type compounds. Fewer studies have been conducted for *m* and *p*-cresol yields, but the results of two studies indicate the yield is approximately 0.05 (Atkinson et al., 1980; Gery et al., 1985; Smith et al., 1998). The data suggests good agreement between the relative yields of the cresols from the product studies at atmospheric pressure and studies at reduced pressures. Thus, H-atom abstraction from adducts formed at all positions appears to represent approximately 20% of the total yield for toluene.

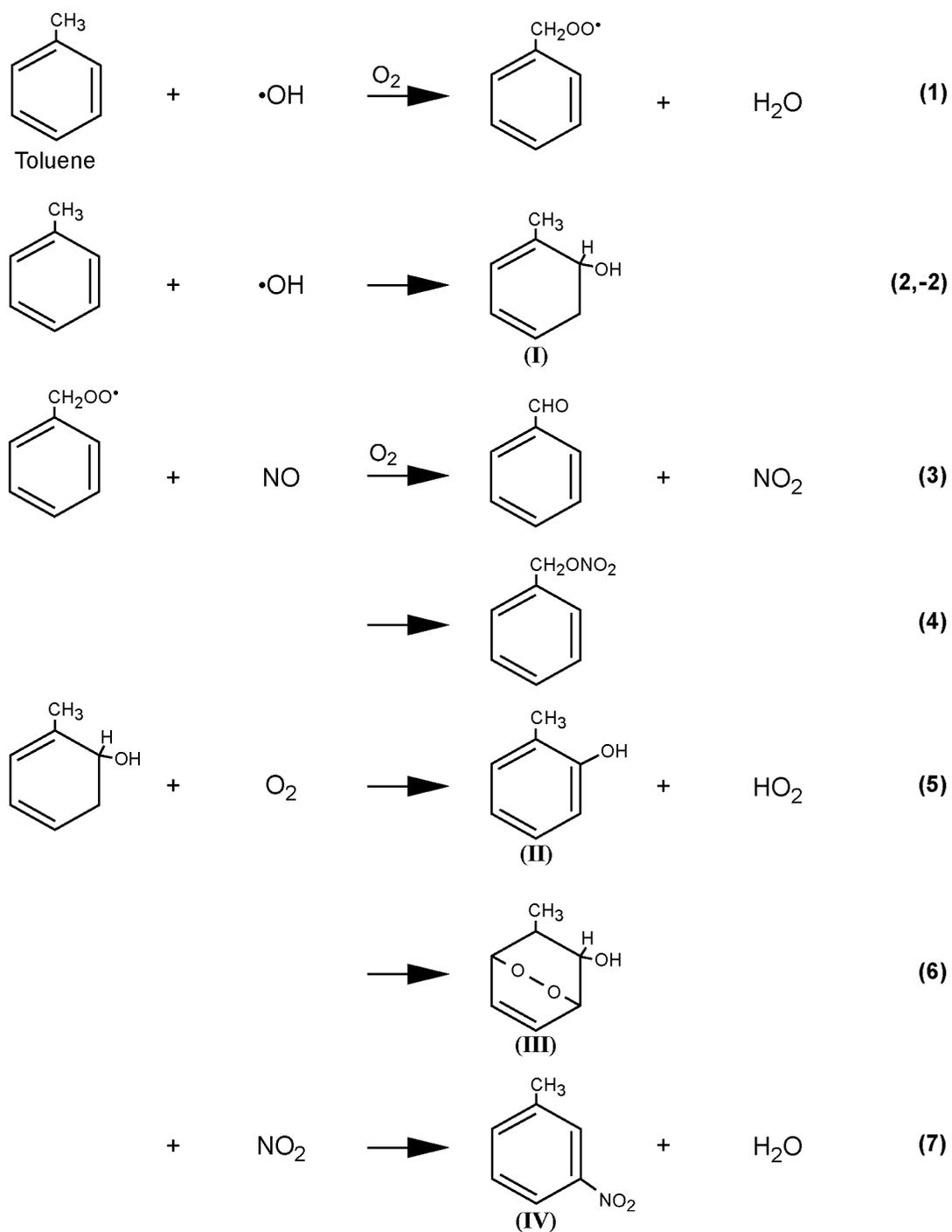


Figure AX2-6. Initial steps in the photooxidation mechanism of toluene initiated by its reaction with OH radicals.

The OH-toluene adduct also reacts with O₂ to form a cyclohexadienyl peroxy radical (III), shown as a product of reaction (6) after rearrangement. This radical can undergo a number of possible processes. Most of these processes lead to ring fragmentation products, many of which have been seen in several studies (Dumdei and O'Brien, 1984; Shepson et al., 1984). Ring-fragmentation products are frequently characterized by multiple double bonds and/or multiple functional groups. As such, these products are highly reactive and extremely difficult to detect and quantify.

Klotz et al. (1997; 1998) have suggested that the intermediate could also follow through a mechanism where toluene oxide/oxepin could be formed following the addition of O₂ to the OH-aromatic adduct. Recent experiments suggest that the formation of *o*-cresol through the photolysis of toluene oxide/oxepin is only a minor contributor to the overall *o*-cresol that has been measured (Klotz et al., 1998). This result contrasts to the high yield observed for the formation of phenol from the photolysis of benzene oxide/oxepin (Klotz et al., 1997). Recently, Berndt et al. (1999) used a flow tube to test the hypothetical formation of benzene oxide/oxepin from the OH + benzene reaction at pressures below 100 torr. They saw very little evidence for its formation.

A few studies have been conducted to identify fragmentation products using a variety of instruments. Several approaches have been used that employ structural methods, particularly mass spectrometry (MS), to identify individual products formed during the photooxidation. In one approach (Dumdei and O'Brien, 1984), the walls of the reaction chamber were extracted following an extended irradiation. In this study, the analysis was conducted by tandem mass spectrometry (MS/MS), which allowed products to be separated without the use of a chromatographic stationary phase. The investigators reported 27 photooxidation products from toluene, with 15 reportedly from ring fragmentation processes. However, the study was purely qualitative and product yields could not be obtained. No distinction could be made between primary and secondary products from the reaction because extended irradiations and species in various isotopic forms could not be differentiated. More refined approaches using atmospheric pressure ionization-tandem mass spectrometry has been used to study toluene (Dumdei et al., 1988) and *m*- and *p*-xylene (Kwok et al., 1997) photooxidation.

In another study, Shepson et al. (1984) demonstrated that a number of these fragmentation products could be analyzed by gas chromatography. Fragmentation products detected in two

investigations (Dumdei and O'Brien, 1984; Shepson et al., 1984) included glyoxal, methyl glyoxal, butenedial, 4-oxo-2-pentenal, hydroxybutenedial, 1-pentene-3,4-dione, 1-butene-3,4-dione, and methyl vinyl ketone. Additional evidence (Shepson et al., 1984) for fragmentation processes came from the detection of 2-methylfuran and furfural. These compounds, although cyclic in structure, result from a bridged oxygen intermediate. Yields of the detected fragmentation products were subsequently measured in a number of studies (e.g., Bandow et al., 1985a,b; Tuazon et al., 1986; Smith et al., 1998), were typically under 15% on a reacted carbon basis.

An additional possible pathway for reaction of the OH-toluene adduct is by reaction with NO₂ to give isomers of nitrotoluene. A yield of approximately 0.015 at NO₂ concentrations of about 1 ppmv has been measured (Atkinson et al., 1991). Although this yield itself is fairly minor, the investigators reported a positive intercept in plotting the nitrotoluene concentration against the NO₂ concentration; however, the data were considerably scattered. The positive intercept has been interpreted as suggesting that the OH-toluene adduct does not add O₂. This finding would require, therefore, another mechanism than that described above to be responsible for the fragmentation products.

The results of this study can be compared to experiments which directly examined the OH radical loss in reactions of OH with toluene and other aromatic compounds. Knipsel and co-workers (Knipsel et al., 1990) have found a double exponential decay for toluene loss in the presence of added O₂, a rapid decay reflective of the initial adduct formation and a slower decay reflecting loss of the adduct by O₂ or other scavengers. From the decay data in the presence of O₂, they determine a loss rate for the OH-toluene of $5.4 \times 10^{-16} \text{ cm}^3 \text{ molec}^{-1} \text{ s}^{-1}$. Use of this rate constant suggests that the loss rate of 2500 s⁻¹ for the adduct in the presence of air at atmospheric pressure. This loss rate compares to a loss due to NO₂ (with a nominal atmospheric concentration of 0.1 ppmv) of about 100 s⁻¹. This finding suggests that removal of the OH-toluene adduct by O₂ is a far more important loss process than removal by NO₂ under atmospheric conditions which is in contrast other findings (Atkinson et al., 1991). This finding was confirmed by the recent experiments from Moschonas et al. (1999).

Therefore, studies on the disposition of toluene following OH reaction can be summarized as follows. It is generally accepted that H-atom abstraction from the methyl group by OH is a relatively minor process accounting for a 6 to 7% yield in the OH reaction with toluene.

Addition of OH to toluene to form an intermediate OH-toluene adduct is the predominant process. At atmospheric pressure, ring-retaining products such as the cresol and nitrotoluenes account for another 20% of the primary reaction products (Smith et al., 1999). The remaining 70 to 75% of the products are expected to be ring fragmentation products in the gas phase, having an uncertain mechanism for formation. Many of these fragmentation products have been detected, but appear to form at low yields, and relatively little quantitative information on their formation yields exists. As noted earlier, some of these products contain multiple double bonds, which are likely to be highly reactive with OH or photolyze which enhances the reactivity of systems containing aromatics. Mechanisms that cannot adequately reflect the formation of fragmentation products are likely to show depressed reactivity for the oxidation of toluene and other aromatic compounds.

The number of studies of the multiple-substituted alkyl aromatics, such as the xylenes or the trimethylbenzenes, is considerably smaller than for toluene. Kinetic studies have focused on the OH rate constants for these compounds. For the xylenes, this rate constant is typically a factor of 2 to 5 greater than that for OH + toluene. Thus, the OH reactivity of the fragmentation products is similar to that of the parent compounds, potentially making the study of the primary products of the xylenes less prone to uncertainties from secondary reactions of the primary products than is the case for toluene.

Products from the OH reaction with the three xylenes have been studied most comprehensively in a smog chamber using long-path FTIR (Bandow and Washida, 1985a) and gas chromatography (Shepson et al., 1984; Atkinson and Aschmann, 1994; Smith et al., 1999). Ring-fragmentation yields of 41, 55, and 36% were estimated for *o*-, *m*-, and *p*-xylene, respectively, based on the dicarbonyl compounds, glyoxal, methyl glyoxal, biacetyl, and 3-hexene-2,5-dione detected during the photooxidation. These values could be lower limits, given that Shepson et al. (1984) report additional fragmentation products from *o*-xylene, including 1-pentene-4,5-dione, butenedial, 4-oxo-pentenal, furan, and 2-methylfuran. In the earlier studies, aromatic concentrations were in the range of 5 to 10 ppmv with NO_x at 2 to 5 ppmv. At atmospheric ratios of NO₂ and O₂, the observed yields could be different. Smith et al. (1999) examined most of the ring retaining products in the OH + *m*-xylene and OH + *p*-xylene systems. In each case, tolualdehyde isomers, dimethylphenol isomers, and nitro xylene isomers specific for each system were detected. The total ring retaining yield for OH + *m*-xylene was 16.3%; the

yield for OH + *p*-xylene it was 24.5%. A mass balance approach suggests that respective ring-fragmentation yields of 84% and 76%, respectively. Kwok et al. (1997) also measured products from the OH + *m*- and *p*-xylene systems using atmospheric pressure ionization-tandem mass spectrometry. Complementary ring-fragmentation products to glyoxal, methylglyoxal, and biacetyl were detected from the parent ion peaks, although the technique did not permit the determination of reaction yields.

Smith et al. (1999) also studied ring fragmentation products from the reaction of OH with 1,2,4- and 1,3,5-trimethylbenzene. Ring-retaining products from the reaction with 1,2,4-trimethylbenzene gave three isomers each of dimethylbenzaldehyde and trimethylphenol as expected by analogy with toluene. However, the ring-retaining products only accounted for 5.8% of the reacted carbon. Seven additional ring-fragmentation products were also detected from the reaction, although the overall carbon yield was 47%. For 1,3,5-trimethylbenzene, its reaction with OH leads to only two ring-retaining products, 3,5-dimethyl-benzaldehyde and 2,4,6-trimethylphenol, given its molecular symmetry. Only a single fragmentation product was detected, methyl glyoxal, at a molar yield of 90%. The overall carbon yield in this case was 61%. The formation of relatively low yields of aromatic aldehydes and methylphenols suggests that NO_x removal by these compound in these reaction systems will be minimized (see below).

In recent years, computational chemistry studies have been applied to reaction dynamics of the OH-aromatic reaction systems. Bartolotti and Edney (1995) used density functional-based quantum mechanical calculations to help identify intermediates of the OH-toluene adduct. These calculations were consistent with the main addition of OH to the ortho position of toluene followed by addition of O₂ to the meta position of the adduct. The reaction energies suggested the formation of a carbonyl epoxide which was subsequently detected in aromatic oxidation systems by Yu and Jeffries, (1997). Andino et al. (1996) conducted ab initio calculations using density functional theory with semiempirical intermediate geometries to examine the energies of aromatic intermediates and determine favored product pathways. The study was designed to provide some insight into the fragmentation mechanism, although only a group additivity approach to calculate ΔH_{rxn} was used to investigate favored reaction pathways. However, the similarity in energies of the peroxy radicals formed from the O₂ reaction with the OH-aromatic adduct were very similar in magnitude making it difficult to differentiate among structures.

A detailed analysis of toluene oxidation using smog chamber experiments and chemical models (Wagner et al., 2003) shows that there are still large uncertainties in the effects of toluene on O₃ formation. A similar situation is likely to be found for other aromatic hydrocarbons.

AX2.2.8.3 The Formation of Secondary Organic Aerosol as a Sink for Ozone Precursors

Aromatic hydrocarbons are known to generate secondary organic aerosol (SOA) following their reaction with OH or other reactive oxidants. Secondary organic aerosol refers to the formation of fine particulate matter either through nucleation processes or through condensation onto existing particles. Over the last 12 years numerous experiments have been conducted in environmental chambers to determine the yield of secondary organic aerosol as a function of the reacted aromatic hydrocarbon. A review of the results of these studies can be found in the latest Air Quality for Particulate Matter Document (U.S. Environmental Protection Agency, 2003).

The extent to which aromatic reaction products are removed from the gas phase and become incorporated in the particle phase will influence the extent to which oxygenated organic compounds will not be available for participation in the aromatic mechanisms that lead to O₃ formation. However, this may be overstated to some degree for products of aromatic precursors. First, at atmospheric loading levels of organic particulate matter, the SOA yields of the major aromatic hydrocarbons are in the low percent range. Second, the aromatic products that are likely to condense on particles are likely to be highly oxygenated and have OH reaction rates that make them largely unreactive. Thus, while there may be some reduction of O₃ formation, it is not expected to be large.

AX2.2.9 Importance of Oxygenated VOCs

The role of oxygenated VOCs in driving O₃ production has generated increasing interest over the past decade. These VOCs include carbonyls, peroxides, alcohols, and organic acids. They are produced in the atmosphere by oxidation of hydrocarbons, as discussed above, but are also directly emitted to the atmosphere, in particular by vegetation (Guenther et al., 2000). In rural and remote atmospheres, oxygenated VOCs often dominate over nonmethane hydrocarbons in terms of total organic carbon mass and reactivity (Singh et al., 2004). The most abundant by mass of these oxygenated VOCs is usually methanol, which is emitted by

vegetation and is present in U.S. surface air at concentrations of typically 1-10 ppbv (Heikes et al., 2002).

Most oxygenated VOCs react with OH to drive O₃ production in a manner similar to the hydrocarbon chemistry discussed in the previous sections. In addition, carbonyl compounds (aldehydes and ketones) photolyze to produce peroxy radicals that can accelerate O₃ production, thus acting as a chemical amplifier (Jaeglé et al., 2001). Photolysis of formaldehyde by (AX2-26b) was discussed in section AX2.2.5. Also of particular importance is the photolysis of acetone (Blitz et al., 2004):



producing organic peroxy radicals that subsequently react with NO to produce O₃. The peroxyacetyl radical CH₃C(O)OO can also react with NO₂ to produce PAN, as discussed in Section AX2.2.4. Photolysis of acetone are a minor but important source of HO₂ radicals in the upper troposphere (Arnold et al., 2004).

AX2.2.10 Influence of Multiphase Chemical Processes

In addition to reactions occurring in the gas phase, reactions occurring on the surfaces of or within cloud droplets and airborne particles also occur. Their collective surface area is huge, implying that collisions with gas phase species occur on very short time scales. The integrated aerosol surface area ranges from $4.2 \times 10^{-7} \text{ cm}^2/\text{cm}^3$ for clean continental conditions to $1.1 \times 10^{-5} \text{ cm}^2/\text{cm}^3$ for urban average conditions (Whitby, 1978). There have been substantial improvements in air quality especially in urban areas since the time these measurements were made and so the U.S. urban values should be scaled downward by roughly a factor of two to four. The resulting surface area is still substantial and the inferred collision time scale of a gaseous molecule with a particle ranges from a few seconds or less to a few minutes. These inferred time scales imply that heterogenous reactions will generally be much less important than gas phase reactions for determining radical concentrations especially when reaction probabilities much less than unity are considered. A large body of research has accumulated recently

regarding chemical processes in cloud droplets, snow and ice crystals, wet (deliquesced) inorganic particles, mineral dust, carbon chain agglomerates and organic carbon-coated particles.

Jacob's (2000) comprehensive review of the potential influences of clouds and aerosols on tropospheric O₃ cycling provides the starting point for this section. Updates to that review will also be provided. Jacob's review evaluates the literature available through late 1999, discusses major areas of uncertainty, recommends experiments to reduce uncertainties, and (based on then current information) recommends specific multiphase pathways that should be considered in models of O₃ cycling. In regard to the latter, Jacob's recommendations should be viewed as conservative. Specifically, only reasonably well constrained pathways supported by strong observational evidence are recommended for inclusion in models. Several poorly resolved and/or controversial pathways that may be significant in the ambient troposphere lack sufficient constraints for reliable modeling. Some of these areas are discussed in more detail below. It should be noted at the outset that many of the studies described in this section involve either aerosols that are not found commonly throughout the United States (e.g., marine aerosol) or correspond to unaged particles (e.g., soot, mineral dust). In many areas of the United States, particles accrete a layer of hydrated H₂SO₄ which will affect the nature of the multiphase processes occurring on particle surfaces.

Major conclusions from this review are summarized as follows (comments are given in parentheses):

HO_x Chemistry

- (1) Catalytic O₃ loss via reaction of O₂⁻ + O_{3(aq)} in clouds appears to be inefficient.
- (2) Aqueous-phase loss of HCHO in clouds appears to be negligible (see also Lelieveld and Crutzen, 1990).
- (3) Scavenging of HO₂ by cloud droplets is significant and can be acceptably parameterized with a reaction probability of $\gamma_{\text{HO}_2} = 0.2$, range 0.1 to 1, for $\text{HO}_2 \rightarrow 0.5 \text{H}_2\text{O}_2$. However, this approach may overestimate HO₂ uptake because the influence of HO_{2(aq)} on the magnitude (and direction) of the flux is ignored.
- (4) The uptake of alkyl peroxy radicals by aerosols is probably negligible.
- (5) Hydrolysis of CH₃C(O)OO in aqueous aerosols may be important at night in the presence of high PAN and aerosol surface area; $\gamma_{\text{CH}_3\text{C(O)OO}} = 4 \times 10^{-3}$ is recommended.

NO_x Chemistry

- (6) Hydrolysis of N₂O₅ to HNO₃ in aqueous aerosols is important (Section AX2.2.4) (and can be parameterized with $\gamma_{\text{HNO}_3} = 0.01$ to 0.1 [Schutze and Herrmann, 2002; Hallquist et al., 2003]).
- (7) Although the mechanism is uncertain, heterogeneous conversion of NO₂ to HONO on aerosol surfaces should be considered with $\gamma_{\text{NO}_2} = 10^{-4}$ (range 10⁻⁶ to 10⁻³) for NO₂ → 0.5 HONO + 0.5 HNO₃. (This reaction also occurs on snow, Crawford et al., 2001). Wet and dry deposition sinks for HONO should also be considered although scavenging by aerosols appears to be negligible.
- (8) There is no evidence for significant multiphase chemistry involving PAN.
- (9) There is no evidence for significant conversion of HNO₃ to NO_x in aerosols.

Heterogeneous ozone loss

- (10) There is no evidence for significant loss of O₃ to aerosol surfaces (except during dust storms observed in East Asia, e.g., Zhang and Carmichael, 1999).

Halogen radical chemistry

- (11) There is little justification for considering BrO_x and ClO_x chemistry (except perhaps in limited areas of the United States and nearby coastal areas).

Most of the above conclusions remain valid but, as detailed below, some should be qualified based on recently published findings and on reevaluation of results from earlier investigations.

AX2.2.10.1 HO_x and Aerosols

Field measurements of HO_x reviewed by Jacob (2000) correspond to regions with relatively low aerosol concentrations (e.g., Mauna Loa [Cantrell et al., 1996]; rural Ontario [Plummer et al., 1996]; and the upper troposphere [Jaeglé et al., 1999]). In all cases, however, significant uptake of HO₂ or HO₂ + RO₂ radicals by aerosols was inferred based on imbalances between measured concentrations of peroxy radicals and photochemical models of gas-phase chemistry. Laboratory studies using artificial aerosols (both deliquesced and solid) confirm uptake but the actual mechanism remains unclear. Several investigations report significant HO_x and H₂O₂ production in cloud water (e.g., Anastasio et al., 1994). However the potential importance of this source is considered unlikely because measurements in continental air show

no evidence of missing sources for HO_x or H₂O₂. No investigations involving the potential influences of marine aerosols as sources or sinks for HO_x were considered in the above analysis.

Relative to conservative seawater tracers such as Mg²⁺ and Na⁺, organic C associated with sea-salt aerosols is typically enriched by 2 to 3 orders of magnitude in both polluted (e.g., Hoffman and Duce, 1976, 1977; Turekian et al., 2003) and remote regions (Chesselet et al., 1981). This organic C originates from three major sources: 1) organic surfactants concentrated from bulk seawater on walls of subsurface bubbles (Tseng et al., 1992), 2) the surface microlayer of the ocean (Gershey, 1983), and 3) condensation of organic gases (Pun et al., 2000). Coagulation of chemically distinct aerosols (e.g., via cloud processing) may also contribute under some conditions.

Resolving chemical processes involving particles in the marine boundary layer (MBL) is constrained by the relative scarcity of measurements of particulate organic carbon (POC) (Penner, 1995) and its molecular composition (Saxena et al., 1995). In MBL regions impacted by direct continental outflow, POC may constitute more than half of the total dry aerosol mass (Hegg et al., 1997). Carbon isotopic compositions in the polluted North Atlantic MBL indicate that, on average, 35% to 40% of POC originates from primary (direct injection) and secondary (condensation of gases) marine sources (Turekian et al., 2003).

The photolysis of dissolved organic compounds is a major source for OH, H₂O₂, and C-centered radicals in both the surface ocean (e.g., Blough and Zepp, 1995; Blough, 1997; Mopper and Kieber, 2000) and in marine aerosols (e.g., McDow et al., 1996). Relative to the surface ocean, however, production rates in the aerosol are substantially greater per unit volume because organic matter is highly enriched (Turekian et al., 2003) and aerosol pH is much lower (Keene et al., 2002). Lower pHs increase rates of many reactions including acid-catalyzed pathways such as the breakdown of the HOCl[•] radical (King et al., 1995), the formation of H₂O₂ from the photolysis of phenolic compounds (Anastasio et al., 1997), and the photolysis of organic acids.

To provide a semi-quantitative context for the potential magnitude of this source, we assume a midday OH production rate in surface seawater of 10⁻¹¹ M sec⁻¹ (Zhou and Mopper, 1990) and a dissolved organic carbon enrichment of 2 to 3 orders of magnitude in sea-salt aerosols. This yields an estimated OH production rate in fresh (alkaline) sea-salt aerosols of 10⁻⁹ to 10⁻⁸ M sec⁻¹. As discussed above, rapid (seconds to minutes) acidification of the aerosol

should substantially enhance these production rates. Consequently, the midday OH production rates from marine-derived organic matter in acidified sea-salt aerosols may rival or perhaps exceed midday OH scavenging rates from the gas phase (approximately 10^{-7} M sec⁻¹; [Chameides and Stelson, 1992]). Scavenging is the only significant source for OH in acidified sea-salt aerosols considered by many current models.

Limited experimental evidence indicates that these pathways are important sources of HO_x and RO_x in marine air and possibly in coastal cities. For example, the absorption of solar energy by organic species dissolved in cloud water (e.g., Faust et al., 1993; Anastasio et al., 1997) and in deliquesced sea-salt aerosols (Anastasio et al., 1999) produces OH, HO₂, and H₂O₂. In addition, Fe(III) complexation by oxalate and similar ligands to metal such as iron can greatly enhance radical production through ligand to metal charge transfer reactions (Faust, 1994; Hoigné et al., 1994). Oxalate and other dicarboxylic anions are ubiquitous components of MBL aerosols in both polluted (e.g., Turekian et al., 2003) and remote regions (Kawamura et al., 1996).

Substantial evidence exists for washout of peroxy radicals. Near solar noon, mixing ratios of total HO_x plus RO_x radicals generally fall in the 50 ppt range, but during periods of rain these values dropped to below the detection limit of 3 to 5 ppt (Andrés Hernández et al., 2001; Burkert et al., 2001a,b, 2003). Such low concentrations cannot be explained by loss of actinic radiation, because nighttime radical mixing ratios were higher.

Burkert et al. (2003) investigated the diurnal behavior of the trace gases and peroxy radicals in the clean and polluted MBL by comparing observations to a time dependant, zero-dimensional chemical model. They identified significant differences between the diurnal behavior of RO₂* derived from the model and that observed possibly attributable to multiphase chemistry. The measured HCHO concentrations differed from the model results and were best explained by reactions involving low levels of Cl.

Finally, photolytic NO₃⁻ reduction is important in the surface ocean (Zafiriou and True, 1979) and could contribute to OH production in sea-salt aerosols. Because of the pH-dependence of HNO₃ phase partitioning, most total nitrate (HNO₃ + particulate NO₃⁻) in marine air is associated with sea salt (e.g., Huebert et al., 1996; Erickson et al., 1999). At high mM concentrations of NO₃⁻ in sea-salt aerosols under moderately polluted conditions (e.g., Keene et al., 2002) and with quantum yields for OH production of approximately 1% (Jankowski et al., 2000), this pathway would be similar in magnitude to that associated with scavenging

from the gas phase and with photolysis of dissolved organics. Experimental manipulations of marine aerosols sampled under relatively clean conditions on the California coast confirms that this pathway is a major source for OH in sea-salt solutions (Anastasio et al., 1999).

Although largely unexplored, the potential influences of these poorly characterized radical sources on O₃ cycling in marine air are probably significant. At minimum, the substantial inferred concentrations of HO₂ in aerosol solutions would diminish and perhaps reverse HO₂ scavenging by marine aerosols and thereby increase O₃ production relative to models based on Jacob's (2000) recommended reaction probability.

AX2.2.10.2 NO_x Chemistry

Jacob (2000) recommended as a best estimate, $\gamma_{\text{N}_2\text{O}_5} = 0.1$ for the reaction probability of N₂O₅ on aqueous aerosol surfaces with conversion to HNO₃. Recent laboratory studies on sulfate and organic aerosols indicates that this reaction probability should be revised downward, to a range 0.01-0.05 (Kane et al., 2001; Hallquist et al., 2003; Thornton et al., 2003). Tie et al. (2003) found that a value of 0.04 in their global model gave the best simulation of observed NO_x concentrations over the Arctic in winter. A decrease in N₂O₅ slows down the removal of NO_x and thus increases O₃ production. Based on the consistency between measurements of NO_y partitioning and gas-phase models, Jacob (2000) considers it unlikely that significant HNO₃ is recycled to NO_x in the lower troposphere. However, only one of the reviewed studies (Schultz et al., 2000) was conducted in the marine troposphere and none were conducted in the MBL. An investigation over the equatorial Pacific reported discrepancies between observations and theory (Singh et al., 1996b) that might be explained by HNO₃ recycling. It is important to recognize that both Schultz et al. (2000) and Singh et al. (1996b) involved aircraft sampling which, in the MBL, significantly under represents sea-salt aerosols and thus most total NO₃ (HNO₃ + NO₃⁻) and large fractions of NO_y in marine air (e.g., Huebert et al., 1996). Consequently, some caution is warranted when interpreting constituent ratios and NO_y budgets based on such data.

Recent work in the Arctic has quantified significant photochemical recycling of NO₃⁻ to NO_x and perturbations of OH chemistry in snow (Honrath et al., 2000; Dibb et al., 2002; Domine and Shepson, 2002), which suggests the possibility of similar multiphase pathways occurring in aerosols. As mentioned above, recent evidence also indicates that NO₃⁻ is

photolytically reduced to NO_2^- (Zafariou and True, 1979) in acidic sea-salt solutions (Anastasio et al., 1999). Further photolytic reduction of NO_2^- to NO (Zafariou and True, 1979) could provide a possible mechanism for HNO_3 recycling. Early experiments reported production of NO_x during the irradiation of artificial seawater concentrates containing NO_3^- (Petroni and Papee, 1972). Based on the above, we believe that HNO_3 recycling in sea-salt aerosols is potentially important and warrants further investigation. Other possible recycling pathways involving highly acidic aerosol solutions and soot are reviewed by Jacob (2000).

Ammann et al. (1998) reported the efficient conversion of NO_2 to HONO on fresh soot particles in the presence of water. They suggest that interaction between NO_2 and soot particles may account for high mixing ratios of HONO observed in urban environments. Conversion of NO_2 to HONO and subsequent photolysis to $\text{NO} + \text{OH}$ would constitute an NO_x -catalyzed O_3 sink involving snow. High concentrations of HONO can lead to the rapid growth in OH concentrations shortly after sunrise, giving a “jump start” to photochemical smog formation. Prolonged exposure to ambient oxidizing agents appears to deactivate this process. Broske et al. (2003) studied the interaction of NO_2 on secondary organic aerosols and concluded that the uptake coefficients were too low for this reaction to be an important source of HONO in the troposphere.

Choi and Leu (1998) evaluated the interactions of nitric acid on a model black carbon soot (FW2), graphite, hexane and kerosene soot. They found that HNO_3 decomposed to NO_2 and H_2O at higher nitric acid surface coverages, i.e., $P(\text{HNO}_3) \geq 10^{-4}$ Torr. None of the soot models used were reactive at low nitric acid coverages, at $P(\text{HNO}_3) = 5 \times 10^{-7}$ Torr or at lower temperatures (220K). They conclude that it is unlikely that aircraft soot in the upper troposphere/lower stratosphere reduces HNO_3 .

Heterogeneous production on soot at night is believed to be the mechanism by which HONO accumulates to provide an early morning source of HO_x in high NO_x environments (Harrison et al., 1996; Jacob, 2000). HONO has been frequently observed to accumulate to levels of several ppb overnight, and has been attributed to soot chemistry (Harris et al., 1982; Calvert et al., 1994; Jacob, 2000).

Longfellow et al. (1999) observed the formation of HONO when methane, propane, hexane and kerosene soots were exposed to NO_2 . They estimate that this reaction may account for some part of the unexplained high levels of HONO observed in urban areas. They comment that

without details about the surface area, porosity and amount of soot available for this reaction, reactive uptake values cannot reliably be estimated. They comment that soot and NO_2 are produced in close proximity during combustion, and that large quantities of HONO have been observed in aircraft plumes.

Saathoff et al. (2001) studied the heterogeneous loss of NO_2 , HNO_3 , $\text{NO}_3/\text{N}_2\text{O}_5$, $\text{HO}_2/\text{HO}_2\text{NO}_2$ on soot aerosol using a large aerosol chamber. Reaction periods of up to several days were monitored and results used to fit a detailed model. They derived reaction probabilities at 294 K and 50% RH for NO_2 , NO_3 , HO_2 and HO_2NO_2 deposition to soot, HNO_3 reduction to NO_2 , and N_2O_5 hydrolysis. When these probabilities were included in photochemical box model calculations of a 4-day smog event, the only noteworthy influence of soot was a 10% reduction in the second day O_3 maximum, for a soot loading of $20 \mu\text{g m}^{-3}$, i.e., a factor of 2 to 10 times observed black carbon loadings seen during extreme U.S. urban pollution events, although such concentrations are observed routinely in the developing world.

Muñoz and Rossi (2002) conducted Knudsen cell studies of HNO_3 uptake on black and grey decane soot produced in lean and rich flames, respectively. They observed HONO as the main species released following nitric acid uptake on grey soot, and NO and traces of NO_2 from black soot. They conclude that these reactions would only have relevance in special situations in urban settings where soot and HNO_3 are present in high concentrations simultaneously.

AX2.2.10.3 Halogen Radical Chemistry

Barrie et al. (1988) first suggested that halogen chemistry on snow surfaces in the Arctic could lead to BrOx formation and subsequent O_3 destruction. More recent work suggests that halogen radical reactions may influence O_3 chemistry in mid latitudes as well.

The weight of available evidence supports the hypothesis that halogen radical chemistry significantly influences O_3 cycling over much of the marine boundary layer at lower latitudes and in at least some other regions of the troposphere. However, proposed chemical mechanisms are associated with substantial uncertainties and, based on available information, it appears unlikely that a simple parameterization (analogous to those recommended by Jacob (2000) for other multiphase transformations) would adequately capture major features of the underlying transformations.

Most of the Cl and Br in the marine boundary layer are produced in association with sea-salt aerosols by wind stress at the ocean surface (e.g., Gong et al., 1997). Fresh aerosols rapidly dehydrate towards equilibrium with ambient water vapor and undergo other chemical processes involving the scavenging of reactive gases, aqueous-phase transformations, and volatilization of products. Many of these processes are strongly pH-dependent (Keene et al., 1998). Throughout most of the marine boundary layer, sea-salt alkalinity is titrated rapidly (seconds to minutes) by ambient acids (Chameides and Stelson, 1992; Erickson et al., 1999) and, under a given set of conditions, the pHs of the super- μm , sea-salt size fractions are buffered to similar values via HCl phase partitioning (Keene and Savoie, 1998; 1999; Keene et al., 2002).

Model calculations based on the autocatalytic halogen activation mechanism (Vogt et al., 1996; Keene et al., 1998; Sander et al., 1999; von Glasow et al., 2002a,b; Pszenny et al., 2004; Sander et al., 2003) predict that most particulate Br^- associated with acidified sea-salt aerosol would react to form Br_2 and BrCl , which subsequently volatilize and photolyze in sunlight to produce atomic Br and Cl. Most Br atoms recycle in the gas phase via



and thereby catalytically destroy O_3 , analogous to Br cycling in the stratosphere (e.g., Mozurkewitch, 1995; Sander and Crutzen, 1996). Side reactions with HCHO and other compounds produce HBr, which is either scavenged and recycled through the aerosol or lost to the surface via wet and dry deposition (Dickerson et al., 1999).

Cl-radical chemistry influences O_3 in two ways (e.g., Pszenny et al., 1993). Some atomic Cl in marine air reacts directly with O_3 initiating a catalytic sequence analogous to that of Br (AX2-42 through AX2-44 above). However, most atomic Cl in the MBL reacts with hydrocarbons (which, relative to the stratosphere, are present at high concentrations) via hydrogen extraction to form HCl vapor. The enhanced supply of odd hydrogen radicals from

hydrocarbon oxidation leads to O₃ production in the presence of sufficient NO_x. Thus, Cl chemistry represents a modest net sink for O₃ when NO_x is less than 20 pptv and a net source at higher NO_x. Although available evidence suggest that significant Cl-radical chemistry occurs in clean marine air, its net influence on O₃ appears to be small relative to that of Br and I.

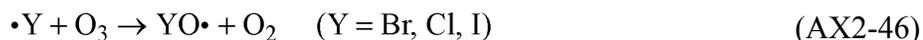
In addition to Br and Cl, several lines of recent evidence suggests that an autocatalytic cycle also sustains I-radical chemistry leading to significant net O₃ destruction in marine air (Vogt et al., 1996, 1999; von Glasow et al., 2002a). The cycle is initiated by photolysis of organoiodine compounds emitted from the ocean surface to generate atomic I (Carpenter et al., 1999). Iodine atoms react almost exclusively with O₃ to form IO. Most IO photodissociates in sunlight to generate I and atomic O, which rapidly recombines with O₂ to form O₃. Consequently, this cycle has no net effect on O₃ (Stutz et al., 1999). However, alternative reaction pathways analogous to reactions AX2-42 through AX2-44 above lead to catalytic O₃ destruction. Model calculations suggest that HOI recycles via acid-catalyzed aerosol scavenging to form ICl and IBr, which subsequently volatilize and photolyze to form halogen atoms. The net effect of this multiphase pathway is to increase concentrations of volatile reactive I. The self reaction of IO to form I and OIO may further enhance O₃ destruction (Cox et al., 1999; Ashworth et al., 2002). IO also reacts with NO₂ to form INO₃, which can be scavenged by aqueous aerosols. This pathway has been suggested as a potentially important sink for NO_x in the remote MBL and would, thus, contribute indirectly to net O₃ destruction (McFiggans et al., 2000).

Various lines of observational evidence support aspects of the above scenarios. Most measurements of particulate Br in marine air reveal large depletions relative to conservative sea-salt tracers (e.g., Sander et al., 2003) and, because HBr is highly soluble in acidic solution, these deficits cannot be explained by simple acid-displacement reactions (e.g., Ayers et al., 1999). Observed Br depletions are generally consistent with predictions based on the halogen activation mechanism. In contrast, available, albeit limited, data indicate that I is highly enriched in marine aerosols relative to bulk seawater (e.g., Sturges and Barrie, 1988), which indicates active multiphase iodine chemistry.

Direct measurements of BrO in marine air by differential optical absorption spectroscopy (DOAS) reveal mixing ratios that are near or below analytical detection limits of about 1 to 3 ppt (Hönninger, 1999; Pszenny et al., 2003; Leser et al., 2003) but within the range of model

predictions. Column-integrated DOAS observations from space reveal substantial mixing ratios of tropospheric BrO (e.g., Wagner and Platt, 1998). Although the relative amounts in the MBL cannot be resolved, these data strongly suggest active destruction of tropospheric O₃ via the reaction sequence of AX2-42 through AX2-44. Similarly, measurements of IO (McFiggans et al., 2000) and OIO (Allan et al., 2001) indicate active O₃ destruction by an analogous pathway involving atomic I. In addition, anticorrelations on diurnal time scales between total volatile inorganic Br and particulate Br and between volatile inorganic I and particulate I have been reported (e.g., Rancher and Kritz, 1980; Pszenny et al., 2004). Although the lack of speciation precludes unambiguous interpretation, these relationships are also consistent with predictions based on the halogen activation mechanism.

Large diurnal variabilities in O₃ measured over the remote subtropical Atlantic and Indian Oceans (Dickerson et al., 1999; Burkert et al., 2003) and early morning depletions of O₃ observed in the remote temperate MBL (Galbally et al., 2000) indicate that only about half of the inferred O₃ destruction in the MBL can be explained by conventional HO_x/NO_x chemistry. Model calculations suggest that Br⁻ and I⁻ radical chemistry could account for a “missing” O₃ sink of this magnitude (Dickerson et al., 1999; Stutz et al., 1999; McFiggans et al., 2000; von Glasow et al., 2002b). In addition to the pathway for O₃ destruction given by R AX2-39 to R AX2-41, in areas with high concentrations of halogen radicals the following generic loss pathways for O₃ can occur in the Arctic at the onset of spring and also over salt flats near the Dead Sea (Hebestreit et al., 1999) and the Great Salt Lake (Stutz et al., 2002) analogous to their occurrence in the lower stratosphere (Yung et al., 1980).



Note that the self reaction of ClO radicals is likely to be negligible in the troposphere. There are three major reaction pathways involved in reaction AX2-47. Short-lived radical species are

produced. These radicals rapidly react to yield monoatomic halogen radicals. In contrast to the situation in marine air, where DOAS measurements indicate BrO concentrations of 1 to 3 ppt, Stutz et al. (2002) found peak BrO concentrations of about 6 ppt and peak ClO concentrations of about 15 ppt. They also derived a correlation coefficient of -0.92 between BrO and O_3 but much smaller values of r between ClO and O_3 . Stutz et al. attributed the source of the reactive halogens to concentrated high molality solutions or crystalline salt around salt lakes, conditions that do not otherwise occur in more dilute or ocean salt water. They also suggest that halogens may be released from saline soils. The inferred atmospheric concentrations of Cl are about $10^5/\text{cm}^3$, or about a factor of 100 higher than found in the marine boundary layer by Rudolph et al. (1997) indicating that, under these conditions, the Cl initiated oxidation of hydrocarbons could be substantial.

Most of the well-established multiphase reactions tend to reduce the rate of O_3 formation in the polluted troposphere. Direct reactions of O_3 and atmospheric particles appears to be too slow to reduce smog significantly. Removal of HO_2 onto hydrated particles will decrease the production of O_3 by the reaction of HO_2 with NO. The uptake of NO_2 and HNO_3 will also result in the production of less O_3 . Conditions leading to high concentrations of Br, Cl, and I radicals can lead to O_3 loss. The oxidation of hydrocarbons (especially alkanes) by Cl radicals, in contrast, may lead to the rapid formation of peroxy radicals and faster smog production in coastal environments where conditions are favorable for the release of gaseous Cl from the marine aerosol. There is still considerable uncertainty regarding the role of multiphase processes in tropospheric photochemistry and so results should be viewed with caution and an appreciation of their potential limitations.

AX2.2.10.4 Reactions on the Surfaces of Crustal Particles

Field studies have shown that O_3 levels are reduced in plumes containing high particle concentrations (e.g., DeReus et al., 2000; Berkowitz et al., 2001; Gaffney et al., 2002). Laboratory studies of the uptake of O_3 on untreated mineral surfaces (Hanisch and Crowley, 2003; Michel et al., 2002, 2003) have shown that O_3 is lost by reaction on these surfaces and this loss is catalytic. Values of γ of $1.2 \pm 0.4 \times 10^{-4}$ were found for reactive uptake on $\alpha\text{-Al}_2\text{O}_3$ and $5 \pm 1 \times 10^{-5}$ for reactive uptake on SiO_2 surfaces. Usher et al. (2003) found mixed behavior for O_3 uptake on coated surfaces with respect to untreated surfaces. They found that γ drops

from $1.2 \pm 0.4 \times 10^{-4}$ to $3.4 \pm 0.6 \times 10^{-5}$ when $\alpha\text{-Al}_2\text{O}_3$ surfaces are coated with NO_3 derived from HNO_3 , whereas they found that γ increases to $1.6 \pm 0.2 \times 10^{-4}$ after these surfaces have been pretreated with SO_2 . Usher et al. also pretreated surfaces of SiO_2 with either a C8-alkene or a C8-alkane terminated organotrichlorosilane. They found that γ increased to $7 \pm 2 \times 10^{-5}$ in the case of treatment with the alkene, but that it decreased to $3 \pm 1 \times 10^{-5}$ for treatment with the alkane. Usher et al. (2003) suggested, on the basis of these results that mineral dust particles coated with nitrates or alkanes will affect O_3 less than dust particles that have accumulated coatings of sulfite or alkenes. These studies indicate the importance of aging of airborne particles on their ability to take up atmospheric gases. Reactions such as these may also be responsible for O_3 depletions observed in dust clouds transiting the Pacific Ocean.

Underwood et al. (2001) studied the uptake of NO_2 and HNO_3 on the surfaces of dry mineral oxides (containing Al, Ca, Fe, Mg, Si and Ti) and naturally occurring mineral dust. A wide range of values of $\gamma(\text{NO}_2)$ were found, ranging from $< 4 \times 10^{-10}$ for SiO_2 to 2×10^{-5} for CaO, with most other values $\sim 10^{-6}$. Values of γ for Chinese loess and Saharan dust were also of the order of 10^{-6} . They found that as the reaction of NO_2 proceeds on the surfaces that reduction to NO occurs. They recommended a value of γ for HNO_3 of about 1×10^{-3} . Not surprisingly, the values of γ increased from those given above if the surfaces were wetted. Underwood et al. (2001) also suggested that the uptake of NO_2 was likely to be only of marginal importance but that uptake of HNO_3 could be of significance for photochemical oxidant cycles.

Li et al. (2001) examined the uptake of acetaldehyde, acetone and propionaldehyde on the same mineral oxide surfaces listed above. They found that these compounds weakly and reversibly adsorb on SiO_2 surfaces. However, on the other oxide surfaces, they irreversibly adsorb and can form larger compounds. They found values of γ ranging from 10^{-6} to 10^{-4} . These reactions may reduce O_3 production efficiency in areas of high mineral dust concentration such as the American Southwest or in eastern Asia as noted earlier.

AX2.2.10.5 Reactions on the Surfaces of Aqueous H_2SO_4 Solutions

The most recent evaluation of Photochemical and Chemical Data by the Jet Propulsion Laboratory (Jet Propulsion Laboratory, 2003) includes recommendations for uptake coefficients of various substances on a variety of surfaces including aqueous H_2SO_4 solutions. Although much of the data evaluated have been obtained mainly for stratospheric applications, there are

studies in which the range of environmental parameters is compatible with those found in the troposphere. In particular, the uptake of N_2O_5 on the surface of aqueous H_2SO_4 solutions has been examined over a wide range of values. Typical values of γ are of the order of 0.1 (e.g., Jet Propulsion Laboratory, 2003). Values of γ for NO_2 are much lower (5×10^{-7} to within a factor of three) and thus the uptake of NO_2 on the surface of aqueous H_2SO_4 solutions is unlikely to be of importance for oxidant cycles. The available data indicate that uptake of OH and HO_2 radicals could be significant under ambient conditions with values of γ of the order of 0.1 or higher for OH, and perhaps similar values for HO_2 .

AX2.2.10.6 Oxidant Formation in Particles

Water is a major component of submicron particles in the atmosphere. However, photochemical reactions in particles have not been studied to the same extent as they have in hydrometeors (e.g., Lelieveld and Crutzen, 1991). Friedlander and Yeh (1998) point out that H_2O_2 and hydroxymethylhydroperoxide (HOCH_2OOH) are especially likely to be found in the aqueous component of atmospheric particles, based on observed gas-phase concentrations and Henry's law solubility data; the concentrations in particles could be higher if the condensed hydroperoxides form peroxyhydrate complexes (Wexler and Sarangapani, 1998). Laboratory studies have found that UV irradiation of dissolved organic carbon (DOC) in collected cloudwater samples is a source of free radicals to the aqueous phase (Faust et al., 1992, 1993) but the mechanisms involved and the atmospheric fate of these radicals are unclear. Chemical reactions involving dissolved transition metal ions could also provide significant sources of radicals in particles (Jacob, 2000). However, only about 10 to 15% of the mass of organic compounds in particles are quantified typically, but many of the compounds, in particular aldehydes, could photolyze to produce free radicals. There are three basic mechanisms for the formation of SOA (Pandis et al., 1992; Seinfeld and Pankow, 2003). These are (1) condensation of oxidized end-products of photochemical reactions (e.g., ketones, aldehydes, organic acids, and hydroperoxides), (2) adsorption of semivolatile organic compounds (e.g., polycyclic aromatic hydrocarbons) onto existing organic particles, and (3) dissolution of water-soluble gases that can then undergo subsequent reactions in particles (e.g., aldehydes). The first and third mechanisms are expected to be of major importance during the summer when photochemistry is at its peak. Information about the chemistry of formation of secondary organic aerosol (SOA) was reviewed

in Section 3.3.1 and available information about the composition of organic compounds in particles was summarized in Appendix 3C of the latest PM AQCD (U.S. Environmental Protection Agency, 2004). It should be noted that reactive oxygen species (ROS) are also formed during the production of SOA. In addition, polymerization of the products of the reaction of α -pinene with O_3 occurs (Tolocka et al., 2004).

Recent measurements of aerosol-phase ROS in Rubidoux, CA and New York City have revealed relatively high concentrations, of the order of 5 to 6×10^{-7} in Rubidoux and 1×10^{-7} $M m^{-3}$ in New York City, expressed as equivalent H_2O_2 (Venkatachari et al., 2005a,b). The ROS were found in particles of all sizes, with particularly high concentrations in the ultrafine range. However, this finding could result from the condensation of vapors onto particles occurring during adiabatic expansion in the nano stages of the sampler. A weak correlation was found with O_3 , but large ROS concentrations were still found at night and in winter. The composition and sources of the ROS are not clear. Millimolar concentrations of hydroperoxides, as estimated by Friedlander and Yeh (1998), would contribute only 10^{-12} $M m^{-3}$ based on a typical liquid water volume fraction in air of 10^{-9} . Formation of peroxyhydrates would lead to higher values but would have to be very large to account for the ROS observations. Ozone and PAN are orders of magnitude less water-soluble than the hydroperoxides (Jacob, 2000) and would not contribute significantly to the ROS. Radical oxidants (e.g., OH or the superoxide ion O_2^-) do not seem to be present in sufficient abundance in the atmosphere to possibly account for the ROS (Jacob, 2000). Low-volatility organic peroxides produced from the oxidation of large substituted organic compounds could possibly make a major contribution. Formation of these peroxides in the aerosol phase could be facilitated by photochemical reactions of dissolved organic components (Anastasio et al., 1997) and by reactions of transition metals (Jacob, 2000). Transition metals participate in the Haber-Weiss set of reactions, including Fenton's reaction, generating free radicals from hydrogen peroxide even in the dark. ROS would also be formed in the reaction of isoprene with O_3 (Claeys et al., 2004b).

Reactions of ozone with monoterpenes have been shown to produce oxidants in the aerosol phase. Docherty et al. (2005) found evidence for the substantial production of organic hydroperoxides in SOA resulting from the reaction of monoterpenes with O_3 . Analysis of the SOA formed in their environmental chamber indicated the SOA was mainly organic hydroperoxides. In particular, they obtained yields of 47% and 85% of organic peroxides from

the oxidation of α - and β -pinene. The hydroperoxides then react with aldehydes in particles to form peroxyhemiacetals, which can either rearrange to form other compounds such as alcohols, esters, and acids or revert back to the hydroperoxides. The aldehydes may be produced in addition to the hydroperoxides during the oxidation of the monoterpenes. Monoterpenes also react with OH radicals resulting, however, in the production of more lower molecular weight products than in their reaction with O₃. Bonn et al. (2004) estimated that hydroperoxides lead to 63% of global SOA formation from the oxidation of terpenes. The oxidation of anthropogenic aromatic hydrocarbons by OH radicals may also produce organic hydroperoxides in SOA (Johnson et al., 2004). Although the results of chamber and modeling studies indicate substantial production of organic hydroperoxides, it should be noted that data for organic hydroperoxides in ambient aerosol samples are sparse.

AX2.2.10.7 Ozone Reaction Indoors

Ozone chemical reactions indoors are analogous to those occurring in ambient air. Ozone reacts with unsaturated VOCs in the indoor environment, primarily terpenes or terpene-related compounds from cleaning products, air fresheners, and wood products. The reactions are dependent on the O₃ indoor concentration, the indoor temperature and, in most cases, the air exchange rate/ventilation rate. Some of the reaction products may more negatively impact human health and artifacts in the indoor environment than their precursors (Wolkoff et al., 1999; Wilkins et al., 2001; Weschler et al., 1992; Weschler and Shields, 1997; Rohr et al., 2002; Nøjgaard et al., 2005). Primary reaction products are Criegee biradicals, nitrate radicals, and peroxyacetyl radicals. Secondary reaction products are hydroxy, alkyl, alkylperoxy, hydroperoxy, and alkoxy radicals. Reactions with alkenes can produce aldehydes, ketones, and organic acids (Weschler and Shields, 2000; Weschler et al., 1992).

AX2.3 PHYSICAL PROCESSES INFLUENCING THE ABUNDANCE OF OZONE

The abundance and distribution of O₃ in the atmosphere is determined by complex interactions between meteorology and chemistry. This section will address these interactions, based mainly on the results of field observations. The importance of a number of transport

mechanisms, whose understanding has undergone significant advances since the last AQCD for O₃, will be discussed in this section.

Major episodes of high O₃ concentrations in the eastern United States and in Europe are associated with slow moving, high pressure systems. High pressure systems during the warmer seasons are associated with the sinking of air, resulting in warm, generally cloudless conditions, with light winds. The sinking of air results in the development of stable conditions near the surface which inhibit or reduce the vertical mixing of O₃ precursors. The combination of inhibited vertical mixing and light winds minimizes the dispersal of pollutants emitted in urban areas, allowing their concentrations to build up. Photochemical activity involving these precursors is enhanced because of higher temperatures and the availability of sunlight. In the eastern United States, high O₃ concentrations during a large scale episode can extend over a hundred thousand square kilometers for several days. These conditions have been described in greater detail in AQCD 96. The transport of pollutants downwind of major urban centers is characterized by the development of urban plumes. However, the presence of mountain barriers can limit mixing as in Los Angeles and Mexico City and will result in even longer periods and a higher frequency of days with high O₃ concentrations. Ozone concentrations in southern urban areas, such as Houston, TX and Atlanta, GA tend to follow this pattern and they tend to decrease with increasing wind speed. In northern cities, like Chicago, IL; New York, NY; and Boston, MA the average O₃ concentrations over the metropolitan areas increase with wind speed indicating that transport of O₃ and its precursors from upwind areas is important (Husar and Renard, 1998; Schichtel and Husar, 2001).

Aircraft observations indicate that there can be substantial differences in mixing ratios of key species between the surface and the atmosphere above (Fehsenfeld et al., 1996a; Berkowitz and Shaw, 1997). Convective processes and small scale turbulence transport O₃ and other pollutants both upward and downward throughout the planetary boundary layer and the free troposphere. Ozone and its precursors were found to be transported vertically by convection into the upper part of the mixed layer on one day, then transported overnight as a layer of elevated mixing ratios and then entrained into a growing convective boundary layer downwind and brought back down to the surface. High concentrations of O₃ showing large diurnal variations at the surface in southern New England were associated with the presence of such layers (Berkowitz et al., 1998). Because of wind shear, winds several hundred meters above the ground

can bring pollutants from the west, even though surface winds are from the southwest during periods of high O₃ in the eastern United States (Blumenthal et al., 1997). Low level nocturnal jets can also transport pollutants hundreds of kilometers. Turbulence associated with them can bring these pollutants to the surface and in many locations result in secondary O₃ maxima in the early morning (Corsmeier et al., 1997). Based on analysis of the output of model studies conducted by Kasibhatla and Chameides (2000), Hanna et al. (2001) concluded that O₃ can be transported over thousands of kilometers in the upper boundary layer of the eastern half of the United States during specific O₃ episodes.

Stratospheric-tropospheric exchange (STE) will be discussed in Section AX2.3.1. The vertical redistribution of O₃ and other pollutants by deep, or penetrating convection is discussed in Section AX2.3.2. The potential importance of transport of O₃ and precursors by low-level jets is the topic of Section AX2.3.3. Issues related to the transport of O₃ from North America are presented in Section AX2.3.4. Relations of O₃ to solar ultraviolet radiation and temperature will then be discussed in Section AX2.3.5.

AX2.3.1 Stratospheric-Tropospheric Ozone Exchange (STE)

In the stratosphere, O₃ formation is initiated by the photodissociation of molecular oxygen (O₂) by solar ultraviolet radiation at wavelengths less than 242 nm. Almost all of this radiation is absorbed in the stratosphere (except for regions near the tropical tropopause), preventing this mechanism from occurring in the troposphere. Some of the O₃ in the stratosphere is transported downward into the troposphere. The potential importance of this source of tropospheric O₃ has been recognized since the early work of Regener (1941), as cited by Junge (1963). Stratospheric-tropospheric exchange (STE) of O₃ and stratospheric radionuclides produced by the nuclear weapons tests of the 1960s is at a maximum during late winter and early spring (e.g., Ludwig et al., 1977). Since AQCD 96 on O₃ substantial new information from numerical models, field experiments and satellite-based observations has become available. The following sections outline the basic atmospheric dynamics and thermodynamics of stratosphere/troposphere exchange and review these new developments.

There are several important mechanisms for injecting stratospheric O₃ into the troposphere, they include tropopause folds (Reed, 1955; Danielsen, 1968), cutoff lows (Price and Vaughan, 1993), clear air turbulence, mesoscale convective complexes and thunderstorms, breaking

gravity waves (Poulida et al., 1996; Langford and Reid, 1998; Stohl et al., 2003) and streamers. Streamers are dry, stratospheric intrusions visible in satellite water vapor imagery that are sheared into long filamentary structures that often roll into vortices and exhibit visible evidence of the irreversible mixing of moist subtropical tropospheric and dry polar stratospheric air (Appenzeller et al., 1996; Wimmers et al., 2003). They are often present at a scale that eludes capture in large scale dynamical models of the atmosphere that cannot resolve features less than 1 degree (~100 km). Empirical evidence for stratospheric intrusions comes from observations of indicators of stratospheric air in the troposphere. These indicators include high potential vorticity, low water vapor mixing ratios, high potential temperature, enhancements in the ratio of ^7Be to ^{10}Be in tropospheric aerosols, as well as enhancements in O_3 mixing ratios and total column amounts. These quantities can be observed with in situ aircraft and balloons, as well as remotely sensed from aircraft and ground-based lidars and both geostationary and polar (low earth orbiting) space platforms.

The exchange of O_3 between the stratosphere and the troposphere in middle latitudes occurs to a major extent by tropopause folding events (Reiter, 1963, 1975; Reiter and Mahlman, 1965; Danielsen, 1968, 1980; Danielsen and Mohnen, 1977). The term, tropopause folding is used to describe a process in which the tropopause intrudes deeply into the troposphere along a sloping frontal zone bringing air from the lower stratosphere with it. Tropopause folds occur with the formation of upper level fronts associated with transverse circulations that develop around the core of the polar jet stream. South of the jet stream core, the tropopause is higher than to the north of it. The tropopause can be imagined as wrapping around the jet stream core and folding beneath it and extending into the troposphere (cf., Figure AX2-7a). Although drawn as a heavy solid line, the tropopause should not be imagined as a material surface, through which there is no exchange. Significant intrusions of stratospheric air occur in “ribbons” ~200 to 1000 km in length, 100 to 300 km wide and about 1 to 4 km thick (Hoskins, 1972; Wimmers et al., 2003). These events occur throughout the year and their location follows the seasonal displacement of the polar jet stream.

The seasonal cycle of O_3 exchange from the stratosphere into the troposphere is not caused by a peak in the seasonal cycle of upper tropospheric cyclone activity. Instead, it is related to the large scale pattern of tracer transport in the stratosphere. During winter in the Northern Hemisphere, there is a maximum in the poleward, downward transport of mass, which moves O_3

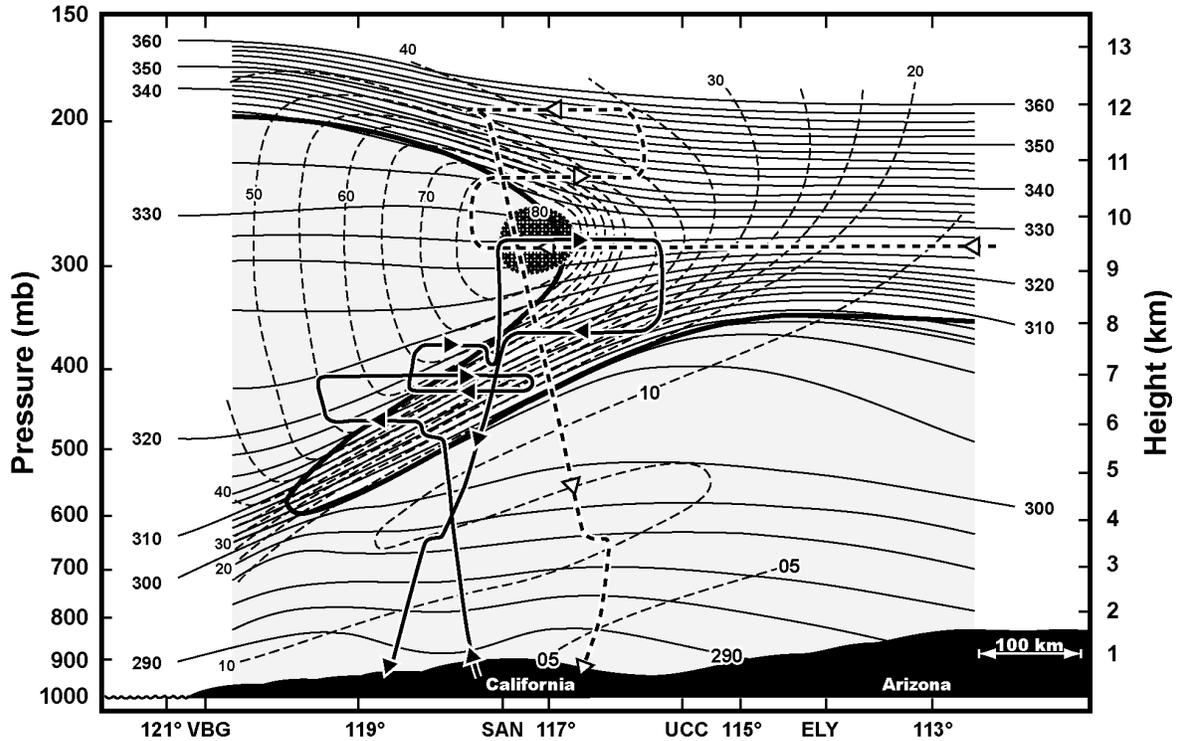


Figure AX2-7a. Cross section through a tropopause folding event on March 13, 1978 at 0000 GMT. Potential temperatures (K) are represented by thin solid lines. Wind speeds (m s^{-1}) are given by thin dashed lines. The hatched area near the center of the figure indicates the location of the jet stream core. The tropopause defined by a potential vorticity of $100 \times 10^{-7} \text{ K mb}^{-1} \text{ s}^{-1}$ is shown as the heavy solid line. The two Sabreliner flight tracks through this cross section are shown as a heavy solid line with filled arrows and heavy dashed line with open arrows. Longitude is shown along the x-axis. Upper air soundings were taken at Vandenberg AFB, CA (VBG); San Diego, CA (SAN); Winnemucca, NV (UCC); and Ely, NV (ELY).

Source: Adapted from Shapiro (1980).

from the tropical upper stratosphere to the lower stratosphere of the polar- and midlatitudes. This global scale pattern is controlled by the upward propagation of large-scale and small-scale waves generated in the troposphere. As the energy from these disturbances dissipates, it drives this stratosphere circulation. As a result of this process, there is a springtime maximum in the total column abundance of O_3 over the poles. The concentrations of O_3 (and other trace

substances) build up in the lower stratosphere until their downward fluxes into the lower stratosphere are matched by increased fluxes into the troposphere. Thus, there would be a springtime maximum in the flux of O₃ into the troposphere even if the flux of stratospheric air through the tropopause by tropopause folding remained constant throughout the year (Holton et al., 1995). Indeed, cyclonic activity in the upper troposphere is active throughout the entire year in transporting air from the lower stratosphere into the troposphere (Mahlman, 1997). Oltmans et al. (1996) and Moody et al. (1996) provide evidence that stratospheric intrusions contribute to the O₃ abundance in the upper troposphere over the North Atlantic even during the summer.

There are a number of techniques that have been used to quantify the amount of O₃ in the free troposphere or even the amount of O₃ reaching the surface that can be attributed to downward transport from the stratosphere. Earlier work, cited in AQCD 96 relied mainly on the use of ⁷Be as a tracer of stratospheric air. However, its use is ambiguous because it is also formed in the upper troposphere. Complications also arise because its production rate is also sensitive to solar activity (Lean, 2000). The ratio of ⁷Be to ¹⁰Be provides a much more sensitive tracer of stratospheric air than the use of ⁷Be alone (Jordan et al., 2003). More recent work than cited in AQCD 96 has focused on the use of potential vorticity (PV) as a tracer of stratospheric air. Potential vorticity is a *dynamical tracer* used in meteorology. Generally, PV is calculated from wind and temperature observations and represents the rotational tendency of a column of air weighted by the static stability, which is just the distance between isentropic surfaces. This quantity is a maximum in the lower stratosphere where static stability is great and along the jet stream where wind shear imparts significant rotation to air parcels. As air moves from the stratosphere to the troposphere, PV is conserved, and therefore it *traces* the motion of O₃. The static stability is lower in the troposphere, so to preserve PV, fluid rotation will increase. This is why STE is associated with cyclogenesis, or the formation of storms along the polar jet stream. Dynamical models clearly capture this correspondence between the location of storm tracks and preferred regions for STE. However, because PV is destroyed at a faster rate with increasing depth, it is not useful as a tracer of stratospheric air reaching the surface. Appenzeller et al. (1996) found that maps of PV coupled with satellite images of humidity can provide indications of the intrusion of stratospheric air into the troposphere, however, they had no measurements of O₃. Even if measurements of O₃ were available, the extrapolation of any relations to other events

would still be problematic as Olsen et al. (2002) have noted that there are seasonal and geographic variations in the relation between O_3 and PV. Recent flights of the NCAR C130 during the TOPSE campaign measured in situ O_3 , and curtains of O_3 above and below the aircraft observed with a lidar and clearly showed a correspondence between high PV and stratospheric levels of O_3 and satellite depictions of dry air indicating the presence of tropopause folding (Wimmers and Moody, 2004a,b).

Detailed cross sections through a tropopause folding event showing atmospheric structure, O_3 mixing ratios and condensation nuclei (CN) counts are given in Figures AX2-7a, AX2-7b, and AX2-7c (Shapiro, 1980). Flight tracks of an NCAR Sabreliner obtaining data through the tropopause fold are also shown. The core of the jet stream is indicated by the hatched area near the center of Figure AX2-7a. As can be seen from Figure AX2-7 a and b, there is a strong relation between the folding of the tropopause, indicated by the heavy solid line and O_3 . CN counts during the portions of the flights in the lower troposphere were tropospheric were typically of the order of several $\times 10^3 \text{ cm}^{-3}$ and 100 or less in the stratospheric portion. However, it is clear that CN counts in the fold are much higher than in the stratosphere proper, suggesting that there was active mixing between tropospheric and stratospheric air in the fold. Likewise, it can also be seen from Figure AX2-7b that O_3 is being mixed outside the fold into the middle and upper troposphere. The two data sets shown in Figures AX2-7b and 7c indicate that small scale turbulent processes were occurring to mediate this exchange and that the folds are mixing regions whose chemical characteristics lie between those of the stratosphere and the troposphere (Shapiro, 1980). Chemical interactions between stratospheric and tropospheric constituents are also possible within tropopause folds. These considerations also imply that in the absence of turbulent mixing, tropopause folding can be a reversible process.

Several recent papers have attempted to demonstrate that the atmosphere is a fluid composed of relatively distinct airstreams with characteristic three-dimensional motions and corresponding trace gas signatures. Based on aircraft observations, satellite imagery, and back trajectories, it has been shown that dry airstreams, or dry intrusions (DA or DI) always advect stratospheric O_3 into the middle and upper troposphere (Cooper et al, 2001; Cooper et al., 2002a), however the seasonal cycle of O_3 in the lowermost stratosphere allows greater quantities of O_3 to enter the troposphere during spring (Cooper et al., 2002b). Other work has focused on the signatures of PV to show specific instances of STE (Olsen and Stanford, 2001). This

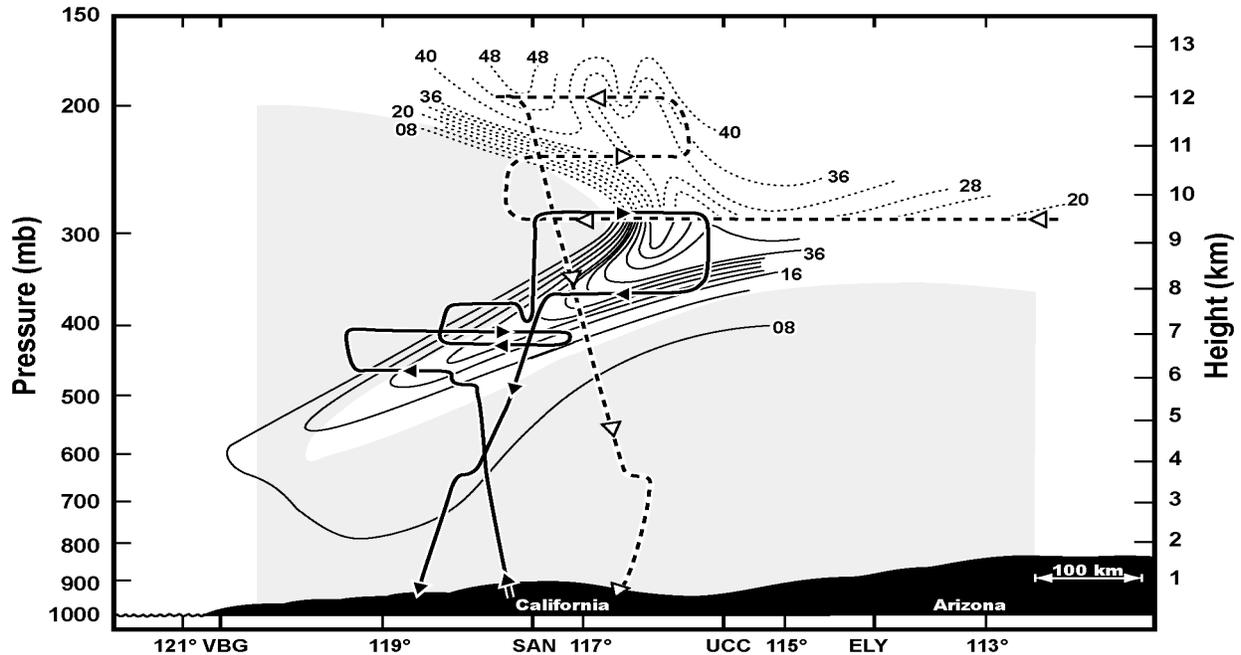


Figure AX2-7b. Ozone mixing ratios pphm (parts per hundred million) corresponding to Figure AX2-7a. The two Sabreliner flight tracks through this cross section are shown as a heavy solid line with filled arrows and a heavy dashed line with open arrows. Longitude is shown along the x-axis. Upper air soundings were taken at Vandenberg AFB, CA (VBG); San Diego, CA (SAN); Winnemucca, NV (UCC); and Ely, NV (ELY).

Source: Adapted from Shapiro (1980).

correlation between TOMS gradients and PV was also used to derive the annual mass flux of O_3 from STE and generated an estimate somewhat higher (500 Tg/yr over the Northern Hemisphere) than the estimates of most general circulation models. The IPCC has reported a large range of model estimates of STE, expressed as the net global flux of O_3 in Tg/yr, from a low of 390 to a high of 1440 (reproduced as Table AX3-15). A few other estimates have been made based on chemical observations in the lower stratosphere, or combined chemistry and dynamics (450 Tg/yr Murphy and Fahey, 1994; 510 Tg/yr extratropics only, Gettleman et al., 1997; and 500 Tg/yr midlatitude NH only (30 to 60N) (Olsen et al., 2002). These values illustrate the large degree of uncertainty that remains in quantifying this important source of O_3 .

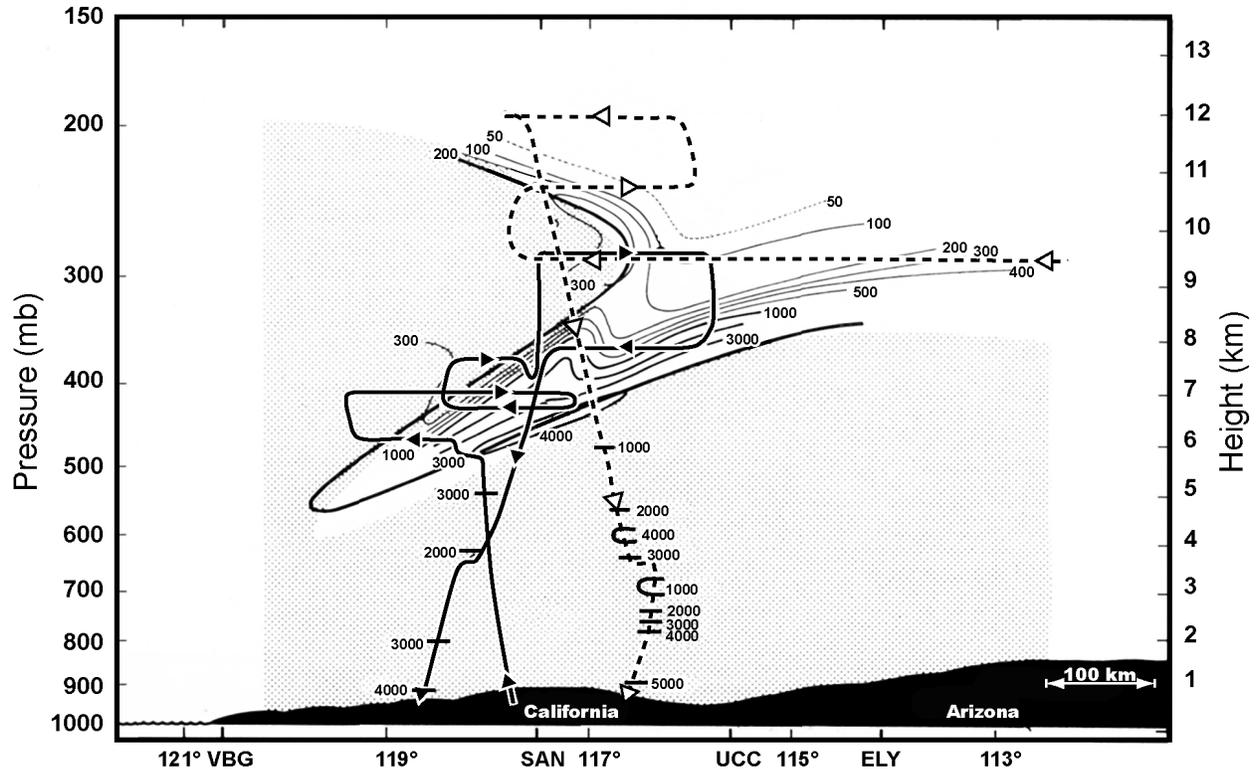


Figure AX2-7c. Condensation nuclei concentrations (particles cm^{-3}) corresponding to Figure AX2-7a. The two flight Sabreliner flight tracks through this cross section are shown as a heavy solid line with filled arrows and a heavy dashed line with open arrows. Longitude is shown along the x-axis. Upper air soundings were taken at Vandenberg AFB, CA (VBG); San Diego, CA (SAN); Winnemucca, NV (UCC); and Ely, NV (ELY).

Source: Adapted from Shapiro (1980).

Based on the concept of tracing airstream motion, a number of Lagrangian model studies have resulted in climatologies that have addressed the spatial and temporal variability in stratosphere to troposphere transport (Stohl, 2001; Wernli and Borqui, 2002; Seo and Bowman, 2002; James et al., 2003a,b; Sprenger and Wernli, 2003; Sprenger et al., 2003). Both Stohl (2001) and Sprenger et al. (2003) produced one year climatologies of tropopause folds based on a 1° by 1° gridded meteorological data set. They each found the probability of deep folds (penetrating to the 800 hPa level) was a maximum during winter (December through February). The highest frequency of folding extended from Labrador down the east coast of North America.

However, these deep folds occurred less than 1% of the six hour intervals for which meteorological data is assimilated for grid points in the United States. They observed a higher frequency of more shallow folds (penetrating to the upper troposphere) and medium folds (penetrating to levels between 500 and 600 hPa) of about 10% and 1 to 2% respectively. These events occur preferentially across the subtropics and the southern United States. At higher latitudes other mechanisms such as the erosion of cutoff lows and the breakup of stratospheric streamers are likely to play an important role in STE. Stohl (2001) also described the region of strong stirring in the upper extratropical troposphere related to the midlatitude storm tracks. Stohl (2001) demonstrated that airstreams with strong vertical motion are all highly incoherent, they stir their air parcels into a new environment, producing filamentary tracer structures and paving the way for subsequent mixing. A 15-year climatology by Sprenger and Wernli (2003) shows the consistent pattern of STE occurring over the primary storm tracks in the Pacific and Atlantic along the Asian and North American coasts. This climatology, and the one of James et al. (2003a,b) both found that recent stratospheric air associated with deep intrusions are relatively infrequent occurrences in these models. Thus, stratospheric intrusions are most likely to directly affect the middle and upper troposphere and not the planetary boundary layer. However, this O₃ can still exchange with the planetary boundary layer through convection as described later in this subsection and in Section AX2.3.2, AX2.3.3 and AX2.3.4.

Interannual variations in STE are related to anomalies in large-scale circulation such as the North Atlantic Oscillation which causes changes in storm track positions and intensities, and the El Niño-Southern Oscillation, which results in anomalous strong convection over the eastern Pacific (James et al., 2003a,b). It should also be remembered that the downward flux of O₃ into the troposphere is related to the depletion of O₃ within the wintertime stratospheric polar vortices. The magnitude of this depletion and the transport of O₃ depleted air to midlatitudes in the stratosphere (Mahlman et al., 1994; Hadjinicolaou and Pyle, 2004) shows significant interannual variability which may also be reflected in the downward flux of O₃ into the troposphere. All of these studies, from the analysis of individual events to multiyear climatologies are based on the consideration of the three-dimensional motion of discrete airstreams in the atmosphere. However, there is a significant body of work that reports that airstreams are not entirely independent of each other (Cooper et al., 2004a,b). Midlatitude cyclones typically form in a sequential manner, some trailing in close proximity along a

quasi-stationary frontal boundary, with each system influenced by remnants of other systems. For example, a rising stream of air ahead of a cold front (also known as a warm conveyor belt or WCB) on the back (western) side of a surface anticyclone may entrain air that has subsided anticyclonically into the surface high pressure system from the upper troposphere and the lower stratosphere (also known as a Dry Airstream or DA) that intruded into the mid-troposphere in a cyclone that is further downstream. Convective mixing of the boundary layer in the WCB will distribute this enhanced O₃ throughout the lower troposphere and down to the surface (Davies and Shuepbach, 1994; Cooper and Moody, 2000). The net effect is that the DA of one cyclone may feed into the WCB of the system immediately upwind. Similarly, the lofting of warm moist air in the WCB may inject surface emissions into the upper troposphere adjacent to the western side of the subsiding Dry Airstream of the storm system immediately downwind, with subsequent interleaving of these two airstreams (Prados et al., 1999; Parrish et al., 2000; Cooper et al., 2004a,b) as illustrated schematically in Figure AX2-8. The ultimate mixing of these airstreams, which inevitably occurs at a scale that is not resolved by current models confounds our ability to attribute trace gases to their sources.

These studies suggest that both downward transport from the stratosphere and upward transport from the atmospheric boundary layer act in concert with their relative roles determined by the balance between the amount of O₃ in the lower stratosphere and the availability of free radicals to initiate the photochemical processes forming O₃ in the boundary layer. Dickerson et al. (1995) pointed out that springtime maxima in O₃ observed in Bermuda correlate well with maxima in carbon monoxide. Carbon monoxide, O₃ and its photochemical precursors may have been transported into the upper troposphere from the polluted continental boundary layer by deep convection. The photochemical processes involve the buildup of precursors during the winter at Northern mid- and high latitudes. Parrish et al. (1999) have noted that reactions occurring during the colder months may tend to titrate O₃. However, as NO_x and its reservoirs are transported southward they can initiate O₃ formation through reactions described in Section AX2.2 (see also Stroud et al., 2003).

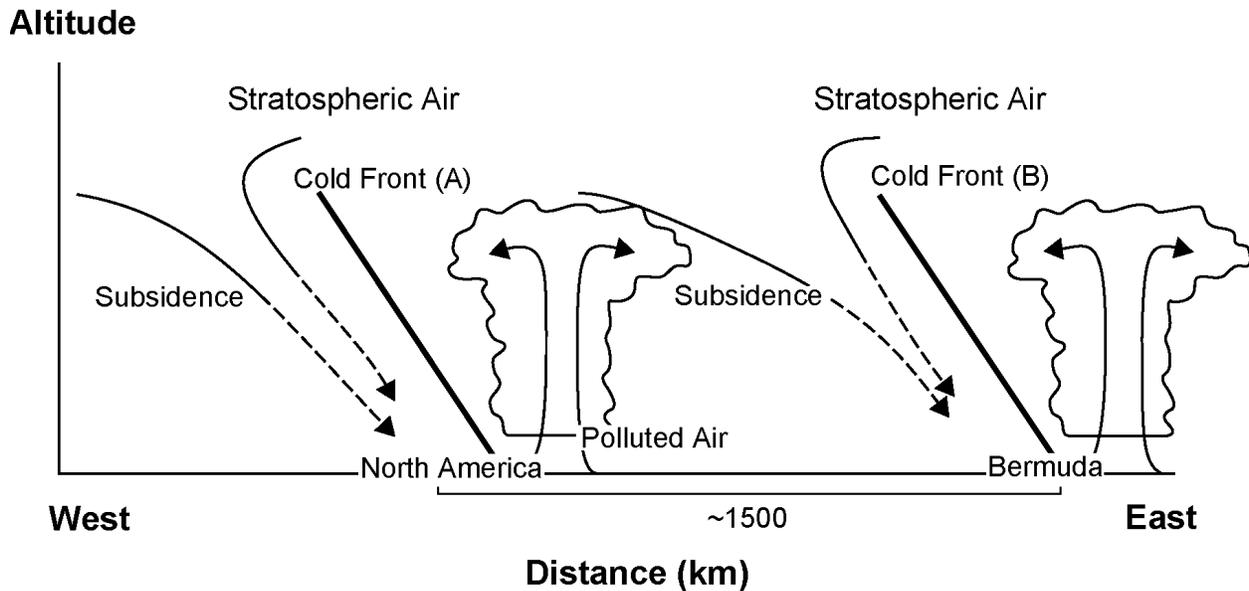


Figure AX2-8. Schematic diagram of a meteorological mechanism involved in high concentrations of O_3 found in spring in the lower troposphere off the American east coast. Subsidence behind the first cold front meets convection ahead of a second cold front such that polluted air and O_3 from the upper troposphere/lower stratosphere are transported in close proximity (or mixed) and advected over the north Atlantic Ocean. The vertical scale is about 10 km; the horizontal scale about 1500 km. (Note that not all cold fronts are associated with squall lines and that mixing occurs even in their absence.)

Source: Prados (2000).

AX2.3.2 Deep Convection in the Troposphere

Much of the upward motion in the troposphere is driven by convergence in the boundary layer and deep convection. Deep convection, as in developing thunderstorms can transport pollutants rapidly to the middle and upper troposphere (Dickerson et al., 1987). The outflow from these systems results in the formation of layers with distinctive chemical properties in the middle troposphere. In addition, layers are formed as the result of stratospheric intrusions. Layers ranging in thickness typically from 0.3 to about 2 km in the middle troposphere (mean altitudes between 5 and 7 km) are ubiquitous and occupy up to 20% of the troposphere to 12 km (Newell et al., 1999). The origin of these layers can be judged by analysis of their chemical

composition (typically by comparing ratios of H₂O, O₃ and CO to each other) or dynamical properties (such as potential vorticity). Thus, pollutants that have been transported into the middle and upper troposphere at one location can then be transported back down into the boundary layer somewhere else.

Crutzen and Gidel (1983), Gidel (1983), and Chatfield and Crutzen (1984) hypothesized that convective clouds played an important role in rapid atmospheric vertical transport of trace species and first tested simple parameterizations of convective transport in atmospheric chemical models. At nearly the same time, evidence was shown of venting of the boundary layer by shallow fair weather cumulus clouds (e.g., Greenhut et al., 1984; Greenhut, 1986). Field experiments were conducted in 1985, which resulted in verification of the hypothesis that deep convective clouds are instrumental in atmospheric transport of trace constituents (Dickerson et al., 1987; Luke, 1997). Once pollutants are lofted to the middle and upper troposphere, they typically have a much longer chemical lifetime and with the generally stronger winds at these altitudes they can be transported large distances from their source regions. Photochemical reactions occur during this long-range transport. Pickering et al. (1990) demonstrated that venting of boundary layer pollutants by convective clouds (both shallow and deep) causes enhanced O₃ production in the free troposphere. Therefore, convection aids in the transformation of local pollution into a contribution to global atmospheric pollution. Downdrafts within thunderstorms tend to bring air with less pollution from the middle troposphere into the boundary layer.

Field studies have established that downward transport of larger O₃ and NO_x mixing ratios from the free troposphere to the boundary layer is an important process over the remote oceans (e.g., Piotrowicz et al., 1991), as well as the upward transport of very low O₃ mixing ratios from the boundary layer to the upper troposphere (Kley et al., 1996). Global modeling by Lelieveld and Crutzen (1994) suggests that the downward mixing of O₃ into the boundary layer (where it is destroyed) is the dominant global effect of deep convection. Some indications of downward transport of O₃ from higher altitudes (possibly from the stratosphere) in the anvils of thunderstorms have been observed (Dickerson et al., 1987; Poulida et al., 1996; Suhre et al., 1997). Ozone is most effective as a greenhouse gas in the vicinity of the tropopause. Therefore, changes in the vertical profile of O₃ in the upper troposphere caused by deep convection have important radiative forcing implications for climate.

Other effects of deep convection include perturbations to photolysis rates, which include enhancement of these rates in the upper portion of the thunderstorm anvil. In addition, thunderstorms are effective in the production of NO by lightning and in wet scavenging of soluble species.

AX2.3.2.1 Observations of the Effects of Convective Transport

Some fraction of shallow fair weather cumulus clouds actively vent boundary layer pollutants to the free troposphere (Stull, 1985). The first airborne observations of this phenomenon were conducted by Greenhut et al. (1984) over a heavily urbanized area, measuring the in-cloud flux of O₃ in a relatively large cumulus cloud. An extension of this work was reported by Greenhut (1986) in which data from over 100 aircraft penetrations of isolated nonprecipitating cumulus clouds over rural and suburban areas were obtained. Ching and Alkezweeny (1986) reported tracer (SF₆) studies associated with nonprecipitating cumulus (fair weather cumulus and cumulus congestus). Their experiments showed that the active cumulus clouds transported mixed layer air upward into the overlying free troposphere and suggested that active cumuli can also induce rapid downward transport from the free troposphere into the mixed layer. A UV-DIAL (Ultraviolet Differential Absorption Lidar) provided space-height cross sections of aerosols and O₃ over North Carolina in a study of cumulus venting reported by Ching et al. (1988). Data collected on evening flights showed regions of cloud debris containing aerosol and O₃ in the lower free troposphere in excess of background, suggesting that significant vertical exchange had taken place during afternoon cumulus cloud activity. Efforts have also been made to estimate the vertical transport by ensembles of nonprecipitating cumulus clouds in regional chemical transport models (e.g., Vukovich and Ching, 1990).

The first unequivocal observations of deep convective transport of boundary layer pollutants to the upper troposphere were documented by Dickerson et al. (1987). Instrumentation aboard three research aircraft measured CO, O₃, NO, NO_x, NO_y, and hydrocarbons in the vicinity of an active mesoscale convective system near the Oklahoma/Arkansas border during the 1985 PRE-STORM experiment. Anvil penetrations about two hours after maturity found greatly enhanced mixing ratios of all of the aforementioned species compared with outside of the cloud. Among the species measured, CO is the best tracer of upward convective transport because it is produced primarily in the boundary layer and has an

atmospheric lifetime much longer than the timescale of a thunderstorm. In the observed storm, CO measurements exceeded 160 ppbv as high as 11 km, compared with ~70 ppbv outside of the cloud (Figure AX2-9a). Cleaner middle tropospheric air appears to have descended in downdrafts forming a pool of lower mixing ratio CO beneath the cloud. Nonmethane hydrocarbons (NMHC) with moderate lifetimes can also serve as tracers of convective transport from the boundary layer. Ozone can also be an indicator of convective transport. In the polluted troposphere large O₃ values will indicate upward transport from the boundary layer, but in the clean atmosphere such values are indicative of downward transport from the uppermost troposphere or lowermost stratosphere. In this case measured O₃ in the upper rear portion of the anvil peaked at 98 ppbv, while boundary layer values were only ~65 ppbv (Figure AX2-9b). It is likely that some higher-O₃ stratospheric air mixed into the anvil.

The large amount of vertical trace gas transport noted by Dickerson et al. (1987) cannot, however, be extrapolated to all convective cells. Pickering et al. (1988) reported airborne measurements of trace gases taken in the vicinity of a line of towering cumulus and cumulonimbus clouds that also occurred during PRE-STORM. In this case trace gas mixing ratios in the tops of these clouds were near ambient levels. Meteorological analyses showed that these clouds were located above a cold front, which prevented entry of air from the boundary layer directly below or near the clouds. Instead, the air entering these clouds likely originated in the layer immediately above the boundary layer which was quite clean. Luke et al. (1992) summarized the air chemistry data from all 18 flights during PRE-STORM by categorizing each case according to synoptic flow patterns. Storms in the maritime tropical flow regime transported large amounts of CO, O₃, and NO_y into the upper troposphere with the midtroposphere remaining relatively clean. During frontal passages a combination of stratiform and convective clouds mixed pollutants more uniformly into the middle and upper levels; high mixing ratios of CO were found at all altitudes.

Prather and Jacob (1997) and Jaeglé et al. (1997) noted that in addition to the primary pollutants (e.g., NO_x, CO, VOCs), precursors of HO_x are also transported to the upper troposphere by deep convection. Precursors of most importance are water vapor, formaldehyde, hydrogen peroxide, methylhydroperoxide, and acetone. HO_x is critical for oxidizing NO to NO₂ in the O₃ production process.

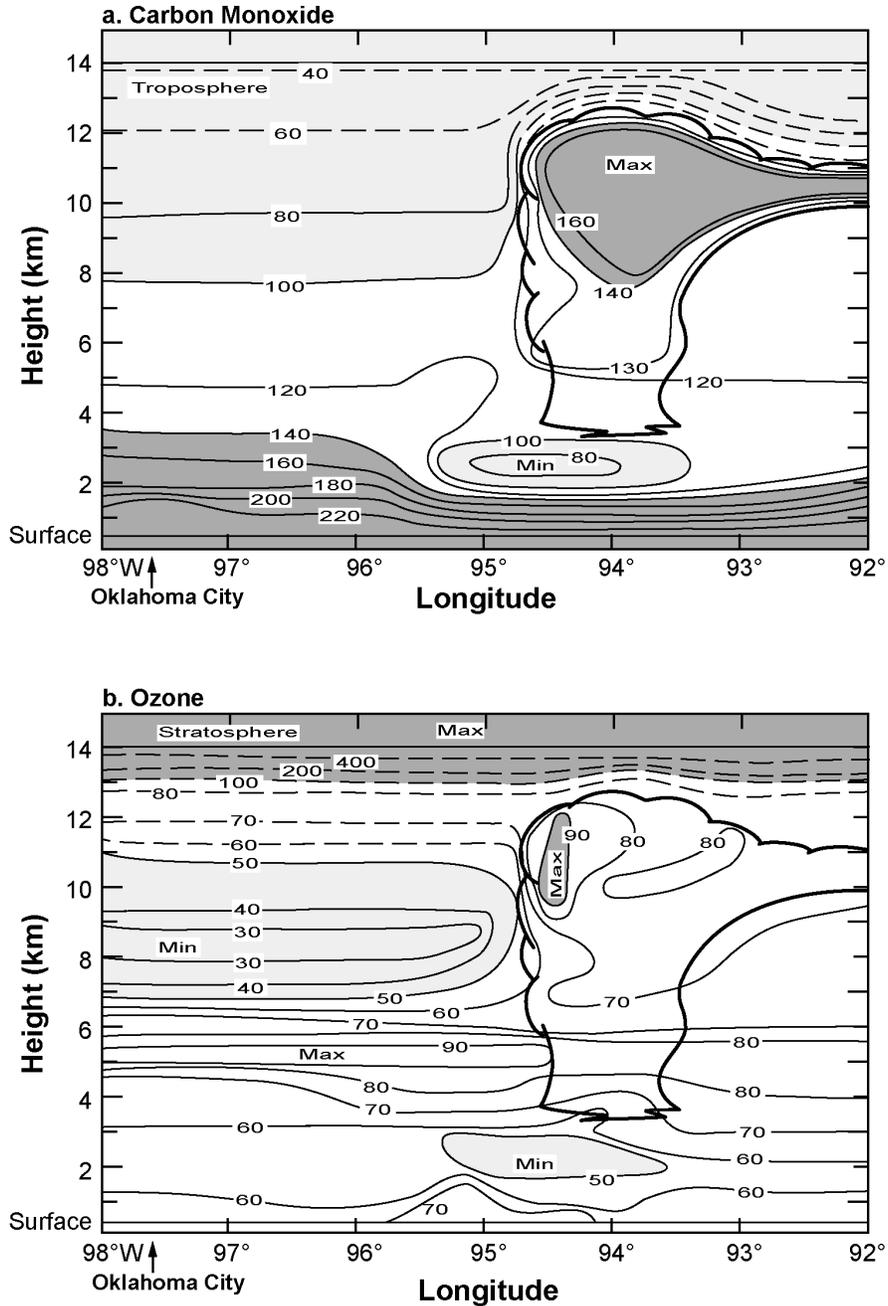


Figure AX2-9a,b. (a) Contour plot of CO mixing ratios (ppbv) observed in and near the June 15, 1985, mesoscale convective complex in eastern Oklahoma. Heavy line shows the outline of the cumulonimbus cloud. Dark shading indicates high CO and light shading indicates low CO. Dashed contour lines are plotted according to climatology since no direct measurements were made in that area. (b) Same as (a) but for O₃ (ppbv).

Source: Dickerson et al. (1987).

Over remote marine areas the effects of deep convection on trace gas distributions differ from that over moderately polluted continental regions. Chemical measurements taken by the NASA ER-2 aircraft during the Stratosphere-Troposphere Exchange Project (STEP) off the northern coast of Australia show the influence of very deep convective events. Between 14.5 and 16.5 km on the February 2 to 3, 1987 flight, perturbations in the chemical profiles were noted that included pronounced maxima in CO, water vapor, and CCN and minima of NO_y and O₃ (Pickering et al., 1993). Trajectory analysis showed that these air parcels likely were transported from convective cells 800 to 900 km upstream. Very low boundary layer mixing ratios of NO_y and O₃ in this remote region were apparently transported upward in the convection. A similar result was noted in CEPEX (Central Equatorial Pacific Experiment; Kley et al., 1996) where a series of ozonesonde ascents showed very low upper tropospheric O₃ following deep convection. It is likely that similar transport of low-O₃ tropical marine boundary layer air to the upper troposphere occurs in thunderstorms along the east coast of Florida. Convection over the Pacific will likely transport halogens to the upper troposphere where they may aid in the destruction of O₃. This low-O₃ convective outflow will likely descend in the subsidence region of the eastern Pacific, leading to some of the cleanest air that arrives at the west coast of the United States.

AX2.3.2.2 Modeling the Effects of Convection

The effects of deep convection may be simulated using cloud-resolving models, or in regional or global models in which the convection is parameterized. The Goddard Cumulus Ensemble (GCE) model (Tao and Simpson, 1993) has been used by Pickering et al. (1991, 1992a,b, 1993, 1996), Scala et al. (1990) and Stenchikov et al. (1996) in the analysis of convective transport of trace gases. The cloud model is nonhydrostatic and contains detailed representation of cloud microphysical processes. Two- and three-dimensional versions of the model have been applied in transport analyses. The initial conditions for the model are usually from a sounding of temperature, water vapor and winds representative of the region of storm development. Model-generated wind fields can be used to perform air parcel trajectory analyses and tracer advection calculations. Once transport calculations are performed for O₃ precursors, a 1-D photochemical model was employed to estimate O₃ production rates in the outflow air from

the convection. These rates were then compared with those prior to convection to determine an enhancement factor due to convection.

Such methods were used by Pickering et al. (1992b) to examine transport of urban plumes by deep convection. Transport of the Oklahoma City plume by the 10–11 June 1985 PRE-STORM squall line was simulated with the 2-D GCE model. In this event forward trajectories from the boundary layer at the leading edge of the storm showed that almost 75% of the low level inflow was transported to altitudes exceeding 8 km. Over 35% of the air parcels reached altitudes over 12 km. Tracer transport calculations were performed for CO, NO_x, O₃, and hydrocarbons. The 3-D version of the GCE model has also been run for the 10–11 June 1985 PRE-STORM case. Free tropospheric O₃ production enhancement of a factor of 2.5 for Oklahoma rural air and ~4 for the Oklahoma City case were calculated.

Stenchikov et al. (1996) used the 2-D GCE model to simulate the North Dakota storm observed by Poulida et al. (1996). This storm showed the unusual feature of an anvil formed well within the stratosphere. The increase of CO and water vapor above the altitude of the preconvective tropopause was computed in the model. The total mass of CO across the model domain above this level increased by almost a factor of two during the convective event. VOCs injected into the lower stratosphere could enhance O₃ production there. Downward transport of O₃ from the stratosphere was noted in the simulation in the rear anvil.

Regional estimates of deep convective transport have been made through use of a traveling 1-D model, regional transport models driven by parameterized convective mass fluxes from mesoscale meteorological models, and a statistical-dynamical approach. Pickering et al. (1992c) developed a technique which uses a combination of deep convective cloud cover statistics from the International Satellite Cloud Climatology Project (ISCCP) and convective transport statistics from GCE model simulations of prototype storms to estimate the amount of CO vented from the planetary boundary layer (PBL) by deep convection. This statistical-dynamical approach was used by Thompson et al. (1994) to estimate the convective transport component of the boundary layer CO budget for the central United States (32.5°–50° N, 90°–105° W) for the month of June. They found that the net upward deep convective flux ($\sim 18 \times 10^5$ kg-CO/month) and the shallow convective flux ($\sim 16 \times 10^5$ kg-CO/month) to the free troposphere accounted for about 80% of the loss of CO from the PBL. These losses roughly balanced horizontal transport of CO ($\sim 28 \times 10^5$ kg-CO/month), the oxidation of hydrocarbons ($\sim 8 \times 10^5$ kg-CO/month) and anthropogenic and

biogenic emissions ($\sim 8 + \sim 1 \times 10^5$ kg-CO/month) into the PBL in the central United States.

In this respect the central United States acts as a “chimney” for venting CO and other pollutants.

Regional chemical transport models have been used for applications such as simulations of photochemical O₃ production, acid deposition, and fine particulate matter. Walcek et al. (1990) included a parameterization of cloud-scale aqueous chemistry, scavenging, and vertical mixing in the chemistry model of Chang et al. (1987). The vertical distribution of cloud microphysical properties and the amount of subcloud-layer air lifted to each cloud layer are determined using a simple entrainment hypothesis (Walcek and Taylor, 1986). Vertically-integrated O₃ formation rates over the northeast U.S. were enhanced by ~50% when the in-cloud vertical motions were included in the model.

Wang et al. (1996) simulated the 10–11 June 1985 PRE-STORM squall line with the NCAR/Penn State Mesoscale Model (MM5; Grell et al., 1994; Dudhia et al., 1993). Convection was parameterized as a subgrid-scale process in MM5 using the Kain and Fritsch (1993) scheme. Mass fluxes and detrainment profiles from the convective parameterization were used along with the 3-D wind fields in CO tracer transport calculations for this convective event. The U.S. Environmental Protection Agency has developed a Community Multiscale Air Quality (CMAQ) modeling system that uses MM5 with the Kain-Fritsch convective scheme as the dynamical driver (Ching et al., 1998).

Convective transport in global chemistry and transport models is treated as a subgrid-scale process that is parameterized typically using cloud mass flux information from a general circulation model or global data assimilation system. While GCMs can provide data only for a “typical” year, data assimilation systems can provide “real” day-by-day meteorological conditions, such that CTM output can be compared directly with observations of trace gases. The NASA Goddard Earth Observing System Data Assimilation System (GEOS-1 DAS and successor systems; Schubert et al., 1993; Bloom et al., 1996) provides archived global data sets for the period 1980 to present, at $2^\circ \times 2.5^\circ$ or better resolution with 20 layers or more in the vertical. Convection is parameterized with the Relaxed Arakawa-Schubert scheme (Moorthi and Suarez, 1992). Pickering et al. (1995) showed that the cloud mass fluxes from GEOS-1 DAS are reasonable for the 10–11 June 1985 PRE-STORM squall line based on comparisons with the GCE model (cloud-resolving model) simulations of the same storm. In addition, the GEOS-1 DAS cloud mass fluxes compared favorably with the regional estimates of convective transport

for the central U.S. presented by Thompson et al. (1994). However, Allen et al. (1997) have shown that the GEOS-1 DAS overestimates the amount and frequency of convection in the tropics and underestimates the convective activity over midlatitude marine storm tracks.

AX2.3.3 Nocturnal Low-Level Jets

Nocturnal low-level jets (LLJ) are coincident with synoptic weather patterns involved with high O₃ episodes implying that they may play an important role in the formation of severe O₃ events (Rao and Zurbenko, 1994). LLJ can transport pollutants hundreds of kilometers from their sources. Figure AX2-10 shows the evolution of the planetary boundary layer (PBL) over land during periods when high-pressure weather patterns prevail (Stull, 1988). During synoptic weather patterns with stronger zonal flow, a schematic of the boundary layer could look quite different with generally more uniform mixing present. As can be seen from Figure AX2-10, the PBL can be divided into three sublayers: a turbulent mixed layer (typically present during daylight hours), a less turbulent residual layer which occupies space that was formerly the mixed layer, and a nocturnal, stable boundary layer that has periods of sporadic turbulence (Stull, 1988). The LLJ forms in the residual layer. It is important to note, that during the nighttime, the PBL often comprises thin, stratified layers with different physical and chemical properties (Stull, 1988).

At night, during calm conditions, the planetary boundary layer is stably stratified and as a result vertical mixing is inhibited. On cloud-free evenings the LLJ begins to form shortly after sunset. The wedge of cool air in the stable nocturnal boundary layer decouples the surface layer from the residual layer and acts like a smooth surface allowing the air just above it (in the residual layer) to flow rapidly past the inversion mostly unencumbered by surface friction (Stull, 1988). As the sun rises, its energy returns to heat the land and the lower atmosphere begins to mix as the warm air rises. The jet diminishes as the nocturnal temperature inversion erodes and surface friction slows wind speeds. If stable synoptic conditions persist, the same conditions the next night could allow the low-level jet to reform with equal strength and similar consequences. LLJ formation results in vertical wind shear that induces mixing between the otherwise stratified layers.

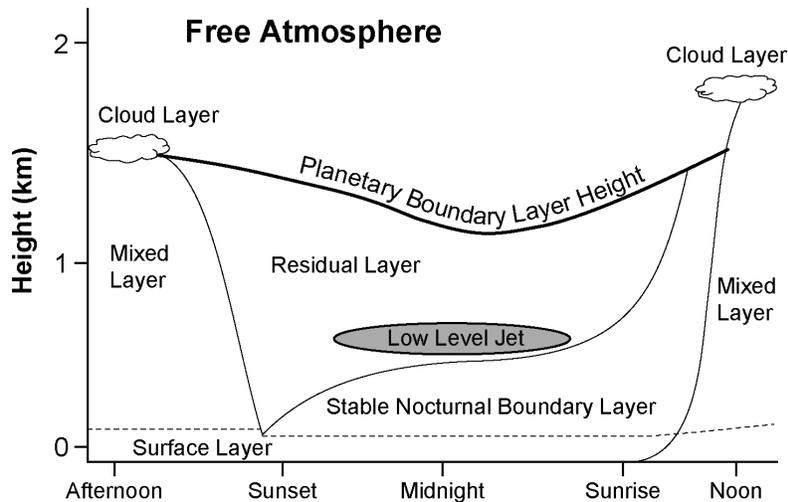


Figure AX2-10. The diurnal evolution of the planetary boundary layer while high pressure prevails over land. Three major layers exist (not including the surface layer): a turbulent mixed layer; a less turbulent residual layer which contains air formerly in the mixed layer; and a nocturnal, stable boundary layer which is characterized by periods of sporadic turbulence.

Source: Adapted from Stull (1988) Figures 1.7 and 12.1.

LLJs are often associated with mountain ranges. Mountains and pressure gradients on either side of a developing LLJ help concentrate the flow of air into a corridor or horizontal stream (Hobbs et al., 1996). Figure AX2-11 shows that LLJs commonly form east of the Rocky Mountains and east of the Appalachian Mountains (Bonner, 1968). There may be other locations in the U.S. where LLJs occur. The width of the jet can vary from location to location and from one weather pattern to another, but is typically less than several hundred km not greater than 1000 km long. In extreme cases, winds in a LLJ can exceed 60 ms^{-1} but average speeds are typically in the range of 10 to 20 ms^{-1} .

Nocturnal low-level jets are not unique to the United States; they have been detected in many other parts of the world (Corsmeier, 1997, Reitebuch, et al., 2000). Corsmeier et al. (1997) observed secondary maxima in surface O_3 at nighttime at a rural site in Germany, supporting the notion that downward transport from the residual layer was occurring. The secondary maxima were, on average, 10% of the next day's O_3 maximum but at times could be as much as 80% of the maximum (Corsmeier et al., 1997). The secondary O_3 maxima were well

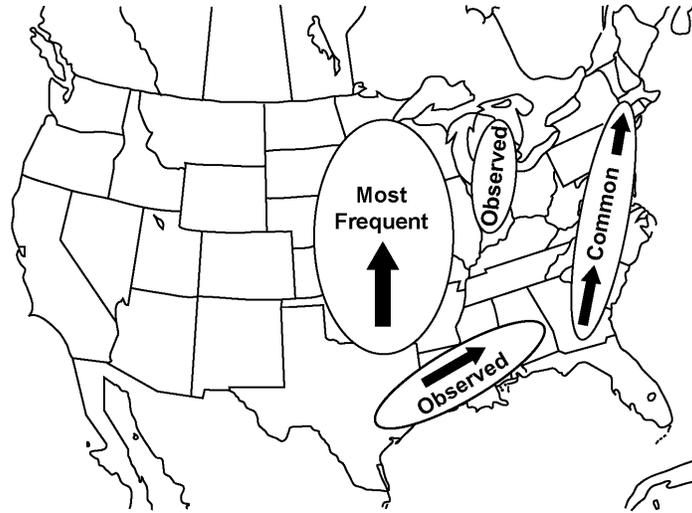


Figure AX2-11. Locations of low-level jet occurrences in decreasing order of prevalence (most frequent, common, observed). These locations are based on 2-years radiosonde data obtained over limited areas. With better data coverage, other low-level jets may well be observed elsewhere in the United States.

Source: Bonner (1968).

correlated with an increase in wind speed and wind shear. The increased vertical shear over the very thin layer results in mechanical mixing that leads a downward flux of O_3 from the residual to the near surface layer (see Low-level jets AX2-12 and AX2-13). Analysis of wind profiles from aerological stations in northeastern Germany revealed the spatial extent of that particular LLJ was up to 600 km in length and 200 km in width. The study concluded the importance of O_3 transport by low-level jets was twofold: O_3 and other pollutants could be transported hundreds of kilometers at the jet core level during the night and then mixed to the ground far from their source region. Salmond and McKendry (2002) also observed secondary O_3 maxima (in the Lower Fraser Valley, British Columbia) associated with low-level jets that occasionally exceeded half the previous day's maximum O_3 concentration. The largest increases in surface O_3 concentration occurred when boundary layer turbulence coincided with O_3 levels greater than 80 parts per billion were observed aloft. In addition, the study suggests horizontal transport efficiency during a low-level jet event could be as much as six times greater than transport with light winds without an LLJ. Reitebuch et al. (2000) observed secondary O_3 maxima associated with low-level jet evolution in an urban area in Germany. The notion that O_3 was transported

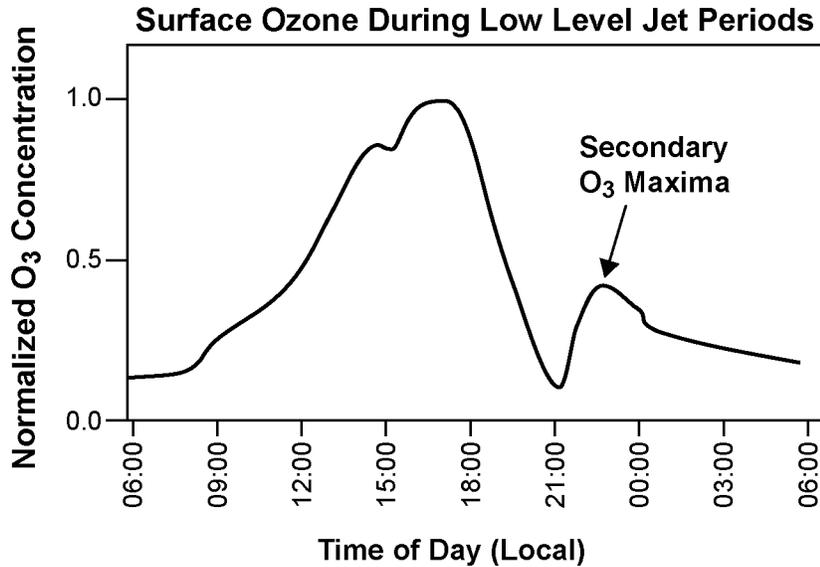


Figure AX2-12. Schematic diagram showing the diurnal behavior of O₃ and the development of secondary O₃ maxima resulting from downward transport from the residual layer when a low-level jet is present.

Source: Adapted from Reitbuch et al. (2000); Corsmeier et al. (1997); and Salmond and McKendry (2002).

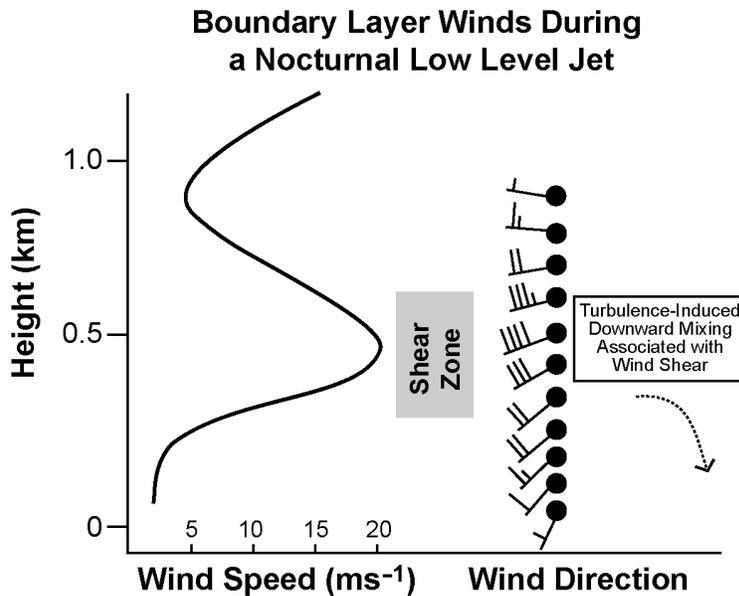


Figure AX2-13. The nocturnal low-level jet occupies a thin slice of the atmosphere near the Earth’s surface. Abrupt changes in wind speed and wind direction with height associated with the low-level jet create conditions favorable for downward transport of air to the surface layer.

Source: Singh et al. (1997); Corsmeier et al. (1997).

downward from the residual layer to the surface was supported by observed decreases in concentrations of NO, NO₂ and CO in the residual layer during secondary O₃ maxima. Unlike O₃ in the residual layer, concentrations of NO, NO₂, and CO should be lower than those found nearer the surface (Reitebuch et al., 2000; Seinfeld and Pandis, 1998). As in other studies, wind speed and directional shear were detected during these events. Calculations of the average wind speed and duration of the LLJ suggested that pollutants were transported several hundred kilometers. A study of the PBL and the vertical structure of O₃ observed at a coastal site in Nova Scotia described how temperature and differences of surface roughness in a marine environment can induce LLJ formation and pollution transport (Gong et al., 2000). In this case, rather strong horizontal sea surface temperature gradients provided the necessary baroclinic forcing.

While the studies mentioned above have shed light on the possible role of the LLJ in the transport of O₃ and its precursors, quantitative statements about the significance of the LLJ in affecting local and regional O₃ budgets cannot yet be made. This inability reflects the lack of available data for wind profiles in the planetary boundary layer in areas where LLJ are likely to occur and because of the inadequacy of numerical models in simulating their occurrence.

AX2.3.4 Intercontinental Transport of Ozone and Other Pollutants

AX2.3.4.1 The Atmosphere/Ocean Chemistry Experiment, AEROCE

The AEROCE experiment, initiated in the early 1990s set out to examine systematically the chemistry and meteorology leading to the trace gas and aerosol composition over the North Atlantic Ocean. One particular focus area was to determine the relative contribution of anthropogenic and natural processes to the O₃ budget and oxidizing capacity of the troposphere over the North Atlantic Ocean. Early results using isentropic back trajectories suggested that periodic pulses of O₃ mixing ratios up to 80 ppb were associated with large-scale subsidence from the mid-troposphere, favoring a natural source (Oltmans and Levy, 1992). Moody et al. (1995) extended this work with a five-year seasonal climatology and found the highest concentrations of O₃ were always associated with synoptic scale postfrontal subsidence off the North American continent behind cold fronts, and this pattern was most pronounced in the April-May time frame. These postfrontal air masses had uniformly low humidity and high concentrations of ⁷Be, a cosmogenic tracer produced in the upper troposphere and lower stratosphere. However, the pulsed occurrence of these postfrontal air masses also frequently

delivered enhanced concentrations of species such as SO_4^{2-} , NO_3^- , ^{210}Pb , etc. suggesting a component originating in North America. In a subsequent analysis of data from one year (1992) when CO observations were available, Dickerson et al. (1995) concluded that anthropogenic sources made a significant contribution to surface O_3 , and using a simple mixing model they determined that 57% of the air had a continental boundary layer origin.

Based on these observations of the synoptically modulated concentrations, AEROCE conducted an aircraft and ozonesonde intensive in the spring of 1996. The intention was to adopt a meteorologically informed sampling strategy to clearly distinguish the characteristics of air masses ahead of and behind eastward progressing cold fronts. Sixteen research flights were conducted with the University of Wyoming King Air research aircraft. The goal was to differentiate the sources of enhanced O_3 mixing ratios observed on Bermuda after the passage of cold fronts, and to identify the major processes controlling the highly variable O_3 mixing ratios in the mid-to-upper troposphere over eastern North America and the North Atlantic Ocean during April and May. In addition to aircraft flights, near-daily ozonesondes were launched in a quasi-zonal transect from Purdue, Indiana, to Charlottesville, Virginia to Bermuda. An effort was made to time the release of ozonesondes to cleanly differentiate pre- and postfrontal air masses.

In several aircraft flights, the presence at altitude of distinct layers of air with elevated concentrations of nonmethane hydrocarbons (NMHCs) attested to the dynamic vertical mixing associated with springtime frontal activity. Layers of mid-tropospheric air of high O_3 (140 ppb) and low background NMHC mixing ratios (1.44 ppbv ethane, 0.034 ppbv propene, 0.247 ppbv propane, and 0.034 ppbv isobutene, 0.041 ppbv n-butane, 0.063 ppbv benzene, 0.038 ppbv toluene) were indicative of descending, stratospherically influenced air on a flight to the east of Norfolk, VA on April 24 (alt 4600m). However layers of elevated NMHC concentrations (1.88 ppbv ethane, 0.092 ppbv propene, 0.398 ppbv propane, 0.063 ppbv isobutene, 0.075 ppbv n-butane, 0.106 ppbv benzene, 0.0102 ppbv toluene) occurred along with 60-70 ppbv of O_3 on a flight west of Bermuda April 28 (alt. 4100m), indicating air had been lofted from the continental boundary layer. Meteorological evidence, supported by ozonesonde observations and earlier King Air flights, indicated that stratosphere/troposphere exchange associated with an upstream frontal system had injected and advected dry, O_3 -rich air into the mid-troposphere region over the continent. This subsiding air mass provided deep layers of enhanced O_3 in the offshore,

postfrontal area. Convection from a developing (upwind) system lifted continental boundary layer air into the proximity of the dry, subsiding air layer (Prados, et al., 1999). This resulted in a mixture of high concentrations of anthropogenic pollutants along with naturally enhanced O₃. Ozone mixing ratios exceeded those attributable to boundary layer venting or in-transit photochemical production. These meteorological processes led to pollution and stratospherically enhanced O₃ co-occurring in postfrontal air masses over the North Atlantic Ocean. A similar event in February 1999 was observed by Parrish et al. (2000). It confirmed the occurrence of thin layers of anthropogenic and stratospheric air that subsequently mix. These results, along with recent modeling studies suggest that North American pollution clearly does contribute to the periodic influx of less-than-pristine air observed in the marine boundary layer over Bermuda (e.g., Li et al., 2002) and yet these incursions are not inconsistent with observing enhancements in O₃ due to stratospheric exchange.

The ozonesonde climatology of AEROCE clearly established that O₃ mixing ratios were always enhanced and increased with height in postfrontal air masses. Postfrontal O₃ in the lower troposphere over Bermuda originates in the postfrontal midtroposphere over the continent, supporting the hypothesis that naturally occurring stratospheric O₃ makes a contribution to air in the marine boundary layer (Cooper et al., 1998). A schematic of the meteorological processes responsible for the close proximity of natural and man-made O₃ can be seen in Figure AX2-8 from Prados (2000). Cold fronts over North America tend to be linked in wave-like patterns such that the subsidence behind one front may occur above with intrusions of convection ahead of the next cold front. Pollutants, including VOC and NO_x, precursors to O₃, may be lofted into the mid-to-upper troposphere where they have the potential to mix with layers of air descending from O₃-rich but relatively unpolluted upper troposphere and lower stratosphere. Through this complex mechanism, both stratospheric and photochemically produced O₃ may be transported to the remote marine environment where they have large-scale impacts on the radiative and chemical properties of the atmosphere. Recent three-dimensional modeling studies of air mass motion over the Pacific provide further evidence that these complex mechanisms are indeed active (Cooper et al., 2004b).

AX2.3.4.2 The North Atlantic Regional Experiment, NARE

NARE was established by the International Global Atmospheric Chemistry Project to study the chemical processes occurring in the marine troposphere of the North Atlantic, the marine region expected to be the most impacted by industrial emissions from eastern North America and western Europe. Surface measurements from several surface sites were initiated in 1991, with major field intensives in summer 1993, spring 1996, early autumn 1997 and a few winter flights in 1999. In the summer of 1993, airborne and ground-based measurements of O_3 and O_3 precursors were made in the North Atlantic region by an international team of scientists to determine how the continents that rim the North Atlantic are affecting atmospheric composition on a hemispheric scale (Fehsenfeld et al., 1996a,b). The focus of NARE was to investigate the O_3 budget of the North Atlantic region. Previous observations indicated that the O_3 produced from anthropogenic sources is greater than that reaching the lower troposphere from the stratosphere and that O_3 derived from anthropogenic pollution has a hemisphere wide effect at northern mid latitudes. This study was performed to better quantify the contribution of continental sources to the O_3 levels over the North Atlantic.

Buhr et al. (1996) measured O_3 , CO, NO, and NO_y as well as meteorological parameters aboard the NCAR King Air in August 1993 during 16 flights over and near the Gulf of Maine. They found that O_3 produced from anthropogenic precursors was dominant throughout the experimental region below 1500 m, in altitude.

The National Research Council of Canada Twin Otter aircraft was used to measure the O_3 and related compounds in the summertime atmosphere over southern Nova Scotia (Kleinman et al., 1996a,b). Forty-eight flights were performed, primarily over the surface sampling site in Chebogue Point, Nova Scotia, or over the Atlantic Ocean. They found that a wide variety of air masses with varying chemical content impact Nova Scotia. The effect depends on flow conditions relative to the locations of upwind emission regions and the degree of photochemical processing associated with transport times ranging from about 1 – 5 d. Moist continental boundary layer air with high concentrations of O_3 and other anthropogenic pollutants was advected to Nova Scotia in relatively thin vertical layers, usually with a base altitude of several hundred meters. Dry air masses with high concentrations of O_3 often had mixed boundary layer and upper atmosphere source regions. When a moist and dry air mass with the same photochemical age and O_3 concentration were compared, the dry air mass had lower

concentrations of NO_y and aerosol particles, which was interpreted as evidence for the selective removal of soluble constituents during vertical lifting.

Due to strong, low-level temperature inversions over the North Atlantic, near surface air is often unrepresentative of the eastward transport of the North American plume because of a decoupling from the air transported aloft (Kleinman et al., 1996a; Daum et al., 1996; Angervine et al., 1996). Pollution plumes were observed in distinct strata up to 1 km. Plume chemical compositions were consistent with the occurrence of considerable photochemical processing during transit from source regions over the eastern seaboard of the U.S. Ozone concentrations reached 150 ppbv, NO_x conversion to its oxidation products exceeded 85%, and high hydrogen peroxide concentrations were observed (median 3.6 ppbv, maximum 11 ppbv). CO and O_3 concentrations were well correlated ($R^2 = 0.64$) with a slope (0.26) similar to previous measurements in photochemically aged air (Parrish et al., 1998). Ozone depended nonlinearly on the NO_x oxidation product concentration, but there was a correlation ($r^2 = 0.73$) found between O_3 and the concentration of radical sink species as represented by the quantity $((\text{NO}_y - \text{NO}_x) + 2\text{H}_2\text{O}_2)$.

Banic et al. (1996) determined that the average mass of O_3 transported through an area 1 m in horizontal extent and 5 km in the vertical over the ocean near Nova Scotia to be 2.8 g s^{-1} , moving from west to east. Anthropogenic O_3 accounted for half of the transport below 1 km, 35 to 50% from 1 to 3 km, 25 to 50% from 3 to 4 km, and only 10% from 4 to 5 km. Merrill and Moody (1996) analyzed the meteorological conditions during the NARE intensive period (August 1 to September 13, 1993). They determined the ideal meteorological scenario for delivering pollution plumes from the U.S. East Coast urban areas over the Gulf of Maine to the Maritime Provinces of Canada to be warm sector flow ahead of an advancing cold front. In the winter phase of NARE, O_3 and CO were measured from the NOAA WP-3D Orion aircraft from St. John's, Newfoundland, Canada, and Keflavik, Iceland, from February 2 to 25, 1999 (Parrish et al., 2000). In the lower troposphere over the western North Atlantic Ocean, the close proximity of air masses with contrasting source signatures was remarkable. High levels of anthropogenic pollution immediately adjacent to elevated O_3 of stratospheric origin were observed, similar to those reported by Prados et al. (1999). In air masses with differing amounts of anthropogenic pollution, O_3 was negatively correlated with CO, which indicates that

emissions from surface anthropogenic sources had reduced O_3 , in this wintertime period, even in air masses transported into the free troposphere.

The influence of the origin and evolution of airstreams on trace gas mixing ratios has been studied in great detail for NARE aircraft data. The typical midlatitude cyclone is composed of four major component airstreams, the warm conveyor belt, the cold conveyor belt, the post cold-front airstream and the dry airstream (Cooper et al., 2001). The physical and chemical processing of trace species was characterized for each airstream, and a conceptual model of a midlatitude cyclones was developed (Cooper et al., 2002a). This showed how airstreams within midlatitude cyclones drew and exported trace gases from the polluted continental boundary layer, and the stratospherically enhanced mid-troposphere. Using back trajectories, airstream composition was related to the origin and transport history of the associated air mass. The lowest O_3 values were associated with airstreams originating in Canada or the Atlantic Ocean marine boundary layer; the highest O_3 values were associated with airstreams of recent stratospheric origin. The highest NO_y values were seen in polluted outflow from New England in the lower troposphere. A steep and positive O_3/NO_y slope was found for all airstreams in the free troposphere regardless of air mass origin. Finally, the seasonal variation of photochemistry and meteorology and their impact on trace gas mixing ratios in the conceptual cyclone model was determined (Cooper et al., 2002b). Using a positive O_3/CO slope as an indicator of photochemical O_3 production, O_3 production during late summer-early autumn is associated with the lower troposphere post-cold-front airstream and all levels of the WCB, especially the lower troposphere. However, in the early spring, there is no significant photochemical O_3 production for airstreams at any level, and negative slopes in the dry air airstream indicate STE causes the O_3 increase in the mid- and upper troposphere.

Stohl et al. (2002) analyzed total odd nitrogen (NO_y) and CO data taken during NARE in spring 1996 and fall 1997. They studied the removal timescales of NO_y originating from surface emissions of NO_x and what fraction reached the free troposphere. NO_x limits O_3 production in the free troposphere and can be regenerated from NO_y after the primary NO_x has been exhausted. It was determined that < 50% of the NO_y observed above 3 km came from anthropogenic surface emissions. The rest had to have been emitted in situ.

Several studies (e.g., Stohl and Trickl, 1999; Brunner et al., 1998; Schumann et al., 2000; Stohl et al., 2003; Traub et al., 2003) have identified plumes that have originated in North

America over Europe and over the eastern Mediterranean basin (e.g., Roelofs et al., 2003; Traub et al., 2003). Modeling studies indicate that North American emissions contribute roughly 20% to European CO levels and 2 to 4 ppb to surface O₃, on average. Episodic events, such as forest fires in North America have also been found to result in elevated CO and O₃ levels and visible haze layers in Europe (Volz-Thomas, et al., 2003). The O₃ is either transported from North America or formed during transport across the North Atlantic Ocean, perhaps as the result of interactions between the photochemical degradation products of acetone with emissions of NO_x from aircraft (Bruhl et al., 2000; Arnold et al., 1997). In addition, North American and European pollution is exported to the Arctic. Eckhardt et al. (2003) show that this transport is related to the phase of the North Atlantic Oscillation which has a period of about 20 years.

AX2.3.5 Small-Scale Circulation Systems

Sub-synoptic scale circulation systems are especially important for determining pollution levels. These systems include sea-land breezes, mountain-valley breezes and circulations driven by the urban heat island. The circulations associated with these phenomena typically occur on spatial scales of tens of kilometers.

AX2.3.5.1 Land-Sea Breeze

Of particular interest is the sea-land breeze, as many urban areas such as those in the Northeast Corridor (Washington, Baltimore, Philadelphia, New York and Boston), Chicago, Houston, and Los Angeles in which high O₃ values are found (see Chapter 3) are located in or near coastal zones.

During the day, heating of the land surface results in upward motion that is compensated by air flowing in from the adjacent water body, i.e., the sea breeze. Winds gradually rotate with height to produce a return flow aloft. This circulation generally reaches maximum strength in late afternoon. Afterwards, the sense of the circulation is reversed and a land breeze develops, which reaches maximum strength shortly after the land-sea temperature contrast is largest. This also implies that winds are rotating at the surface as the sense of the circulation changes. The circulation can interact with the larger synoptic scale flow pattern to either attenuate surface winds or to increase them.

Because of these effects, sea-land breezes can exert significant effects on concentrations of pollutants emitted in coastal areas. If there is onshore flow (sea breeze) when there is opposing large scale flow, a transition zone (sometimes called a sea breeze front) in which convergence of the opposing flows forms. In this zone, horizontal winds are weak. Furthermore, air pollutants are concentrated and are transported upwards. This situation was found during O₃ episodes occurring in Houston in August 2000, in which a “wall of pollution” formed (Banta et al., 2005). If the sea breeze is dominant, it can transport pollutants well inland, even to central-eastern Texas. During the land breeze phase, pollutants at the surface tend to be transported out over the adjacent water body, resulting in dilution and dispersion of pollutants. Observational studies of the effects of small scale circulations on O₃ concentrations are lacking.

AX2.3.6 The Relation of Ozone to Solar Ultraviolet Radiation, Aerosols, and Air Temperature

AX2.3.6.1 Solar Ultraviolet Radiation and Ozone

The effects of sunlight on photochemical oxidant formation, aside from the role of solar radiation in meteorological processes, are related to its intensity and its spectral distribution. Intensity varies diurnally, seasonally, and with latitude, but the effect of latitude is strong only in the winter. Ultraviolet radiation from the sun plays a key role in initiating the photochemical processes leading to O₃ formation and affects individual photolytic reaction steps. However, there is little empirical evidence in the literature, directly linking day-to-day variations in observed UV radiation levels with variations in O₃ levels.

In urban environments the rate of O₃ formation is sensitive to the rate of photolysis of several species including H₂CO, H₂O₂, O₃, and especially NO₂. Monte Carlo calculations suggest that model calculations of photochemical O₃ production are most sensitive to uncertainty in the photolysis rate coefficient for NO₂ (Thompson and Stewart, 1991; Baumann et al., 2000). The International Photolysis Frequency Measurement and Modeling Intercomparison (IPMMI) hosted recently by NCAR in Boulder, CO brought together more than 40 investigators from 8 institutions from around the world (Bais et al., 2003; Cantrell et al., 2003 and Shetter et al., 2003). They compared direct actinometric measurements, radiometric measurements, and numerical models of photolysis rate coefficients, focusing on O₃ to O(¹D) and NO₂, referred to as j(O₃) and j(NO₂).

The combination of direct measurements and comparisons to model calculations indicated that for clear skies, zenith angles less than 70° , and low aerosol loadings, the absolute value of the $j(\text{NO}_2)$ at the Earth's surface is known to better than 10% with 95% confidence. The results suggest that the cross sections of Harder et al. (1997a) may yield more accurate values when used in model calculations of $j(\text{NO}_2)$. Many numerical models agreed among themselves and with direct measurements (actinometers) and semi-direct measurements (radiometers) when using ATLAS extraterrestrial flux from Groebner and Kerr (2001). The results of IPMMI indicate numerical models are capable of precise calculation of photolysis rates at the surface and that uncertainties in calculated chemical fields arise primarily from uncertainties in the variation of actinic flux with altitude in addition to the impact of clouds and aerosols on radiation.

AX2.3.6.2 Impact of Aerosols on Radiation and Photolysis Rates and Atmospheric Stability

Because aerosol particles influence the UV flux there is a physical link between particles and gases that depends on the concentration, distribution, and refractive index of the particles. Scattering of UV radiation by tropospheric aerosol particles can strongly impact photolysis rates and thus photochemical O_3 production or destruction. The effect shows high sensitivity to the properties of the aerosol. Particles in the boundary layer can accelerate photochemistry if the single scattering albedo is near unity, such as for sulfate and ammoniated sulfate aerosols, or inhibit O_3 production if the single scattering albedo is low, such as for mineral dust or soot (Dickerson et al., 1997; Jacobson, 1998; Liao et al., 1999; Castro et al., 2001; Park et al., 2001). Any aerosol layer in the free troposphere will reduce photolysis rates in the boundary layer.

The interaction of aerosols, photochemistry, and atmospheric thermodynamic processes can impact radiative transport, cloud microphysics, and atmospheric stability with respect to vertical mixing. Park et al. (2001) developed a single-column chemical transport model that simulates vertical transport by convection, turbulent mixing, photochemistry, and interactive calculations of radiative fluxes and photolysis rates. Results from simulations of an episode over the eastern United States showed strong sensitivity to convective mixing and aerosol optical depth. The aerosol optical properties observed during the episode produced a surface cooling of up to 120 W/m^2 and stabilized the atmosphere suppressing convection. This suggests two

possible feedback mechanisms between aerosols and O₃-reduced vertical mixing would tend to increase the severity of O₃ episodes, while reduced surface temperatures would decrease it.

AX2.3.6.3 Temperature and Ozone

An association between surface O₃ concentrations and temperature has been demonstrated from measurements in outdoor smog chambers and from measurements in ambient air. Numerous ambient studies done over more than a decade have reported that successive occurrences or episodes of high temperatures characterize high O₃ years (Clark and Karl, 1982; Kelly et al., 1986). The relation of daily maximum 8-h average O₃ concentration to daily maximum temperature from May to September 1994 to 2004 is illustrated in Figure AX2-14 for the Baltimore Air Quality Forecast Area. The relation, based on daily maximum 1-h average O₃ concentration is illustrated in Figure AX2-15. The relations are very similar in the two figures, reflecting the high degree of correlation ($r = 0.98$) between the daily maximum 1-h and 8-h O₃ concentrations. The relation of daily maximum 8-h average O₃ to daily maximum temperature from May to September 1994 to 2004 is illustrated in Figure AX2-15 for the three sites downwind of Phoenix, AZ on high O₃ days (cf., Figure AX3-32). As can be seen from a comparison of Figures AX2-14 and AX2-16, O₃ concentrations in the Phoenix area are not as well correlated with daily maximum temperature ($r = 0.14$) as they are in the Baltimore Area ($r = 0.74$). There appears to be an upper-bound on O₃ concentrations that increases with temperature. Likewise, Figure AX2-16 shows that a similar qualitative relationship exists between O₃ and temperature even at a number of nonurban locations.

The notable trend in these plots is the apparent upper-bound to O₃ concentrations as a function of temperature. It is clear that, at a given temperature, there is a wide range of possible O₃ concentrations because other factors (e.g., cloudiness, precipitation, wind speed) can reduce O₃ production rates. The upper edge of the curves may represent a practical upper bound on the maximum O₃ concentration achieved under the most favorable conditions. Relationships between peak O₃ and temperature also have been recorded by Wunderli and Gehrig (1991) for three locations in Switzerland. At two sites near Zurich, peak O₃ increased 3 to 5 ppb/°C for diurnal average temperatures between 10 and 25 °C, and little change in peak O₃ occurred for temperatures below 10 °C. At the third site, a high-altitude location removed from anthropogenic influence, a much smaller variation of O₃ with temperature was observed.

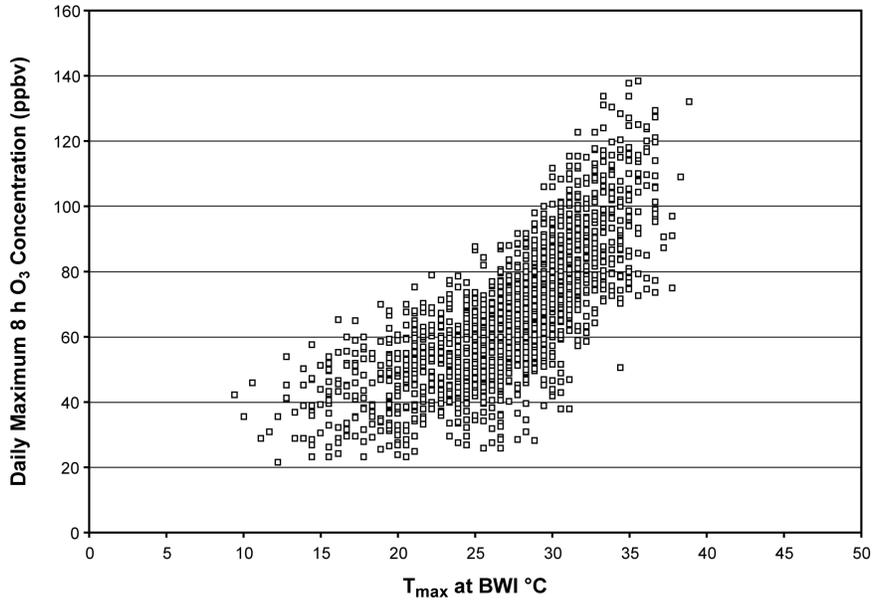


Figure AX2-14. A scatter plot of daily maximum 8-h O₃ concentration versus daily maximum temperature in the Baltimore, MD Air Quality Forecast Area.

Source: Piety (2005)

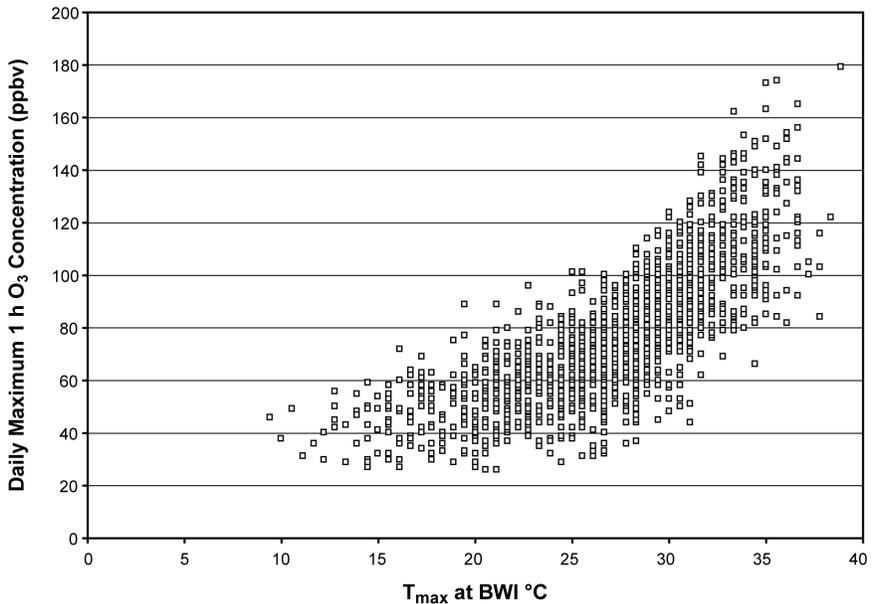


Figure AX2-15. A scatter plot of daily maximum 1-h average O₃ concentration versus daily maximum temperature in the Baltimore, MD Air Quality Forecast Area.

Source: Piety (2005)

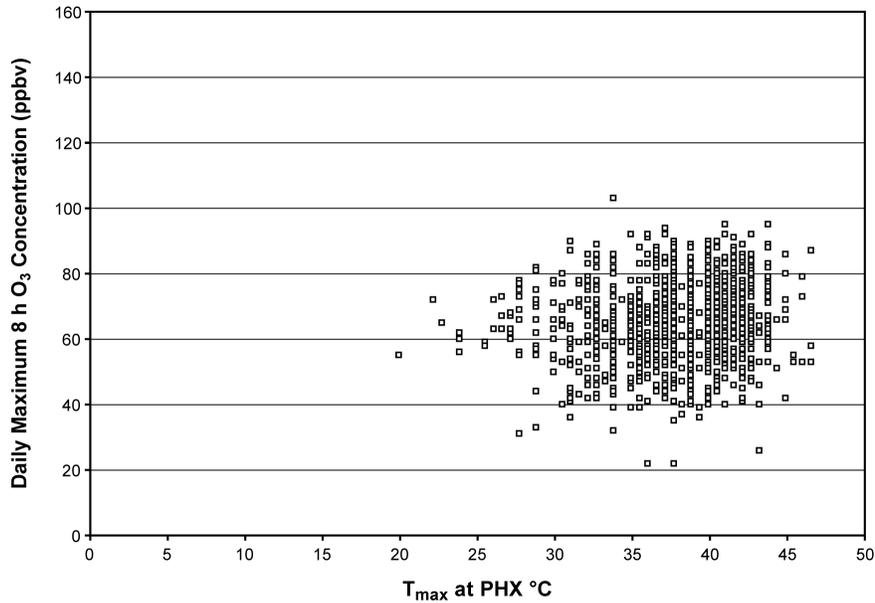


Figure AX2-16. A scatter plot of daily maximum 8-h average O₃ concentrations versus daily maximum temperature downwind of Phoenix, AZ.

Source: Piety (2005)

Some possible explanations for the correlation of O₃ with temperature include:

- (1) Increased photolysis rates under meteorological conditions associated with higher temperatures;
- (2) Increased H₂O concentrations with higher temperatures as this will lead to greater OH production via R(2-6);
- (3) Enhanced thermal decomposition of PAN and similar compounds to release NO_x at higher temperatures;
- (4) Increase of anthropogenic hydrocarbon (e.g., evaporative losses) emissions or NO_x emissions with temperature or both;
- (5) Increase of natural hydrocarbon emissions (e.g., isoprene) with temperature; and
- (6) Relationships between high temperatures and stagnant circulation patterns.
- (7) Advection of warm air enriched with O₃.

Cardelino and Chameides (1990) and Sillman and Samson (1995) both identified the temperature-dependent thermal decomposition of PAN as the primary cause of the observed O₃-temperature relationship. When temperatures are low, PAN is relatively stable. Formation of PAN represents a significant sink for NO_x (in low NO_x rural areas) and radicals (in high NO_x urban areas). This has the effect of slowing the rate of O₃ production. Sillman and Samson found that the impact of the PAN decomposition rate could explain roughly half of the observed correlation between O₃ and temperature. Jacob et al. (1993) found that warm events in summer in the United States were likely to occur during stagnant meteorological conditions, and the concurrence between warm temperatures and meteorological stagnation also explained roughly half of the observed O₃-temperature correlation. Other possible causes include higher solar radiation during summer, the strong correlation between biogenic emission of isoprene and temperature, and the somewhat weaker tendency for increased anthropogenic emissions coinciding with warmer temperatures.

However, it should also be noted that a high correlation of O₃ with temperature does not necessarily imply a causal relation. Extreme episodes of high temperatures (a heat wave) are often multiday events, high O₃ episodes are also multiday events, concentrations build, temperatures rise, but both are being influenced by larger-scale regional or synoptic meteorological conditions. It also seems apparent, that while there is a trend for higher O₃ associated with higher temperatures, there is also much greater variance in the range of O₃ mixing ratios at higher temperatures.

AX2.4 THE RELATION OF OZONE TO ITS PRECURSORS AND OTHER OXIDANTS

Ozone is unlike many other species whose rates of formation vary directly with the emissions of their precursors. Ozone changes in a nonlinear fashion with the concentrations of its precursors. At the low NO_x concentrations found in most environments, ranging from remote continental areas to rural and suburban areas downwind of urban centers the net production of O₃ increases with increasing NO_x. At the high NO_x concentrations found in downtown metropolitan areas, especially near busy streets and roadways, and in power plant plumes there is net destruction (titration) of O₃ by reaction with NO. In between these two regimes there is a

transition stage in which O_3 shows only a weak dependence on NO_x concentrations. In the high NO_x regime, NO_2 scavenges OH radicals which would otherwise oxidize VOCs to produce peroxy radicals, which in turn would oxidize NO to NO_2 . In the low NO_x regime, the oxidation of VOCs generates, or at least does not consume, free radicals and O_3 production varies directly with NO_x . Sometimes the terms VOC limited and NO_x limited are used to describe these two regimes. However, there are difficulties with this usage because (1) VOC measurements are not as abundant as they are for nitrogen oxides, (2) rate coefficients for reaction of individual VOCs with free radicals vary over an extremely wide range, and (3) consideration is not given to CO nor to reactions that can produce free radicals without invoking VOCs. The terms NO_x -limited and NO_x -saturated (e.g., Jaeglé et al., 2001) will be used wherever possible to describe these two regimes more adequately. However, the terminology used in original articles will also be kept. The chemistry of OH radicals, which are responsible for initiating the oxidation of hydrocarbons, shows behavior similar to that for O_3 with respect to NO_x concentrations (Hameed et al., 1979; Pinto et al., 1993; Poppe et al., 1993; Zimmerman and Poppe, 1993). These considerations introduce a high degree of uncertainty into attempts to relate changes in O_3 concentrations to emissions of precursors.

Various analytical techniques have been proposed that use ambient NO_x and VOC measurements to derive information about O_3 production and O_3 - NO_x -VOC sensitivity. It has been suggested that O_3 formation in individual urban areas could be understood in terms of measurements of ambient NO_x and VOC concentrations during the early morning (e.g., National Research Council, 1991). In this approach, the ratio of summed (unweighted by chemical reactivity) VOC to NO_x is used to determine whether conditions were NO_x -sensitive or VOC sensitive. This procedure is inadequate because it omits many factors that are recognized as important for O_3 production: the impact of biogenic VOCs (which are not present in urban centers during early morning); important individual differences in the ability of VOCs to generate free radicals (rather than just total VOC) and other differences in O_3 forming potential for individual VOCs (Carter, 1995); the impact of multiday transport; and general changes in photochemistry as air moves downwind from urban areas (Milford et al., 1994).

Jacob et al. (1995) used a combination of field measurements and a chemistry-transport model (CTM) to show that the formation of O_3 changed from NO_x -limited to NO_x -saturated as the season changed from summer to fall at a monitoring site in Shenandoah National Park, VA.

Photochemical production of O₃ generally occurs simultaneously with the production of various other species: nitric acid (HNO₃), organic nitrates, and hydrogen peroxide. The relative rate of production of O₃ and other species varies depending on photochemical conditions, and can be used to provide information about O₃-precursor sensitivity.

There are no hard and fast rules governing the levels of NO_x at which the transition from NO_x-limited to NO_x-saturated conditions occurs. The transition between these two regimes is highly spatially and temporally dependent. Similar responses to NO_x additions from commercial aircraft have also been found for the upper troposphere (Bruhl et al., 2000). Bruhl et al. (2000) found that the NO_x levels for O₃ production versus loss are highly sensitive to the radical sources included in model calculations. They found that the inclusion of only CH₄ and CO oxidation leads to a decrease in net O₃ production in the North Atlantic flight corridor due to NO emissions from aircraft. However, the inclusion of acetone photolysis was found to shift the maximum in O₃ production to higher NO_x mixing ratios, thereby reducing or eliminating areas in which there is a decrease in O₃ production rates due to aircraft emissions.

Trainer et al. (1993) suggested that the slope of the regression line between O₃ and summed NO_x oxidation products (NO_z, equal to the difference between measured total reactive nitrogen, NO_y, and NO_x) can be used to estimate the rate of O₃ production per NO_x (also known as the O₃ production efficiency, or OPE). Ryerson et al. (1998, 2001) used measured correlations between O₃ and NO_z to identify different rates of O₃ production in plumes from large point sources.

Sillman (1995) and Sillman and He (2002) identified several secondary reaction products that show different correlation patterns for NO_x-limited conditions and NO_x-saturated conditions. The most important correlations are for O₃ versus NO_y, O₃ versus NO_z, O₃ versus HNO₃, and H₂O₂ versus HNO₃. The correlations between O₃ and NO_y, and O₃ and NO_z are especially important because measurements of NO_y and NO_x are widely available. Measured O₃ versus NO_z (Figure AX2-17) shows distinctly different patterns in different locations. In rural areas and in urban areas such as Nashville, TN, O₃ shows a strong correlation with NO_z and a relatively steep slope to the regression line. By contrast, in Los Angeles O₃ also increases with NO_z, but the rate of increase of O₃ with NO_z is lower and the O₃ concentrations for a given NO_z value are generally lower.

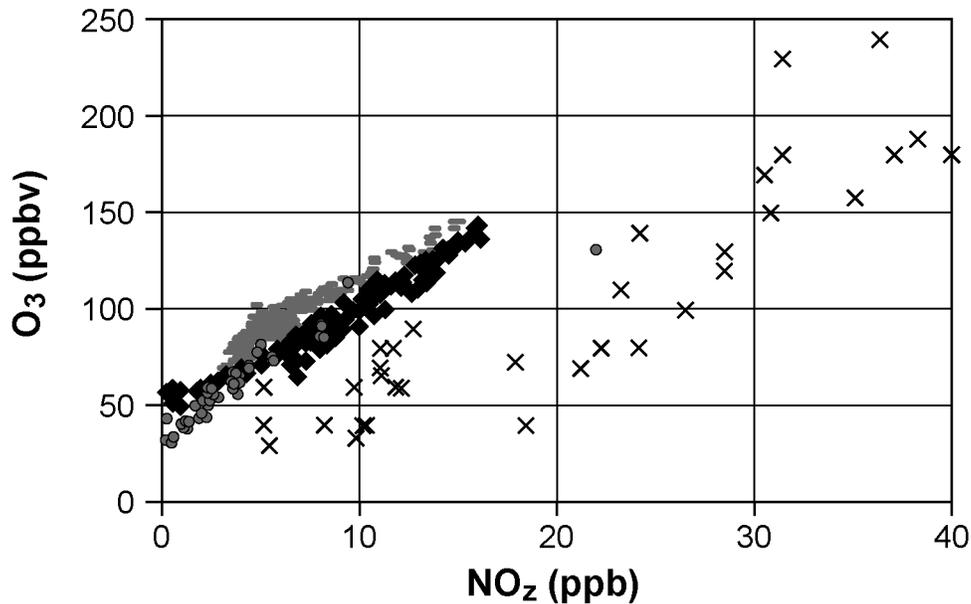


Figure AX2-17. Measured values of O₃ and NO_z (NO_y-NO_x) during the afternoon at rural sites in the eastern United States (gray circles) and in urban areas and urban plumes associated with Nashville, TN (gray dashes), Paris, FR (black diamonds) and Los Angeles, CA (X's).

Sources: Trainer et al. (1993), Sillman et al. (1997, 1998, 2003).

The difference between NO_x-limited and NO_x-saturated regimes is also reflected in measurements of hydrogen peroxide (H₂O₂). Hydrogen peroxide production is highly sensitive to the abundance of free radicals and is thus favored in the NO_x-limited regime, typical of summer conditions. Differences between these two regimes are also related to the preferential formation of sulfate during summer and to the inhibition of sulfate and hydrogen peroxide during winter (Stein and Lamb, 2003). Measurements in the rural eastern United States (Jacob et al., 1995) Nashville (Sillman et al., 1998), and Los Angeles (Sakugawa and Kaplan, 1989) show large differences in H₂O₂ concentrations between likely NO_x-limited and NO_x-saturated locations.

The discussion in Section AX2.4.1 centers mainly on the relations among O₃, NO_x and its oxidation products, represented as NO_z (NO_y-NO_x) and VOCs derived from the results of field studies. Most of these studies examined processes occurring in power plant and urban plumes.

AX2.4.1 Summary of Results for the Relations Among Ozone, its Precursors and Other Oxidants from Recent Field Experiments

AX2.4.1.1 Results from the Southern Oxidant Study and Related Experiments

The Southern Oxidant Study (SOS) was initiated to describe the sources, variation, and distribution of O₃ and its precursors in the southeastern United States during the summer season (Hübler et al., 1998; Meagher et al., 1998; Goldan et al., 2000). Specific issues that were addressed included: (1) the role of biogenic VOC and NO_x emissions on local and regional O₃ production, (2) the effect of urban-rural exchange/interchange on local and regional O₃ production, (3) sub-grid-scale photochemical and meteorological processes, and (4) the provision of a high-quality chemical and meteorological data set to test and improve observation and emission-based air quality forecast models. Some of the more significant findings of the 1994 to 1995 studies include the following: (1) Ozone production in Nashville was found to be close to the transition between NO_x-limited and NO_x-saturated regimes. (2) The number of molecules of O₃ produced per molecule of NO_x oxidized in power plant plumes, or the O₃ production efficiency (OPE) was found to be inversely proportional to the NO_x emission rate, with the plants having the highest NO_x emissions exhibiting the lowest OPE. (3) During stagnant conditions, winds at night dominated pollutant transport and represent the major mechanism for advecting urban pollutants to rural areas—specific findings follow.

As part of SOS, the Tennessee Valley Authority's instrumented helicopter conducted flights over Atlanta, Georgia to investigate the evolution of the urban O₃ plume (Imhoff et al., 1995). Ozone peak levels occurred at 20 – 40 km downwind of the city center. The OPE obtained from five afternoon flights ranged between 4 and 10 molecules of O₃ per molecule of NO_x.

Berkowitz and Shaw (1997) measured O₃ and its precursors at several altitudes over a surface site near Nashville during SOS to determine the effects of turbulent mixing on atmospheric chemistry. Early morning measurements of O₃ aloft revealed values near 70 ppb, while those measured at the surface were closer to 25 ppb. As the daytime mixed layer deepened, surface O₃ values steadily increased until they reached 70 ppb. The onset of turbulence increased isoprene mixing ratios aloft by several orders of magnitude and affected the slope of O₃ as a function of NO_y for each of the flight legs. Measurements from nonturbulent flight legs yielded slopes that were considerably steeper than those from measurements made in

turbulence. This study shows that the concentration of O₃ precursors aloft is dependent on the occurrence of turbulence, and turbulent mixing could explain the evolution of O₃ concentrations at the surface. In general, conclusions regarding pollutant concentrations must account for both chemical and local dynamic processes.

Gillani et al. (1998) analyzed data from instrumented aircraft during SOS that flew through the plumes of three large, tall-stack, base-load, Tennessee Valley Authority (TVA) coal-fired power plants in northwestern Tennessee. They determined that plume chemical maturity and peak O₃ and NO_z production occurred within 30 to 40 km and 4 hours of summer daytime convective boundary layer (CBL) transport time for a coal-fired power plant in the Nashville, TN urban O₃ nonattainment area (Gallatin). For a rural coal-fired power plant in an isoprene-rich forested area about 100 km west of Nashville (Cumberland), plume chemical maturity and peak O₃ and NO_z production were realized within approximately 100 km and 6 hours of CBL transport time. Their findings included approximately 3 molecules of O₃ and more than 0.6 molecules of NO_z may be produced in large isolated rural power plant plumes (PPPs) per molecule of NO_x release; the corresponding peak yields of O₃ and NO_z may be significantly greater in urban PPPs. Both power plants can contribute as much as 50 ppb of excess O₃ to the Nashville area, raising the local levels to well above 100 ppb. Also using aircraft data collected during SOS, Ryerson et al. (1998) concluded that the lower and upper limits to O₃ production efficiency in the Cumberland and Paradise PPPs (located in rural Tennessee) were 1 and 2 molecules of O₃ produced per molecule of NO_x emitted. The estimated lower and upper limits to O₃ production efficiency in the Johnsonville PPP (also located in rural Tennessee) were higher, at 3 and 7.

The NOAA airborne O₃ lidar provided detailed, three-dimensional lower tropospheric O₃ distribution information during June and July 1995 in the Nashville area (Senff et al., 1998; Alvarez et al., 1998). The size and shape of power plant plumes as well as their impacts on O₃ concentration levels as the plume is advected downwind were studied. Specific examples include: the July 7 Cumberland plume that was symmetrical and confined to the boundary layer, and the July 19 Cumberland plume that was irregularly shaped with two cores, one above and the other within the boundary layer. The disparate plume characteristics on these two days were the result of distinctly different meteorological conditions. Ozone in the plume was destroyed at a rate of 5 to 8 ppbv h⁻¹ due to NO_x titration close to the power plant, while farther downwind,

O₃ was produced at rates between 1.5 and 4 ppbv h⁻¹. The lidar O₃ measurements compared reasonably well with in situ values, with the average magnitude of the offsets over all the flights at 4.3 ppbv (7%).

The highest O₃ concentrations observed during the 1995 SOS in middle Tennessee occurred during a period of strong, synoptic-scale stagnation from July 11 through July 15. This massive episode covered most of the eastern United States (e.g., Ryan et al., 1998). During this time, the effects of vertical wind profiles on the buildup and transport of O₃ were studied by Banta et al. (1998) using an airborne differential absorption lidar (DIAL) system. Vertical cross sections showed O₃ concentrations exceeding 120 ppb extending to nearly 2 km above ground level, but that O₃ moved little horizontally. Instead, it formed a dome of pollution over or near Nashville. Due to the stagnant daytime conditions (boundary layer winds ~1 to 3 m s⁻¹), nighttime transport of O₃ became disproportionately important. At night, in the layer between 100 and 2000 m AGL (which had been occupied by the daytime mixed layer), the winds could be accelerated to 5 to 10 m s⁻¹ as a result of nocturnal decoupling from surface friction. Data from surface and other aircraft measurements taken during this period suggest that the background air and the edges of the urban plume were NO_x sensitive and the core of the urban plume was hydrocarbon sensitive (Valente et al., 1998). Also revealed was the fact that the surface monitoring network failed to document the maximum surface O₃ concentrations. Thus, monitoring networks, especially in medium-sized urban areas under slow transport conditions, may underestimate the magnitude and frequency of urban O₃ concentrations greater than 120 ppb.

Nunnermacker et al. (1998) used both aircraft and surface data from SOS to perform a detailed kinetic analysis of the chemical evolution of the Nashville urban plume. The analysis revealed OH concentrations around 1.2 x 10⁷ cm⁻³ that consumed 50% of the NO_x within approximately 2 hours, at an OPE of 2.5 to 4 molecules for each molecule of NO_x. Anthropogenic hydrocarbons provided approximately 44% of the fuel for O₃ production by the urban plume.

Surface and aircraft observations of O₃ and O₃ precursors were compared during SOS to assess the degree to which midday surface measurements may be considered representative of the larger planetary boundary layer (PBL) (Luke et al., 1998). Overall agreement between surface and aircraft O₃ measurements was excellent in the well-developed mixed layer

($r^2 = 0.96$), especially in rural-regional background air and under stagnant conditions, where surface concentrations change only slowly. Vertical variations in trace gas concentrations were often minimal in the well-mixed PBL, and measurements at the surface always agreed well with aircraft observations up to the level of measurements (460 m above ground level). Under conditions of rapidly varying surface concentrations (e.g., during episodes of power plant plume fumigation and early morning boundary layer development), agreement between surface and aloft was dependent upon the spatial (aircraft) and temporal (ground) averaging intervals used in the comparison. Under these conditions, surface sites were representative of the PBL only to within a few kilometers horizontally.

On four days during SOS, air samples were taken in the plume of the Cumberland Power Plant in central Tennessee using an instrumented helicopter to investigate the evolution of photochemical smog (Luria et al., 1999, 2000). Twelve crosswind air-sampling traverses were made between 35 and 116 km from this Power Plant on 16 July 1995. Winds, from the west-northwest during the sampling period, directed the plume toward Nashville. Ten of the traverses were performed upwind of Nashville, where the plume was isolated, and two were made downwind of the city. The results indicated that even six hours after the plume left the stacks, excess O_3 production was limited to the edges of the plume. Excess O_3 production within the plume was found to vary from 20 ppb up to 55 ppb. It was determined that this variation corresponded to differences in ambient isoprene levels. Excess O_3 (up to 109 ppbv, 50 to 60 ppbv above background), was produced in the center of the plume when there was sufficient mixing upwind of Nashville. The power plant plume apparently mixed with the urban plume also, producing O_3 up to 120 ppbv 15 to 25 km downwind of Nashville.

Nunnermacker et al. (2000) used data from the DOE G-1 aircraft to characterize emissions from a small power plant plume (Gallatin) and a large power plant plume (Paradise) in the Nashville region. Observations made on July 3, 7, 15, 17, and 18, 1995, were compiled, and a kinetic analysis of the chemical evolution of the power plant plumes was performed. OPEs were found to be 3 in the Gallatin and 2 in the Paradise plumes. Lifetimes for NO_x (2.8 and 4.2 hours) and NO_y (7.0 and 7.7 hours) were determined in the Gallatin and Paradise plumes, respectively. These NO_x and NO_y lifetimes imply rapid loss of NO_z (assumed to be primarily HNO_3), with a lifetime determined to be 3.0 and 2.5 hours for the Gallatin and Paradise plumes, respectively.

AX2.4.1.2 Results from Studies on Biogenic and Anthropogenic Hydrocarbons and Ozone Production

Williams et al. (1997) made the first airborne measurements of peroxy-methacrylic nitric anhydride (MPAN), which is formed from isoprene-NO_x chemistry and is an indicator of recent O₃ production from isoprene and therefore biogenic hydrocarbons (BHC). They also measured peroxyacetic nitric anhydride (PAN), peroxypropionic nitric anhydride (PPN), and O₃ to estimate the contributions of anthropogenic hydrocarbons (AHC) and BHC to regional tropospheric O₃ production.

Airborne measurements of MPAN, PAN, PPN, and O₃ were made during the 1994 and 1995 Nashville intensive studies of SOS to determine the fraction of O₃ formed from anthropogenic NO_x and BHC (Roberts et al., 1998). It was found that PAN, a general product of hydrocarbon-NO_x photochemistry, could be well represented as a simple linear combination of contributions from BHC and AHC as indicated by MPAN and PPN, respectively. The PAN/MPAN ratios, characteristic of BHC-dominated chemistry, ranged from 6 to 10. The PAN/PPN ratios, characteristic of AHC-dominated chemistry, ranged from 5.8 to 7.4. These ratios were used to estimate the contributions of AHC and BHC to regional tropospheric O₃ production. It was estimated that substantial O₃ (50 to 60 ppbv) was produced from BHC when high NO_x from power plants was present in areas of high BHC emission.

AX2.4.1.3 Results of Studies on Ozone Production in Mississippi and Alabama

Aircraft flights made in June 1990 characterized the variability of O₃ and reactive nitrogen in the lower atmosphere over Mississippi and Alabama. The variety and proximity of sources and the photochemical production and loss of O₃ were found to be contributing factors (Ridley et al., 1998). Urban, biomass burning, electrical power plant, and paper mill plumes were all encountered during these flights. Urban plumes from Mobile, AL had OPEs as high as 6 to 7 ppbv O₃ per ppbv of NO_x. Emissions measured from biomass burning had lower efficiencies of 2 to 4 ppbv O₃ per ppbv of NO_x, but the average rate of production of O₃ was as high as 58 ppbv hr⁻¹ for one fire where the plume was prevented from vertical mixing. Near-source paper mill and power plant plumes showed O₃ titration, while far-field observations of power plant plumes showed net O₃ production. Early morning observations below a nocturnal inversion provided evidence for the nighttime oxidation of NO_x to reservoir species.

Aircraft measurements of O₃ and oxides of nitrogen were made downwind of Birmingham, AL to estimate the OPE in the urban plume (Trainer et al., 1995). NO_x emission rates were estimated at 0.6 x 10²⁵ molecules s⁻¹ with an uncertainty of a factor of 2. During the summertime it was determined that approximately seven O₃ molecules could be formed for every molecule of NO_x emitted by the urban and proximately located power plant plumes. The regional O₃, the photochemical production of O₃ during the oxidation of the urban emissions, and wind speed and direction all combined to dictate the magnitude and location of the peak O₃ concentrations observed in the vicinity of the Birmingham metropolitan area.

Aircraft observations of rural U.S. coal-fired power plant plumes in the middle Mississippi and Tennessee Valleys were used to quantify the nonlinear dependence of tropospheric O₃ formation on plume NO_x concentration, determined by plant NO_x emission rate and atmospheric dispersion (Ryerson et al., 2001). The ambient availability of reactive VOCs, primarily biogenic isoprene, was also found to affect O₃ production rate and yield in these rural plumes. Plume O₃ production rates and yields as a function of NO_x and VOC concentrations differed by a factor of 2 or more. These large differences indicate that power plant NO_x emission rates and geographic locations play a large role in tropospheric O₃ production.

AX2.4.1.4 The Nocturnal Urban Plume over Portland, Oregon

Aircraft observations of aerosol surface area, O₃, NO_y and moisture were made at night in the Portland, Oregon urban plume (Berkowitz et al., 2001). Shortly after sunset, O₃, relative humidity, NO_y and aerosol number density were all positively correlated. However, just before dawn, O₃ mixing ratios were highly anti-correlated with aerosol number density, NO_y and relative humidity. Back-trajectories showed that both samples came from a common source to the northwest of Portland. The predawn parcels passed directly over Portland, while the other parcels passed to the west of Portland. Several hypotheses were put forward to explain the loss of O₃ in the parcels that passed over Portland, including homogeneous gas-phase mechanisms and a heterogeneous mechanism on the aerosol particle surface.

AX2.4.1.5 Effects of VOCs in Houston on Ozone Production

Aircraft Observations of O₃ and O₃ precursors over Houston, TX, Nashville, TN; New York, NY; Phoenix, AZ, and Philadelphia, PA showed that despite similar NO_x concentrations,

high concentrations of VOCs in the lower atmosphere over Houston led to calculated O₃ production rates that were 2 to 5 times higher than in the other 4 cities (Kleinman et al., 2002). Concentrations of VOCs and O₃ production rates are highest in the Ship Channel region of Houston, where one of the largest petrochemical complexes in the world is located. As a result, Houston lays claim to the highest recorded hourly average O₃ concentrations in the United States within the last 5 years (in excess of 250 ppb).

AX2.4.1.6 Chemical and Meteorological Influences on the Phoenix Urban Ozone Plume

The interaction of chemistry and meteorology for western cities can contrast sharply with that of eastern cities. A 4-week field campaign in May and June of 1998 in the Phoenix area comprised meteorological and chemical measurements (Fast et al., 2000). Data from models and observations revealed that heating of the higher terrain north and east of Phoenix produced regular, thermally driven circulations during the afternoon from the south and southwest through most of the boundary layer, advecting the urban O₃ plume to the northeast. Deep mixed layers and moderate winds aloft ventilated the Phoenix area during the study period so that multiday buildups of locally produced O₃ did not appear to contribute significantly to O₃ levels. Sensitivity simulations estimated that 20% to 40% of the afternoon surface O₃ mixing ratios (corresponding to 15 to 35 ppb) was due to the entrainment of O₃ reservoirs into the growing convective boundary layer. The model results also indicated that O₃ production in this arid region is NO_x-saturated, unlike most eastern U.S. sites.

AX2.4.1.7 Transport of Ozone and Precursors on the Regional Scale

Instrumented aircraft flights by the University of Maryland in a Cessna 172 and Sonoma Technology, Inc. in a Piper Aztec measured the vertical profiles of trace gases and meteorological parameters in Virginia, Maryland, and Pennsylvania on July 12–15, 1995 during a severe O₃ episode in the mid-Atlantic region (Ryan et al., 1998). Ozone measured upwind of the urban centers reached 80 to 110 ppbv. Layers of high O₃ aloft were associated with local concentration maxima of SO₂ and NO_y, but not CO or NO_x. This, together with a back trajectory analysis, implicated coal-fired power plants in the industrialized Midwest as the source of the photochemically aged air in the upwind boundary of the urban centers. When the PBL over the Baltimore-Washington area deepened, the O₃ and O₃ precursors that had been transported from

the west and northwest mixed with the local emissions and O₃ in excess of 125 ppbv was measured at the surface.

During the blackout of August 14, 2003 Marufu et al. (2004) measured profiles of O₃, SO₂ and CO over areas in western Pennsylvania, Maryland and Virginia. They found notable decreases in O₃, SO₂, and NO_x, over areas affected by the blackout but not over those that were not affected. They also found that CO concentrations aloft were comparable over areas affected and not affected by the blackout. They attributed the differences in concentrations between what was observed and what was expected to the reduction in emissions from power plants mainly in the Ohio Valley. They also reasoned that the CO concentrations were relatively unaffected because they arise from traffic emissions, which may have been largely unaffected by the blackout. However, the blackout also disrupted many industries, small scale emission sources, and rail and air transportation.

The Department of Energy G-1 aircraft flew in the New York City metropolitan area in the summer of 1996 as part of the North American Research Strategy for Tropospheric Ozone-Northeast effort to ascertain the causes leading to high O₃ levels in the northeastern United States (Kleinman et al., 2000). Ozone, O₃ precursors, and other photochemically active trace gases were measured upwind and downwind of New York City to characterize the O₃ formation process and its dependence on NO_x and VOCs. During two flights, the wind was south southwesterly and O₃ levels reached 110 ppb. On two other flights, the wind was from the north-northwest and O₃ levels were not as high. When the G-1 observed O₃ around 110 ppb, the NO_x/NO_y ratio measured at the surface was between 0.20 and 0.30, indicating an aged plume.

AX2.4.1.8 Model Calculations and Aircraft Observations of Ozone Over Philadelphia

Regional-scale transport and local O₃ production over Philadelphia was estimated using a new meteorological-chemical model (Fast et al., 2002). Surface and airborne meteorological and chemical measurements made during a 30-day period in July and August of 1999 as part of the Northeast Oxidant and Particulate Study were used to evaluate the model performance. Both research aircraft and ozonesondes, during the morning between 0900 and 1100 LST, measured layers of O₃ above the convective boundary layer. The model accounted for these layers through upwind vertical mixing the previous day, subsequent horizontal transport aloft, and NO titration of O₃ within the stable boundary layer at night. Entrainment of the O₃ aloft into the growing

convective boundary contributed to surface O₃ concentrations. During the study period, most of the O₃ appeared to result from local emissions in the vicinity of Philadelphia and the Chesapeake Bay area, but during high O₃ episodes, up to 30 to 40% of the O₃ was due to regional transport from upwind sources.

AX2.4.1.9 The Two-Reservoir System

Studies described above and over 500 aircraft flights over the mid-Atlantic region show that a two-reservoir system illustrated schematically in Figure AX2-18 may represent both the dynamics and photochemistry of severe, multiday haze and O₃ episodes over the eastern United States (Taubman et al., 2004, 2005). The first reservoir is the PBL, where most precursor species are injected, and the second is the lower free troposphere (LFT), where photochemical processes are accelerated and removal via deposition is rare. Bubbles of air lifted from urban and industrial sources were rich in CO and SO₂, but not O₃, and contained greater numbers of externally mixed primary sulfate and black carbon (BC) particles. Correlations among O₃, air parcel altitude, particle size, and relative humidity suggest that greater O₃ concentrations and relatively larger particles are produced in the LFT and mix back down into the PBL. Backward trajectories indicated source regions in the Midwest and mid-Atlantic urban corridor, with southerly transport up the urban corridor augmented by the Appalachian lee trough and nocturnal low-level jet (LLJ). This concept of two-reservoirs may facilitate the numerical simulation of multiday events in the eastern United States. A relatively small number of vertical layers will be required if accurate representation of the sub-gridscale transport can be parameterized to represent the actual turbulent exchange of air between the PBL and lower free troposphere.

AX2.5 METHODS USED TO CALCULATE RELATIONS BETWEEN OZONE AND ITS PRECURSORS

Atmospheric chemistry and transport models are the major tools used to calculate the relations between O₃, its precursors, and other oxidation products. Other techniques, involving statistical relations between O₃ and other variables have also been used. Chemistry-transport models (CTM) are driven by emissions inventories for O₃ precursor compounds and by meteorological fields. Emissions of precursor compounds can be divided into anthropogenic and

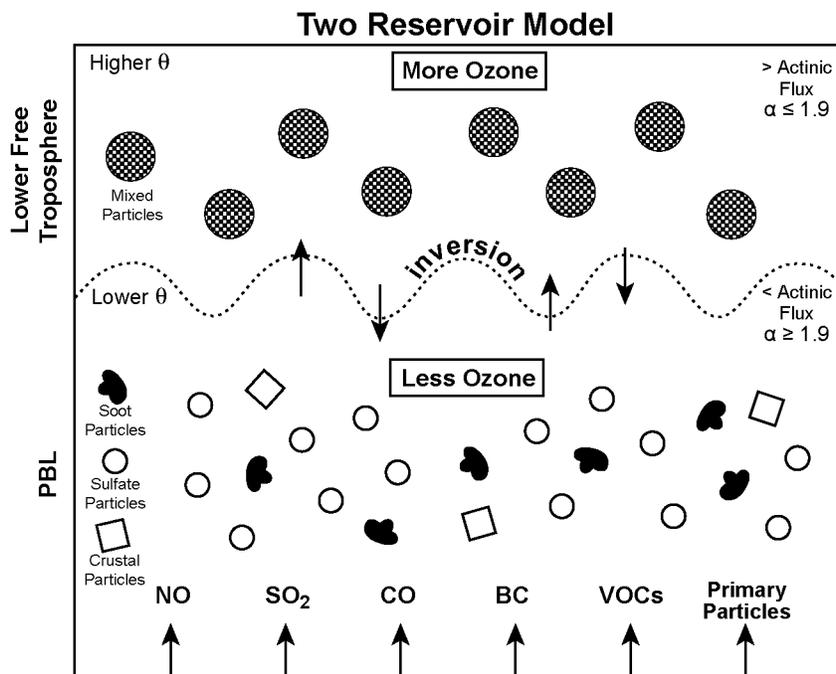


Figure AX2-18. Conceptual two-reservoir model showing conditions in the PBL and in the lower free troposphere during a multiday O₃ episode. The dividing line, the depth of the mixed layer, is about 1000 m. Emissions occur in the PBL, where small, unmixed black carbon, sulfate, and crustal particles in the PM_{2.5} size range are also shown. Ozone concentrations as well as potential temperature (θ) and actinic flux are lower in the PBL than in the lower free troposphere, while RH is higher. Larger, mixed sulfate and carbonaceous particles (still in the PM_{2.5} size range) and more O₃ exist in the lower free troposphere.

Source: Taubman et al. (2004, 2005).

natural source categories. Natural sources can be further divided into biotic (vegetation, microbes, animals) and abiotic (biomass burning, lightning) categories. However, the distinction between natural sources and anthropogenic sources is often difficult to make as human activities affect directly, or indirectly, emissions from what would have been considered natural sources during the preindustrial era. Emissions from plants and animals used in agriculture are usually referred to as anthropogenic. Wildfire emissions may be considered natural, except that forest management practices may have led to the buildup of fuels on the forest floor, thereby altering the frequency and severity of forest fires. Needed meteorological quantities such as winds and

temperatures are taken from operational analyses, reanalyses, or circulation models. In most cases, these are off-line analyses, i.e., they are not modified by radiatively active species such as O₃ and particles generated by the model.

A brief overview of atmospheric chemistry-transport models is given in Section AX2.5.1. A discussion of emissions inventories of precursors that are used by these models is given in Section AX2.5.2. Uncertainties in emissions estimates have also been discussed in Air Quality Criteria for Particulate Matter (U.S. Environmental Protection Agency, 2000). So-called “observationally based models” which rely more heavily on observations of the concentrations of important species are discussed in Section AX2.5.3. Chemistry-transport model evaluation and an evaluation of the reliability of emissions inventories are presented in Section AX2.5.4.

AX2.5.1 Chemistry-Transport Models

Atmospheric chemistry-transport models (CTMs) are used to obtain better understanding of the processes controlling the formation, transport, and destruction of O₃ and other air pollutants; to understand the relations between O₃ concentrations and concentrations of its precursors such as NO_x and VOCs; and to understand relations among the concentration patterns of O₃ and other oxidants that may also exert health effects. Detailed examination of the concentrations of short-lived species in a CTM can provide important insights into how O₃ is formed under certain conditions and can suggest likely avenues for data analysis and future experiments and field campaigns. The dominant processes leading to the formation of O₃ in a particular time period, questions about whether NO_x or VOCs were more important, the influence of meteorology and of emissions from a particular geographic region, and the transformation or formation of other pollutants could be examined using a CTM.

CTMs are also used for determining control strategies for O₃ precursors. However, this application has met with varying degrees of success because of the highly nonlinear relations between O₃ and emissions of its precursors. CTMs include mathematical descriptions of atmospheric transport, emissions, the transfer of solar radiation through the atmosphere, chemical reactions, and removal to the surface by turbulent motions and precipitation for chemical species of interest. Increasingly, the trend is for these processes to be broken down and handled by other models or sub-models, so a CTM will likely use emissions and meteorological data from at least two other models.

There are two major formulations of CTMs in current use. In the first approach, grid-based, or Eulerian, air quality models, the region to be modeled (the modeling domain) is subdivided into a three-dimensional array of grid cells. Spatial derivatives in the species continuity equations are cast in finite-difference form over this grid, and a system of equations for the concentrations of all the chemical species in the model are solved numerically at each grid point. The modeling domain may be limited to a particular airshed or provide global coverage and extend through several major atmospheric layers. Time dependent continuity (mass conservation) equations are solved for each species including terms for transport, chemical production and destruction, and emissions and deposition (if relevant), in each cell. Chemical processes are simulated with ordinary differential equations, and transport processes are simulated with partial differential equations. Because of a number of factors such as the different time scales inherent in different processes, the coupled, nonlinear nature of the chemical process terms, and computer storage limitations, all of the terms in the equations are not solved simultaneously in three dimensions. Instead, a technique known as operator splitting, in which terms involving individual processes are solved sequentially, is used. In the second application of CTMs, trajectory or Lagrangian models, a large number of hypothetical air parcels are specified as following wind trajectories. In these models, the original system of partial differential equations is transformed into a system of ordinary differential equations.

A less common approach is to use a hybrid Lagrangian/Eulerian model, in which certain aspects of atmospheric chemistry and transport are treated with a Lagrangian approach and others are treated in a Eulerian manner (e.g., Stein et al., 2000). Both modeling approaches have their advantages and disadvantages. The Eulerian approach is more general in that it includes processes that mix air parcels and allows integrations to be carried out for long periods during which individual air parcels lose their identity. There are, however, techniques for including the effects of mixing in Lagrangian models such as FLEXPART (e.g., Zanis et al., 2003), ATTILA (Reithmeir and Sausen, 2002), and CLaMS (McKenna et al., 2002).

Major modeling efforts within the U.S. Environmental Protection Agency center on the Models3/Community Modeling for Air Quality (CMAQ, Byun et al., 1998) and the Multi Scale Air Quality Simulation Platform (MAQSIP, Odman and Ingram, 1996) whose formulations are based on the regional acid deposition model (RADM, Chang et al., 1987). A number of other modeling platforms using the Lagrangian and Eulerian frameworks have been reviewed in

AQCD 96. CTMs currently in use are summarized in the review by Russell and Dennis (2000). Evaluations of the performance of CMAQ are given in Arnold et al. (2003) and Fuentes and Raftery (2005). The domains of MAQSIP and CMAQ are flexible and can extend from several hundred km to the hemispherical scale. In addition, both of these classes of models allow the resolution of the calculations over specified areas to vary. CMAQ and MAQSIP are both driven by the MM5 mesoscale meteorological model (Seaman, 2000), though both may be driven by other meteorological models (e.g., RAMS and Eta). Simulations of regional O₃ episodes have been performed with a horizontal resolution of 4 km. In principle, calculations over limited domains can be accomplished to even finer scales. However, simulations at these higher resolutions require better parameterizations of meteorological processes such as boundary layer fluxes, deep convection and clouds (Seaman, 2000), and knowledge of emissions. Resolution at finer scales will likely be necessary to resolve smaller-scale features such as the urban heat island; sea, bay, and land breezes; and the nocturnal low-level jet.

Currently, the most common approach to setting up the horizontal domain is to nest a finer grid within a larger domain of coarser resolution. However, a number of other strategies are currently being developed, such as the stretched grid (e.g., Fox-Rabinowitz et al., 2002) and the adaptive grid. In a stretched grid, the grid's resolution continuously varies throughout the domain, thereby eliminating any potential problems with the sudden change from one resolution to another at the boundary. One must be careful in using such a formulation, because certain parameterizations that are valid on a relatively coarse grid scale (such as convection, for example) are not valid or should not be present on finer scales. Adaptive grids are not set at the start of the simulation, but instead adapt to the needs of the simulation as it evolves (e.g., Hansen et al., 1994). They have the advantage that, if the algorithm is properly set up, the resolution is always sufficient to resolve the process at hand. However, they can be very slow if the situation to be modeled is complex. Additionally, if one uses adaptive grids for separate meteorological, emissions, and photochemical models, there is no reason a priori why the resolution of each grid should match; and the gains realized from increased resolution in one model will be wasted in the transition to another model. The use of finer and finer horizontal resolution in the photochemical model will necessitate finer-scale inventories of land use and better knowledge of the exact paths of roads, locations of factories, and, in general, better methods for locating

sources. The present practice of locating a source in the middle of a county or distributing its emissions throughout a county if its location is unknown will likely not be adequate in the future.

The vertical resolution of these models continues to improve as more layers are added to capture atmospheric processes and structures. This trend will likely continue because a model with 25 vertical layers, for example, may have layers that are 500 m thick at the top of the planetary boundary layer. Though the boundary layer height is generally determined through other methods, the chemistry in the model is necessarily confined by such layering schemes. Because the height of the boundary layer is of critical importance in simulations of air quality, improved resolution of the boundary layer height would likely improve air quality simulations. The difficulty of properly establishing the boundary layer height is most pronounced when considering tropopause folding events, which are important in determining the chemistry of the background atmosphere. In the vicinity of the tropopause, the vertical resolution of most any large scale model is quite unlikely to be able to capture such a feature. Additionally, any current model is likely to have trouble adequately resolving fine scale features such as the low-level jet. Finally, models must be able to treat emissions, meteorology, and photochemistry differently in different areas. Emissions models are likely to need better resolution near the surface and possibly near any tall stacks. Photochemical models, on the other hand, may need better resolution away from the surface and be more interested in resolving the planetary boundary layer height, terrain differences, and other higher altitude features. Meteorological models share some of the concerns of photochemical models, but are less likely to need sufficient resolution to adequately treat a process such as dry deposition beneath a stable nocturnal boundary layer. Whether the increased computational power necessary for such increases in resolution will be ultimately justified by improved results in the meteorological and subsequent photochemical simulations remains to be seen.

CTMs require time dependent, three-dimensional wind fields for the time period of simulation. The winds may be either generated by a model using initial fields alone or four dimensional data assimilation can be used to improve the model's meteorological fields (i.e., model equations can be updated periodically [or "nudged"] to bring results into agreement with observations). Most modeling efforts have focused on simulations of several days duration (a typical time scale for individual O₃ episodes), but there have been several attempts at modeling longer periods. For example, Kasibhatla and Chameides (2000) simulated a four month period

from May to September of 1995 using MAQSIP. The current trend appears to be toward simulating longer time periods. This will impose additional strains on computational resources, as most photochemical modeling until recently has been performed with an eye toward simulating only summertime episodes of peak O₃. With the shift toward modeling an entire year being driven by the desire to understand observations of periods of high wintertime PM (e.g., Blanchard et al., 2002), models will be further challenged to simulate air quality under conditions for which they may not have been used previously.

Chemical kinetics mechanisms (a set of chemical reactions) representing the important reactions that occur in the atmosphere are used in air quality models to estimate the net rate of formation of each pollutant simulated as a function of time. Chemical mechanisms that explicitly treat the chemical reactions of each individual reactive species are too lengthy and demanding of computer resources to be incorporated into three-dimensional atmospheric models. As an example, a master chemical mechanism includes approximately 10,500 reactions involving 3603 chemical species (Derwent et al., 2001). Instead, “lumped” mechanisms, that group compounds of similar chemistry together, are used. The chemical mechanisms used in existing photochemical O₃ models contain significant uncertainties that may limit the accuracy of their predictions; the accuracy of each of these mechanisms is also limited by missing chemistry. Because of different approaches to the lumping of organic compounds into surrogate groups, chemical mechanisms, can produce somewhat different results under similar conditions. The CB-IV chemical mechanism (Gery et al., 1989), the RADM II mechanism (Stockwell et al., 1990), the SAPRC (e.g., Wang et al., 2000a,b; Carter, 1990) and the RACM mechanisms can be used in CMAQ. Jimenez et al. (2003) provide brief descriptions of the features of the main mechanisms in use and they compared concentrations of several key species predicted by seven chemical mechanisms in a box model simulation over 24 h. The average deviation from the average of all mechanism predictions for O₃ and NO over the daylight period was less than 20%, and 10% for NO₂ for all mechanisms. However, much larger deviations were found for HNO₃, PAN, HO₂, H₂O₂, C₂H₄ and C₃H₈ (isoprene). An analysis for OH radicals was not presented. The large deviations shown for most species imply differences between the calculated lifetimes of atmospheric species and the assignment of model simulations to either NO_x limited or radical limited regimes between mechanisms. Gross and Stockwell (2003) found small differences between mechanisms for clean conditions with differences becoming more significant for

polluted conditions, especially for NO₂ and organic peroxy radicals. They caution modelers to consider carefully the mechanisms they are using.

As CTMs incorporate more processes and knowledge of aerosol- and gas-phase chemistry improves, a “one atmosphere” approach is evolving. For example, CMAQ and PM-CAMx now incorporate some aerosol processes, and several attempts are currently underway to study feedbacks of chemistry on atmospheric dynamics using meteorological models, usually MM5 (e.g., Grell et al., 2000; Liu et al., 2001a; Lu et al., 1997; Park et al., 2001). This coupling may be necessary to accurately simulate cases such as the heavy aerosol loading found in forest fire plumes (Lu et al., 1997; Park et al., 2001).

Spatial and temporal characterizations of anthropogenic and biogenic precursor emissions must be specified as inputs to a CTM. Emissions inventories have been compiled on grids of varying resolution for many hydrocarbons, aldehydes, ketones, CO, NH₃, and NO_x. Emissions inventories for many species require the application of some algorithm for calculating the dependence of emissions on physical variables such as temperature. For many species, information concerning the temporal variability of emissions is lacking, so long term (e.g., annual or O₃-season) averages are used in short term, episodic simulations. Annual emissions estimates are often modified by the emissions model to produce emissions more characteristic of the time of day and season. Significant errors in emissions can occur if an inappropriate time dependence or a default profile is used. Additional complexity arises in model calculations because different chemical mechanisms are based on different species, and inventories constructed for use with another mechanism must be adjusted to reflect these differences. This problem also complicates comparisons of the outputs of these models because one chemical mechanism will necessarily produce species that are different from those in another and neither output will necessarily agree with the measurements.

The effects of clouds on atmospheric chemistry are complex and introduce considerable uncertainty into CTM calculations. Thunderstorm clouds are optically very thick and have major effects on radiative fluxes and thus on photolysis rates. Madronich (1987) provided modeling estimates of the effects of clouds of various optical depths on photolysis rates. In the upper portion of a thunderstorm anvil, photolysis is likely to be enhanced (as much as a factor of 2 or more) due to multiple reflections off the ice crystals. In the lower portion of the cloud and beneath the cloud, photolysis is substantially decreased. Thunderstorm updrafts, which contain

copious amounts of water, are regions where efficient scavenging of soluble species occurs (Balkanski et al., 1993). Direct field measurements of the amounts of specific trace gases scavenged in observed storms are sparse. Pickering et al. (2001) used a combination of model estimates of soluble species that did not include wet scavenging and observations of these species from the upper tropospheric outflow region of a major line of convection observed near Fiji. Over 90% of the nitric acid and hydrogen peroxide in the outflow air appeared to have been removed by the storm. Walcek et al. (1990) included a parameterization of cloud-scale aqueous chemistry, scavenging, and vertical mixing in the regional scale, chemistry-transport model of Chang et al. (1987). The vertical distribution of cloud microphysical properties and the amount of subcloud-layer air lifted to each cloud layer were determined using a simple entrainment hypothesis (Walcek and Taylor, 1986). Vertically-integrated O₃ formation rates over the northeastern United States were enhanced by ~50% when the in-cloud vertical motions were included in the model.

In addition to wet deposition, dry deposition (the removal of chemical species from the atmosphere by interaction with ground-level surfaces) is an important removal process for pollutants on both urban and regional scales and must be included in CTMs. The general approach used in most models is the three-resistance method, in which where dry deposition is parameterized with a deposition velocity, which is represented as $v_d = (r_a + r_b + r_c)^{-1}$ where r_a , r_b , and r_c represent the resistance due to atmospheric turbulence, transport in the fluid sublayer very near the elements of surface such as leaves or soil, and the resistance to uptake of the surface itself. This approach works for a range of substances although it is inappropriate for species with substantial emissions from the surface or for species whose deposition to the surface depends on its concentration at the surface itself. The approach is also modified somewhat for aerosols: the terms r_b and r_c are replaced with a surface deposition velocity to account for gravitational settling. In their review, Wesley and Hicks (2000) point out several shortcomings of current knowledge of dry deposition. Among those shortcomings are difficulties in representing dry deposition over varying terrain where horizontal advection plays a significant role in determining the magnitude of r_a and difficulties in adequately determining a deposition velocity for extremely stable conditions such as those occurring at night (e.g., Mahrt, 1998). Under the best of conditions, when a model is exercised over a relatively small area where dry deposition measurements have been made, models still commonly show uncertainties at least as

large as $\pm 30\%$ (e.g., Massman et al., 1994; Brook et al., 1996; Padro, 1996). Wesley and Hicks (2000) state that an important result of these comparisons is that the current level of sophistication of most dry deposition models is relatively low and relies heavily on empirical data. Still larger uncertainties exist when the surface features are not well known or when the surface comprises a patchwork of different surface types, as is common in the eastern United States.

The initial conditions, i.e., the concentration fields of all species computed by a model, and the boundary conditions, i.e., the concentrations of species along the horizontal and upper boundaries of the model domain throughout the simulation must be specified at the beginning of the simulation. It would be best to specify initial and boundary conditions according to observations. However, data for vertical profiles of most species of interest are sparse. Ozonesonde data have been used to specify O_3 fields, but the initial and boundary values of many other species are often set equal to zero because of a lack of observations. Further, ozonesondes are thought to be subject to errors in measurement and differences arising from improper corrections for pump efficiency and the solutions used (e.g., Hilsenrath et al., 1986; Johnson et al., 2002). The results of model simulations over larger, preferably global, domains can also be used. As may be expected, the influence of boundary conditions depends on the lifetime of the species under consideration and the time scales for transport from the boundaries to the interior of the model domain (Liu et al., 2001b).

Each of the model components described above has an associated uncertainty, and the relative importance of these uncertainties varies with the modeling application. The largest errors in photochemical modeling are still thought to arise from the meteorological and emissions inputs to the model (Russell and Dennis, 2000). Within the model itself, horizontal advection algorithms are still thought to be significant source of uncertainty (e.g., Chock and Winkler, 1994) though more recently those errors are thought to have been reduced (e.g., Odman et al., 1996). There are also indications that problems with mass conservation continue to be present in photochemical and meteorological models (e.g., Odman and Russell, 1999); these can result in significant simulation errors. Uncertainties in meteorological variables and emissions can be large enough that they would lead one to make the wrong decision when considering control strategies (e.g., Russell and Dennis, 2000; Sillman et al., 1995). The effects of errors in initial conditions can be minimized by including several days “spin-up” time in a simulation to

allow species to come to chemical equilibrium with each other before the simulation of the period of interest begins.

While the effects of poorly specified boundary conditions propagate through the model's domain, the effects of these errors remain undetermined. Many regional models specify constant O₃ profiles (e.g., 35 ppb) at their lateral and upper boundaries; ozonesonde data, however, indicate that the mixing ratio of O₃ increases vertically in the troposphere (to over 100 ppb at the tropopause) and into the stratosphere (e.g., Newchurch et al., 2003). The practice of using constant O₃ profiles strongly reduces the potential effects of vertical mixing of O₃ from above the planetary boundary layer (via mechanisms outlined in Section AX2.3) on surface O₃ levels. The use of an O₃ climatology (e.g., Fortuin and Kelder, 1998) might reduce the errors that would otherwise be incurred. Because many meteorological processes occur on spatial scales which are smaller than the grid spacing (either horizontally or vertically) and thus are not calculated explicitly, parameterizations of these processes must be used and these introduce additional uncertainty.

Uncertainty also arises in modeling the chemistry of O₃ formation because it is highly nonlinear with respect to NO_x concentrations. Thus, the volume of the grid cell into which emissions are injected is important because the nature of O₃ chemistry (i.e., O₃ production or titration) depends in a complicated way on the concentrations of the precursors and the OH radical. The use of ever-finer grid spacing allows regions of O₃ titration to be more clearly separated from regions of O₃ production. The use of grid spacing fine enough to resolve the chemistry in individual power-plant plumes is too demanding of computer resources for this to be attempted in most simulations. Instead, parameterizations of the effects of subgrid scale processes such as these must be developed; otherwise serious errors can result if emissions are allowed to mix through an excessively large grid volume before the chemistry step in a model calculation is performed. In light of the significant differences between atmospheric chemistry taking place inside and outside of a power plant plume (e.g., Ryerson et al., 1998 and Sillman, 2000), inclusion of a separate, meteorological module for treating large, tight plumes is necessary. Because the photochemistry of O₃ and many other atmospheric species is nonlinear, emissions correctly modeled in a tight plume may be incorrectly modeled in a more dilute plume. Fortunately, it appears that the chemical mechanism used to follow a plume's development need not be as detailed as that used to simulate the rest of the domain, as the

inorganic reactions are the most important in the plume (e.g., Kumar and Russell, 1996). The need to include explicitly plume-in-grid chemistry disappears if one uses the adaptive grid approach mentioned previously, though such grids are more computationally intensive. The differences in simulations are significant because they can lead to significant differences in the calculated sensitivity of O₃ to its precursors (e.g., Sillman et al., 1995).

Because the chemical production and loss terms in the continuity equations for individual species are coupled, the chemical calculations must be performed iteratively until calculated concentrations converge to within some preset criterion. The number of iterations and the convergence criteria chosen also can introduce error.

The importance of global transport of O₃ and its contribution to regional O₃ levels in the United States is slowly becoming apparent. There are presently on the order of 20 three-dimensional global models that have been developed by various groups to address problems in tropospheric chemistry. These models resolve synoptic meteorology, O₃-NO_x-CO-hydrocarbon photochemistry, wet and dry deposition, and parameterize sub-grid scale vertical mixing such as convection. Global models have proven useful for testing and advancing scientific understanding beyond what is possible with observations alone. For example, they can calculate quantities of interest that we do not have the resources to measure directly, such as export of pollution from one continent to the global atmosphere or the response of the atmosphere to future perturbations to anthropogenic emissions.

The finest horizontal resolution at which global simulations are typically conducted is ~200 km² although rapid advances in computing power continuously change what calculations are feasible. The next generation of models will consist of simulations that link multiple horizontal resolutions from the global to the local scale. Finer resolution will only improve scientific understanding to the extent that the governing processes are more accurately described at that scale. Consequently there is a critical need for observations at the appropriate scales to evaluate the scientific understanding represented by the models.

Observations of specific chemical species have been useful for testing transport schemes. Radon-222 simulations in sixteen global models have been evaluated with observations to show that vertical mixing is captured to within the constraints offered by the mean observed concentrations (Jacob et al., 1997). Tracers such as cosmogenic ⁷Be and terrigenic ²¹⁰Pb have been used to test and constrain model transport and wet deposition (e.g., Liu et al., 2001b).

Other chemical species obtained from various platforms (surface measurements, aircraft, satellites) are useful for evaluating the simulation of chemical and dynamical processing in global models. For example, Emmons et al. (2000) compiled available measurements of 12 species relevant to O₃ photochemistry from a number of aircraft campaigns in different regions of the world and used this data composite to evaluate two global models. They concluded that one model (MOZART) suffered from weak convection and an underestimate of nitrogen oxide emissions from biomass burning, while another model (IMAGES) transported too much O₃ from the stratosphere to the troposphere (Emmons et al., 2000). The global coverage available from satellite observations offers new information for testing models. Recent efforts are using satellite observations to evaluate the emission inventories of O₃ precursors that are included in global models; such observations should help to constrain the highly uncertain natural emissions of isoprene and nitrogen oxides (e.g., Palmer et al., 2003; Martin et al., 2003).

A comparison of numerous global chemistry-transport models developed by groups around the world was included in Section 4.4 of the recent report of the Intergovernmental Panel on Climate Change (Prather and Ehhalt, 2001). In that report, monthly mean O₃ (O₃) and carbon monoxide (CO) simulated by the various models was evaluated with O₃ observations from global ozonesonde stations at 700, 500, and 300 hPa and with surface CO measurements from 17 selected NOAA/CMDL sites. The relevant figures (Figures AX2-4-10 and AX2-4-11) are reproduced here (as Figures AX2-19 for O₃ and AX2-20 for CO) along with the references in their Table AX2-10 (as Table AX2-4). Overall, the models capture the general features of the O₃ and CO seasonal cycles but meet with varying levels of success at matching the observed concentrations and the amplitude of the observed seasonal cycle. For O₃, the models show less disagreement in the lower troposphere than in the upper troposphere, reflecting the difficulty of representing the exchange between the stratosphere and troposphere and the loose constraints on the net O₃ flux that are provided by observations.

An evaluation of five global models with data from the Measurement of Ozone and Water Vapor by Airbus In-Service Aircraft (MOZAIC) project over New York City and Miami indicates that the models tend to underestimate the summer maximum in the middle and lower troposphere over northern mid-latitude cities such as New York City and to underestimate the variability over coastal cities such as Miami which are strongly influenced by both polluted continental and clean marine air masses (Law et al., 2000). Local maxima and minima are

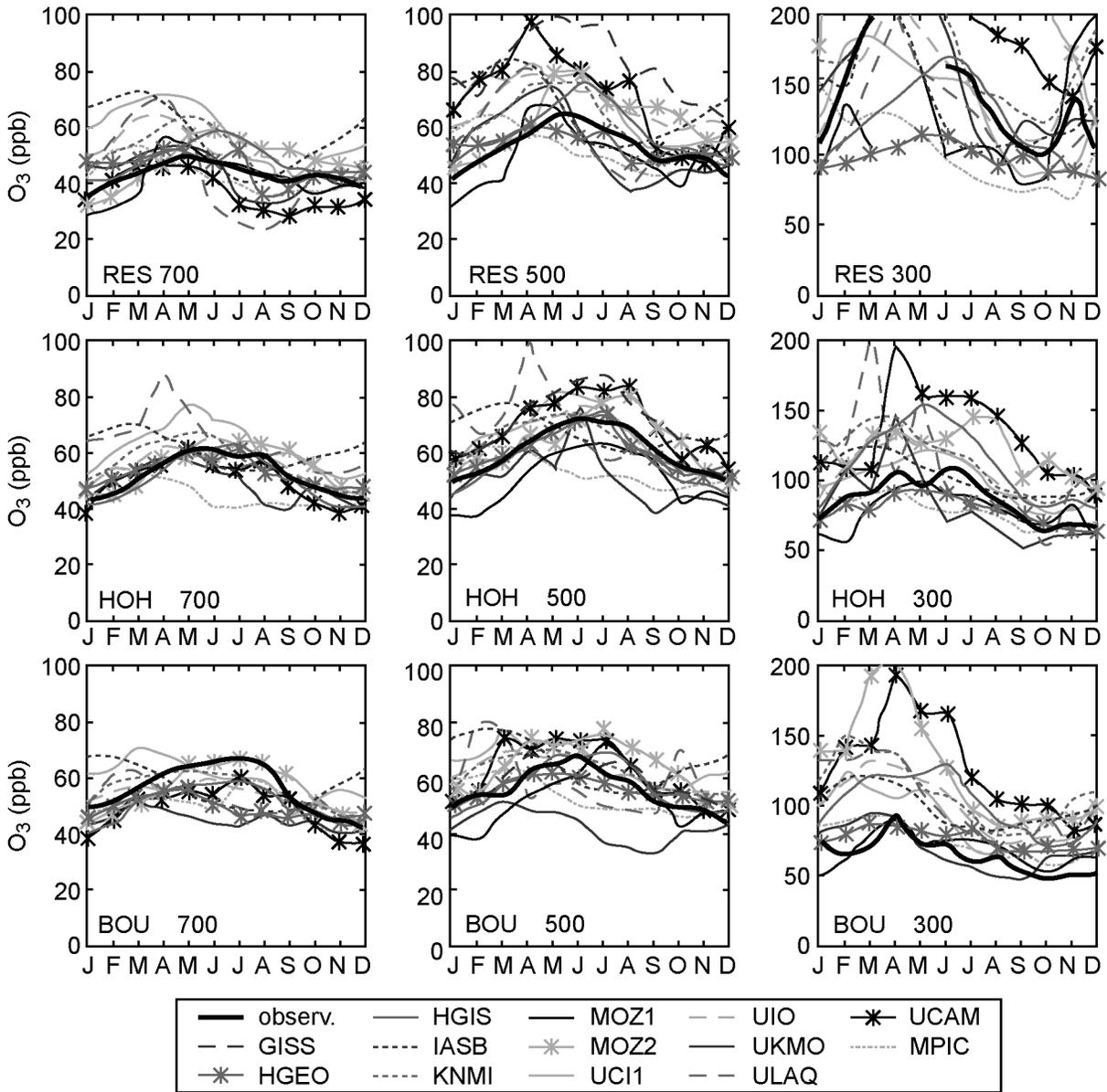


Figure AX2-19. Seasonal variability in O₃ concentrations observed at a number of pressure surfaces at six ozonesonde sites and the predictions of 13 global scale chemistry-transport models.

Source: IPCC Third Assessment Report (2001).

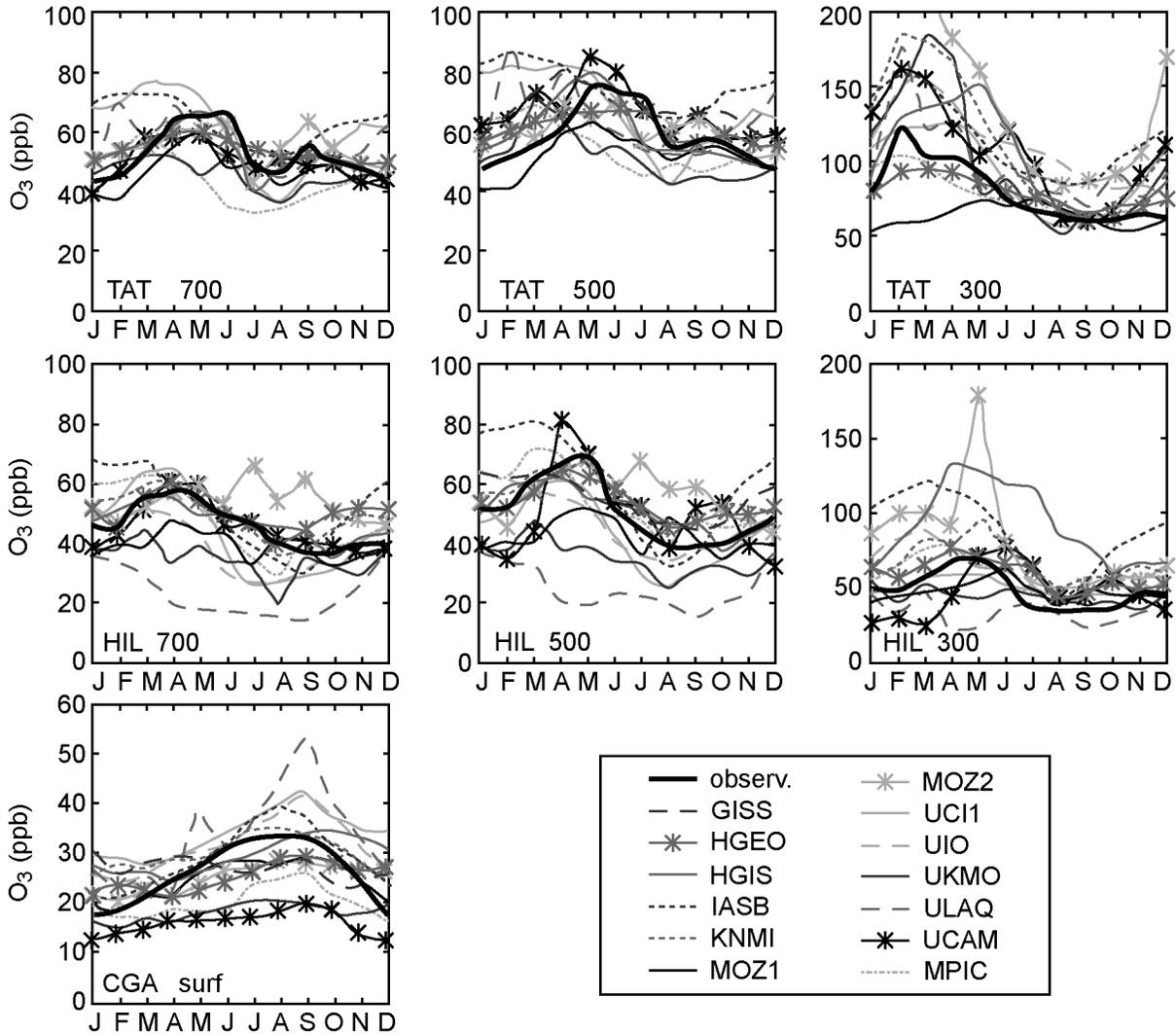


Figure AX2-20. Seasonal variability in O₃ concentrations observed at a number of pressure surfaces at six ozonesonde sites and the predictions of 13 global scale chemistry-transport models.

Source: IPCC Third Assessment Report (2001).

difficult to reproduce with global models because processes are averaged over an entire model grid cell. Much of the spatial and temporal variability in surface O₃ over the United States is modulated by synoptic meteorology (e.g., Logan, 1989; Eder et al., 1993; Vukovich, 1995, 1997; Cooper and Moody, 2000) which is resolved in the current generation of global models. For example, an empirical orthogonal function analysis on observed and simulated fields over

Table AX2-4. Chemistry-Transport Models (CTM) Contributing to the Oxcomp Evaluation of Predicting Tropospheric O₃ and OH (Prather and Ehhalt, 2001)

CTM	Institute	Contributing Authors	References
GISS	GISS	Shindell/Grenfell	Hansen et al. (1997)
HGEO	Harvard U.	Bey/Jacob	Bey et al. (2001a)
HGIS	Harvard U.	Mickley/Jacob	Mickley et al. (1999)
IASB	IAS/Belg.	Müller	Müller and Brasseur (1995, 1999)
KNMI	KNMI/Utrecht	van Weele	Jeuken et al. (1999), Houweling et al. (2000)
MOZ1	NCAR/CNRS	Hauglustaine/Brasseur	Brasseur et al. (1998), Hauglustaine et al. (1998)
MOZ2	NCAR	Horowitz/Brasseur	Brasseur et al. (1998), Hauglustaine et al. (1998)
MPIC	MPI/Chem	Kuhlmann/Lawrence	Crutzen et al. (1999), Lawrence et al. (1999)
UCI	UC Irvine	Wild	Hannegan et al. (1998), Wild and Prather (2000)
UIO	U. Oslo	Berntsen	Berntsen and Isaksen (1997), Fuglestad et al. (1999)
UIO2	U. Oslo	Sundet	Sundet (1997)
UKMO	UK Met Office	Stevenson	Collins et al. (1997), Johnson et al. (1999)
ULAQ	U. L. Aquila	Pitari	Pitari et al. (1997)
UCAM	U. Cambridge	Plantevin/Johnson (TOMCAT)	Law et al. (1998, 2000)

the eastern United States in summer has shown that a 2° × 2.5° horizontal resolution global model (GEOS-CHEM) captures the synoptic-scale processes that control much of the observed variability (Fiore et al., 2003). Further evaluation of the same model showed that it can also capture many of the salient features of the observed distributions of O₃ as well as its precursors in surface air over the United States in summer, including formaldehyde concentrations and

correlations between O₃ and the oxidation products of nitrogen oxides (O₃: NO_y-NO_x), all of which indicate a reasonable photochemical simulation (Fiore et al., 2002).

A significant amount of progress in evaluating the performance of three-dimensional global models with surface, aircraft, and satellite data has been made in recent years. Disagreement among model simulations mainly stems from differences in the driving meteorology and emissions. The largest discrepancies amongst models and between models and observations occur in the upper troposphere and likely reflect uncertainties in exchange between the stratosphere and troposphere and photochemical processes there; the models agree better with observations closer to the surface. Synoptic-scale meteorology is resolved in these models, enabling them to simulate much of the observed variability in pollutants in the lower troposphere.

AX2.5.2 Emissions of Ozone Precursors

Estimated annual emissions of nitrogen oxides, VOCs, CO, and NH₃ for 1999 (U.S. Environmental Protection Agency, 2001) are shown in Tables AX2-5, AX2-6, AX2-7, and AX2-8. Methods for estimating emissions of criteria pollutants, quality assurance procedures and examples of emissions calculated by using data are given in U.S. Environmental Protection Agency (1999).

Emissions of nitrogen oxides associated with combustion arise from contributions from both fuel nitrogen and atmospheric nitrogen. Sawyer et al. (2000) have reviewed the factors associated with NO_x emissions by mobile sources. Estimates of NO_x emissions from mobile sources are generally regarded as fairly reliable although further work is needed to clarify this point (Sawyer et al., 2000). Both nitrifying and denitrifying bacteria in the soil can produce NO_x, mainly in the form of NO. Emission rates depend mainly on fertilization levels and soil temperature. About 60% of the total NO_x emitted by soils occurs in the central corn belt of the United States. The oxidation of NH₃, emitted mainly by livestock and soils, leads to the formation of NO. Estimates of emissions from natural sources are less certain than those from anthropogenic sources.

Natural sources of oxides of nitrogen include lightning, oceans, and soil. Of these, as reviewed in AQCD 96, only soil emissions appear to have the potential to impact surface O₃ over the U.S. On a global scale, the contribution of soil emissions to the oxidized nitrogen budget is

Table AX2-5. Emissions of Nitrogen Oxides by Various Sources in the United States in 1999

Source	Emissions¹ (10¹² g/y)	Notes
On-road vehicle exhaust	7.8	Gasoline (58%) and diesel (42%) vehicles.
Non-road vehicle exhaust	5	Diesel (49%) and gasoline (3%) vehicles; railroads (22%); marine vessels (18%); other sources (8%).
Fossil fuel combustion	9.1	Electric utilities (57%); industry (31%); commercial, institutional and residential combustion (12%).
Industrial Processes	0.76	Mineral products (43%); petrochemical products (17%); chemical mfg. (16%); metal processing (11%); misc. industries (12%).
Biomass burning	0.35	Residential wood burning (11%); open burning (8%); wildfires (81%).
Waste disposal	0.053	Non-biomass incineration.
Natural sources ²	3.1	Lightning (50%); soils(50%).
<i>Total</i>	<i>26</i>	

¹Emissions are expressed in terms of NO₂.

²Estimated on the basis of data given in Guenther et al. (2000).

Source: U.S. Environmental Protection Agency (2001).

on the order of 10% (van Aardenne et al., 2001; Finlayson-Pitts and Pitts, 2000; Seinfeld and Pandis, 1998), but attempts to quantify emissions of NO_x from fertilized fields show great variability. Soil NO emissions can be estimated from the fraction of the applied fertilizer nitrogen emitted as NO_x, but the flux varies strongly with land use and temperature. The fraction nitrogen. Estimated globally averaged fractional applied nitrogen loss as NO varies from 0.3% (Skiba et al., 1997) to 2.5% (Yienger and Levy, 1995). Variability within biomes to which fertilizer is applied, such as shortgrass versus tallgrass prairie, accounts for a factor of three in uncertainty (Williams et al., 1992; Yienger and Levy, 1995; Davidson and Kinglerlee, 1997).

The local contribution can be much greater than the global average, particularly in summer especially where corn is grown extensively. Williams et al. (1992) estimated that contributions from soils in Illinois contribute about 26% of the emissions from industrial and commercial

Table AX2-6. Emissions of Volatile Organic Compounds by Various Sources in the United States in 1999

Source	Emissions (10¹² g/y)	Notes
On-road vehicles	4.8	Exhaust and evaporative losses from gasoline (95%) and diesel (5%) vehicles.
Non-road vehicles	2.9	Exhaust and evaporative losses from gasoline (80%) and diesel (12%) vehicles; aircraft and other sources (8%).
Fossil fuel combustion	0.27	Electrical utilities; industrial, commercial, institutional, and residential sources.
Chemical industrial processes	0.36	Mfg. of organic chemicals, polymers and resins, and misc. products.
Petroleum industrial processes	0.39	Oil and gas production (64%); refining (36%).
Other industrial processes	0.48	Metal processing (15%); wood processing (32%); agricultural product processing (21%); misc. processes (18%).
Solvent volatilization	4.4	Surface coatings (44%); other industrial uses (20%); non-industrial uses (e.g., pesticide application, consumer solvents) (36%).
Storage and transport of volatile compounds	1.1	Evaporative losses from petroleum products and other organic compounds.
Biomass burning	1.2	Residential wood combustion (37%); open burning (22%); agricultural burning (22%); wildfires (19%).
Waste disposal	0.53	Residential burning (63%); waste water (23%); landfills (6%); non-biomass incineration (8%).
Biogenic sources ¹	4.4	Approximately 98% emitted by vegetation. (Isoprene [35%], monoterpenes [25%], and all other reactive and non-reactive compounds [40%]).
<i>Total</i>	<i>21</i>	

¹Estimated on the basis of data given in Guenther et al. (2000).

Source: U.S. Environmental Protection Agency (2001).

Table AX2-7. Emissions of Ammonia by Various Sources in the United States in 1999

Source	Emissions (10¹² g/y)	Notes
Exhaust from on-road and non-road engines and vehicles	0.25	Exhaust from on-road (96%) and non-road (4%) vehicles.
Fossil fuel combustion	0.044	Combustion by electric utilities, industry, commerce, institutions, residences.
Industry	0.18	Chemical manufacturing (67%); petroleum refining (9%); other industries (25%).
Agriculture	3.9	Livestock (82%); fertilizer application (18%).
Waste disposal and recycling	0.08	Wastewater treatment (99%).
Natural sources	0.032	Unmanaged soils; wild animals.
<i>Total</i>	<i>4.5</i>	

Source: U.S. Environmental Protection Agency (2001).

processes in that State. In Iowa, Kansas, Minnesota, Nebraska, and South Dakota soil emissions may dominate. Conversion of ammonium to nitrate (nitrification) in aerobic soils appears to be the dominant pathway to NO. The mass and chemical form of nitrogen (reduced or oxidized) applied to soils, the vegetative cover, temperature, soil moisture, and agricultural practices such as tillage all influence the amount of fertilizer nitrogen released as NO.

As pointed out in the previous AQCD for O₃, emissions of NO from soils peak in summer when O₃ formation is at a maximum. A recent NRC report outlined the role of agricultural in emissions of air pollutants including NO and NH₃ (NRC, 2002). That report recommends immediate implementation of best management practices to control these emissions, and further research to quantify the magnitude of emissions and the impact of agriculture on air quality. Civerolo and Dickerson (1998) report that use of the no-till cultivation technique on a fertilized cornfield in Maryland reduced NO emissions by a factor of seven.

Annual global production of NO by lightning is the most uncertain source of reactive nitrogen. In the last decade literature values of the production rate range from 2 to 20 Tg-N per year. However, the most likely range is from 3 to 8 Tg-N per year, because the majority of the

Table AX2-8. Emissions of Carbon Monoxide by Various Sources in the United States in 1999

Source	Emissions (10¹² g/y)	Notes
On-road vehicle exhaust	50	Gasoline-fueled light-duty cars (54%) and trucks (32%), heavy-duty trucks (9%); diesel vehicles (5%); motorcycles (0.4%).
Non-road engines and vehicle exhaust	25	Gasoline-fueled (lawn and garden [44%], light commercial [17%], recreational [14%], logging [4%], industry and construction [6%, other [1%]]); diesel-fueled (5%); aircraft (4%); other (5%).
Fossil fuel combustion	2	Electric utilities (22%); industry (58%); commercial, institutional and residential combustion (20%).
Industrial Processes	3.7	Metal processing (45%); chemical mfg. (29%); petrochemical production; (10%); mineral products (5%); wood products (10%); misc. industries (1%).
Biomass burning	16	Residential wood burning (21%); open burning (21%); agricultural burning (41%); wildfires (17%).
Waste disposal	0.42	Non-biomass incineration.
Other	0.19	Structural fires (45%); storage and transport (38%); misc. sources (17%).
Biogenic emissions ¹	4.7+	Primary emissions from vegetation and soils; secondary formation (?).
<i>Total</i>	<i>102+</i>	

¹Estimated on the basis of data given in Guenther et al. (2000).

Source: U.S. Environmental Protection Agency (2001).

recent estimates fall in this range. The large uncertainty stems from several factors: (1) a large range of NO production rates per flash (as much as two orders of magnitude); (2) the open question of whether cloud-to-ground (CG) flashes and intracloud flashes (IC) produce substantially different amounts of NO; (3) the global flash rate; and (4) the ratio of the number of IC flashes to the number of CG flashes. Estimates of the amount of NO produced per flash have been made based on theoretical considerations (e.g., Price et al., 1997), laboratory experiments (e.g., Wang et al., 1998a); field experiments (e.g., Stith et al., 1999; Huntrieser et al., 2002), and

through a combination of cloud-resolving model simulations, observed lightning flash rates, and anvil measurements of NO (e.g., DeCaria et al., 2000). The latter method was also used by Pickering et al. (1998), who showed that only ~5% to 20% of the total NO production by lightning in a given storm exists in the boundary layer at the end of a thunderstorm. Therefore, the direct contribution to boundary layer O₃ production by lightning NO is thought to be small. However, lightning NO production can contribute substantially to O₃ production in the middle and upper troposphere. DeCaria et al. (2000) estimated that up to 7 ppbv of O₃ were produced in the upper troposphere in the first 24 hours following a Colorado thunderstorm due to the injection of lightning NO. A major uncertainty in mesoscale and global chemical transport models is the parameterization of lightning flash rates. Model variables such as cloud top height, convective precipitation rate, and upward cloud mass flux have been used to estimate flash rates. Allen and Pickering (2002) have evaluated these methods against observed flash rates from satellite, and examined the effects on O₃ production using each method.

Literally tens of thousands of organic compounds have been identified in plant tissues. However, most of these compounds either have sufficiently low volatility or are constrained so that they are not emitted in significant quantities. Less than 40 compounds have been identified by Guenther et al. (2000) as being emitted in large enough quantities to affect atmospheric composition. These compounds include terpenoid compounds (isoprene, 2-methyl-3-buten-2-ol, monoterpenes), compounds in the hexanal family, alkenes, aldehydes, organic acids, alcohols, ketones and alkanes. As can be seen from Table AX2-6, the major species emitted by plants are isoprene (35%), 19 other terpenoid compounds (25%) and 17 non-terpenoid compounds (40%) (Guenther et al., 2000). Of the latter, methanol contributes 12% of total emissions.

Because isoprene has been identified as the most abundant of biogenic VOCs (Guenther et al., 1995, 2000; Geron et al., 1994), it has been the focus of air quality model analyses in many published studies (Roselle, 1994; Sillman et al., 1995). The original Biogenic Emission Inventory System (BEIS) of Pierce and Waldruff (1991) used a branch-level isoprene emission factor of $14.7 \mu\text{g (g-foliar dry mass)}^{-1} \text{h}^{-1}$ for high isoprene emitting species (e.g., oaks, or North American *Quercus* species). When considering self-shading of foliage within branch enclosures, this is roughly equivalent to a leaf level emission rate of 20 to 30 $\mu\text{g-C (g-foliar dry mass)}^{-1} \text{h}^{-1}$ (Guenther et al., 1995). Geron et al (1994) reviewed studies between 1990 and 1994 and found that a much higher leaf-level rate of $70 \mu\text{g-C (g-foliar dry mass)}^{-1} \text{h}^{-1} \pm 50\%$ was more realistic,

and this rate was used in BEIS2 for high isoprene emitting tree species. BEIS3 (Guenther et al., 2000) applied similar emission factors at tree species levels (Geron et al 2000a, 2001) and more recent canopy environment models to estimate isoprene fluxes.

The results from several studies of isoprene emission measurements made at leaf, branch, tree, forest stand, and landscape levels have been used to test the accuracy of BEIS2 and BEIS3. These comparisons are documented in Geron et al. (1997) and Guenther et al. (2000). The results of these studies support the higher emission factors used in BEIS2 and BEIS3. Typically, leaf emission factors (normalized to standard conditions of PAR = 1000 $\mu\text{mol m}^{-2}$ and leaf temperature of 30 °C) measured at the top of tree canopies equal or exceed those used in BEIS2/3, while those in more shaded portions of the canopy tend to be lower than those assumed in the models, likely due to differences in developmental environments of leaves within the canopy (Monson et al., 1994; Sharkey et al., 1996; Harley et al., 1996; Geron et al., 2000b). Uncertainty in isoprene emissions due to variability in forest composition and leaf area remain in BVOC emission models and inventories. Seasonality and moisture stress also impact isoprene emission, but algorithms to simulate these effects are currently fairly crude (Guenther et al, 2000). The bulk of biogenic emissions occur during the summer, because of their dependence on temperature and incident sunlight. Biogenic emissions are also higher in southern states than in northern states for these reasons. The uncertainty associated with natural emissions ranges from about 50% for isoprene under midday summer conditions to about a factor of ten for other compounds (Guenther et al., 2000). In assessing the relative importance of these compounds, it should be borne in mind that the oxidation of many of the classes of compounds result in the formation of secondary organic aerosol and that many of the intermediate products may be sufficiently long lived to affect O₃ formation in areas far removed from where they were emitted. The oxidation of isoprene can also contribute about 10% of the source of CO (U.S. Environmental Protection Agency, 2000). Direct emissions of CO by vegetation is of much smaller importance. Soil microbes both emit and take up atmospheric CO, however, soil microbial activity appears to represent a net sink for CO.

Emissions from biomass burning depend strongly on the stage of combustion. Smoldering combustion, especially involving forest ecosystems favors the production of CH₄, NMHC and CO at the expense of CO₂, whereas active combustion produces more CO₂ relative to the other compounds mentioned above. Typical emissions ratios (defined as moles of compound per

moles of emitted CO₂ expressed as a percentage) range from 6 to 14% for CO, 0.6 to 1.6% for CH₄, and 0.3 to 1.1% for NMHCs (Andreae, 1991). Most NMHC emissions are due to emissions of lighter compounds, containing 2 or 3 carbon atoms.

AX2.5.3 Observationally-Based Models

As an alternative to chemistry-transport models, observationally-based methods (OBMs), which seek to infer O₃-precursor relations by relying more heavily on ambient measurements, can be used. Observationally-based methods are intuitively attractive because they provide an estimate of the O₃-precursor relationship based directly on observations of the precursors. These methods rely on observations as much as possible to avoid many of the uncertainties associated with chemistry/transport models (e.g., emission inventories and meteorological processes). However, these methods have large uncertainties with regards to photochemistry. As originally conceived, the observation-based approaches were intended to provide an alternative method for evaluating critical issues associated with urban O₃ formation. The proposed OBMs include calculations driven by ambient measurements (Chameides et al., 1992; Cardelino et al., 1995) and proposed “rules of thumb” that seek to show whether O₃ is primarily sensitive to NO_x or to VOC concentrations (Sillman, 1995; Chang et al., 1997; Tonnesen and Dennis, 2000a,b; Blanchard et al., 1999; Blanchard, 2000). These methods are controversial when used as “stand-alone” rules, because significant uncertainties and possible errors have been identified for all the methods (Chameides et al., 1988, Lu and Chang, 1998, Sillman and He, 2002; Blanchard and Stoeckenius, 2001). Methods such as these are most promising for use in combination with chemistry/transport models principally for evaluating the accuracy of model predictions.

Recent results (Tonnesen and Dennis, 2000a; Kleinman et al., 1997; 2000, 2001; Kleinman, 2000) suggest that ambient VOC and NO_x data can be used to identify the instantaneous production rate for O₃ and how the production rate varies with concentrations of NO_x and VOCs. The instantaneous production rate for O₃ is only one of the factors that affect the total O₃ concentration, because O₃ concentrations result from photochemistry and transport over time periods ranging from several hours to several days in regional pollution events. Ozone concentrations can be affected by distant emissions and by photochemical conditions at upwind locations, rather than instantaneous production at the site. Despite this limitation, significant information can be obtained by interpreting ambient NO_x and VOC measurements. Kleinman

et al. (1997, 2000, 2001) and Tonnesen and Dennis (2000a) both derived simple expressions that relate the NO_x -VOC sensitivity of instantaneous O_3 production to ambient VOC and NO_x . These expressions usually involve summed VOC weighted by reactivity.

Cardelino et al. (1995, 2000) developed a method that seeks to identify O_3 - NO_x -VOC sensitivity based on ambient NO_x and VOC data. Their method involves an area-wide sum of instantaneous production rates over an ensemble of measurement sites, which serve to represent the photochemical conditions associated with O_3 production in metropolitan areas. Their method, which relies on routine monitoring methods, is especially useful because it permits evaluation for a full season rather than just for individual episodes.

AX2.5.4 Chemistry-Transport Model Evaluation

The comparison of model predictions with ambient measurements represents a critical task for establishing the accuracy of photochemical models and evaluating their ability to serve as the basis for making effective control strategy decisions. The evaluation of a model's performance, or its adequacy to perform the tasks for which it was designed can only be conducted within the context of measurement errors and artifacts. Not only are there analytical problems, but there are also problems in assessing the representativeness of monitors at ground level for comparison with model values which represent typically an average over the volume of a grid box.

Chemistry-transport models for O_3 formation at the urban/regional scale have traditionally been evaluated based on their ability to correctly simulate O_3 . A series of performance statistics that measure the success of individual model simulations to represent the observed distribution of ambient O_3 , as represented by a network of surface measurements were recommended in U.S. Environmental Protection Agency (1991; see also Russell and Dennis, 2000). These statistics consist of the following:

- Unpaired peak O_3 within a metropolitan region (typically for a single day).
- Normalized bias equal to the summed difference between model and measured hourly concentrations divided by the sum of measured hourly concentrations.
- Normalized gross error, equal to the summed unsigned (absolute value) difference between model and measured hourly concentrations divided by the sum of measured hourly concentrations.

Unpaired peak prediction accuracy, A_u ;

$$A_u = \frac{C_p(x,t)_{\max} - C_o(x',t')_{\max}}{C_o(x',t')_{\max}} * 100\%, \quad (\text{AX2-49})$$

Normalized bias, D ;

$$D = \frac{1}{N} \sum_{i=1}^N \frac{\{C_p(x_i,t) - C_o(x_i,t)\}}{C_o(x_i,t)}, \quad t = 1, 24. \quad (\text{AX2-50})$$

Gross error, E_d (for hourly observed values of $O_3 > 60$ ppb)

$$E_d = \frac{1}{N} \sum_{i=1}^N \frac{|C_p(x_i,t) - C_o(x_i,t)|}{C_o(x_i,t)}, \quad t = 1, 24. \quad (\text{AX2-51})$$

The following performance criteria for regulatory models were recommended in U.S. Environmental Protection Agency (1991): unpaired peak O_3 to within $\pm 15\%$ or $\pm 20\%$; normalized bias within $\pm 5\%$ to $\pm 15\%$; and normalized gross error less than 30% to 35%, but only when $O_3 > 60$ ppb. This can lead to difficulties in evaluating model performance since nighttime and diurnal cycles are ignored. A major problem with this method of model evaluation is that it does not provide any information about the accuracy of O_3 -precursor relations predicted by the model. The process of O_3 formation is sufficiently complex that models can predict O_3 correctly without necessarily representing the O_3 formation process properly. If the O_3 formation process is incorrect, then the modeled source-receptor relations will also be incorrect.

Studies by Sillman et al. (1995, 2003), Reynolds et al. (1996) and Pierce et al. (1998) have identified instances in which different model scenarios can be created with very different O_3 -precursor sensitivity, but without significant differences in the predicted O_3 fields. Figures AX2-21a,b provide an example. Referring to the O_3 - NO_x -VOC isopleth plot (Figure AX2-22), it can be seen that similar O_3 concentrations can be found for photochemical conditions that have very different sensitivity to NO_x and VOCs.

Global-scale chemistry-transport models have generally been evaluated by comparison with measurements for a wide array of species, rather than just for O₃ (e.g., Wang et al., 1998b; Emmons et al., 2000; Bey et al., 2001b; Hess, 2001; Fiore et al., 2002). These have included evaluation of major primary species (NO_x, CO, and selected VOCs) and an array of secondary species (HNO₃, PAN, H₂O₂) that are often formed concurrently with O₃. Models for urban/regional O₃ have also been evaluated against a broader ensemble of measurements in a few cases, often associated with measurement intensives (e.g., Jacobson et al., 1996, Lu et al., 1997; Sillman et al., 1998). The results of a comparison between observed and computed concentrations from Jacobson et al. (1996) for the Los Angeles Basin are shown in Figures AX2-23a,b.

The highest concentrations of primary species usually occur in close proximity to emission sources (typically in urban centers) and at times when dispersion rates are low. The diurnal cycle includes high concentrations at night, with maxima during the morning rush hour, and low concentrations during the afternoon (Figure AX2-23a). The afternoon minima are driven by the much greater rate of vertical mixing at that time. Primary species also show a seasonal maximum during winter, and are often high during fog episodes in winter when vertical mixing is suppressed. By contrast, secondary species such as O₃ are typically highest during the afternoon (the time of greatest photochemical activity), on sunny days and during summer. During these conditions concentrations of primary species may be relatively low. Strong correlations between primary and secondary species are generally observed only in downwind rural areas where all anthropogenic species are high simultaneously. The difference in the diurnal cycles of primary species (CO, NO_x and ethane) and secondary species (O₃, PAN and HCHO) is evident in Figure AX2-23b.

Models for urban/regional O₃ have been evaluated less extensively than global-scale models in part because the urban/regional context presents a number of difficult challenges. Global-scale models typically represent continental-scale events and can be evaluated effectively against a sparse network of measurements. By contrast, urban/regional models are critically dependent on the accuracy of local emission inventories and event-specific meteorology, and must be evaluated separately for each urban area that is represented.

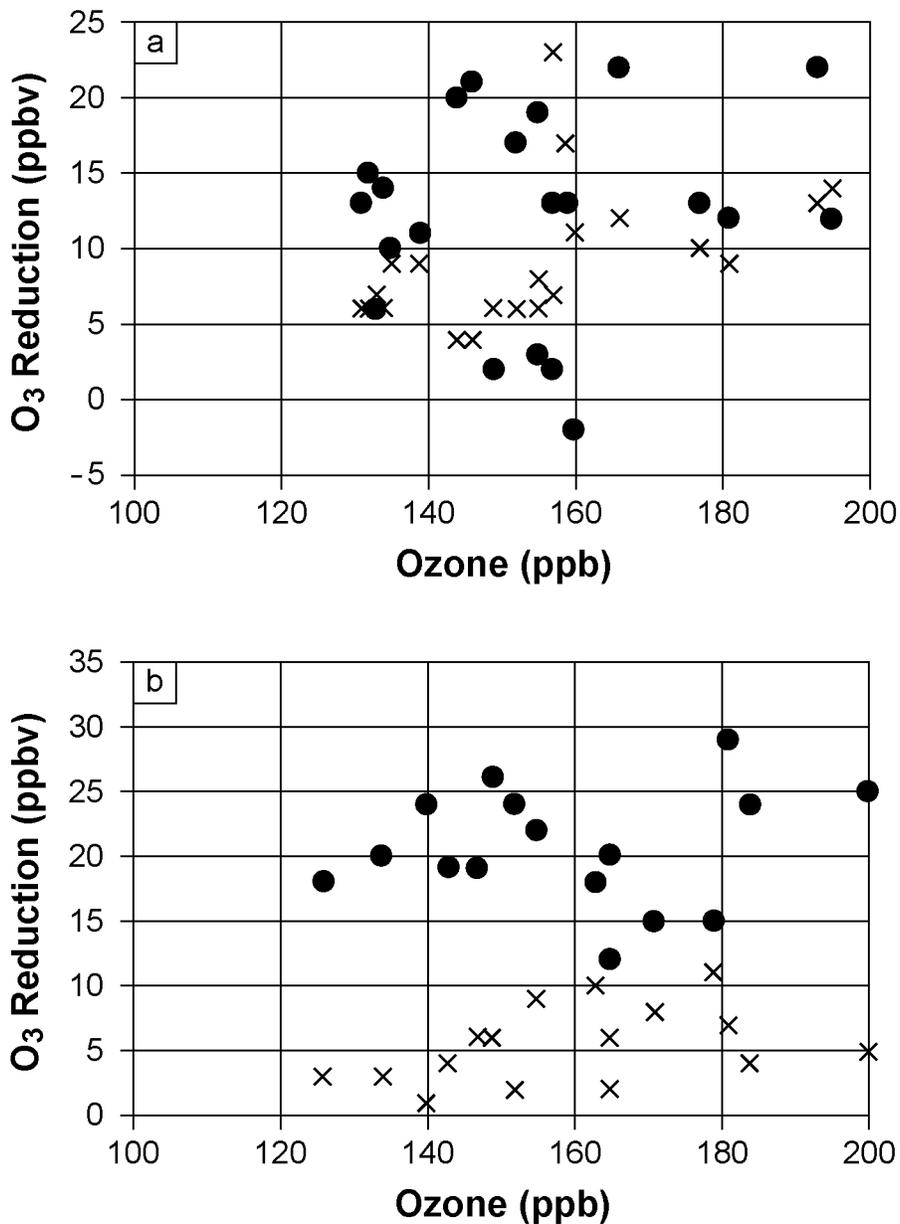


Figure AX2-21a,b. Impact of model uncertainty on control strategy predictions for O₃ for two days (August 10[a] and 11[b], 1992) in Atlanta, GA. The figures show the predicted reduction in peak O₃ resulting from 35% reductions in anthropogenic VOC emissions (crosses) and from 35% reductions in NO_x (solid circles) in a series of model scenarios with varying base case emissions, wind fields, and mixed layer heights.

Source: Results are plotted from tabulated values published in Sillman et al. (1995, 1997).

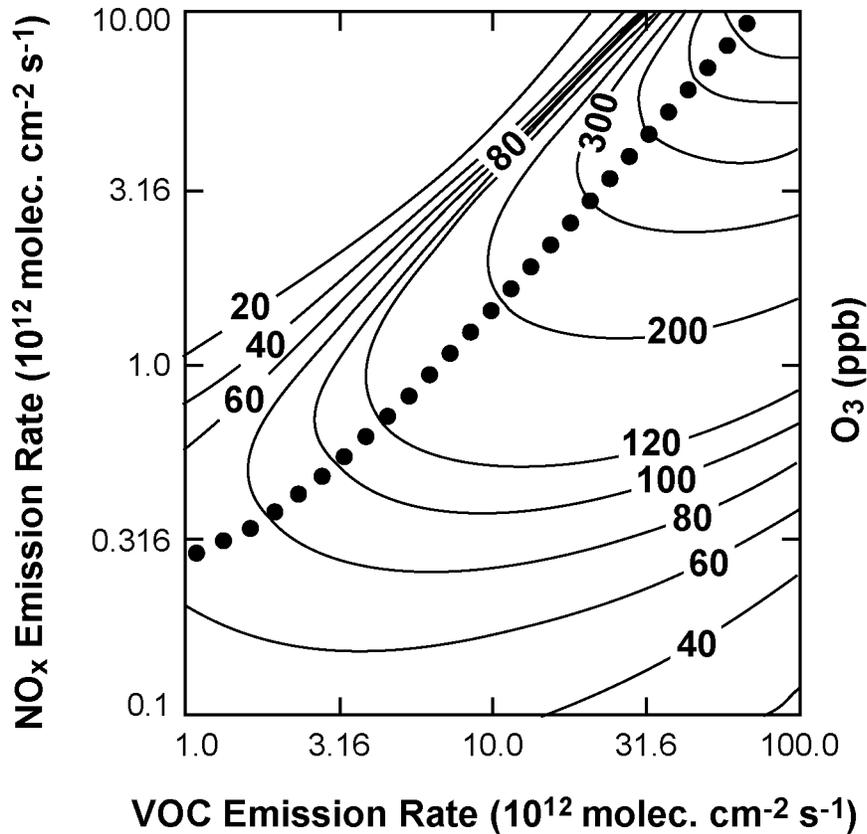


Figure AX2-22. Ozone isopleths (ppb) as a function of the average emission rate for NO_x and VOC (10¹² molec. cm⁻² s⁻¹) in zero dimensional box model calculations. The isopleths (solid lines) represent conditions during the afternoon following 3-day calculations with a constant emission rate, at the hour corresponding to maximum O₃. The ridge line (shown by solid circles) lies in the transition from NO_x-saturated to NO_x-limited conditions.

The evaluation of urban/regional models is also limited by the availability of data. Measured NO_x and speciated VOC concentrations are widely available through the EPA PAMs network, but questions have been raised about the accuracy of those measurements and the data have not yet been analyzed thoroughly. Evaluation of urban/regional models versus measurements has generally relied on results from a limited number of field studies in the United States. Short term research-grade measurements for species relevant to O₃ formation, including VOCs, NO_x, PAN, nitric acid (HNO₃) and hydrogen peroxide (H₂O₂) are also widely available at

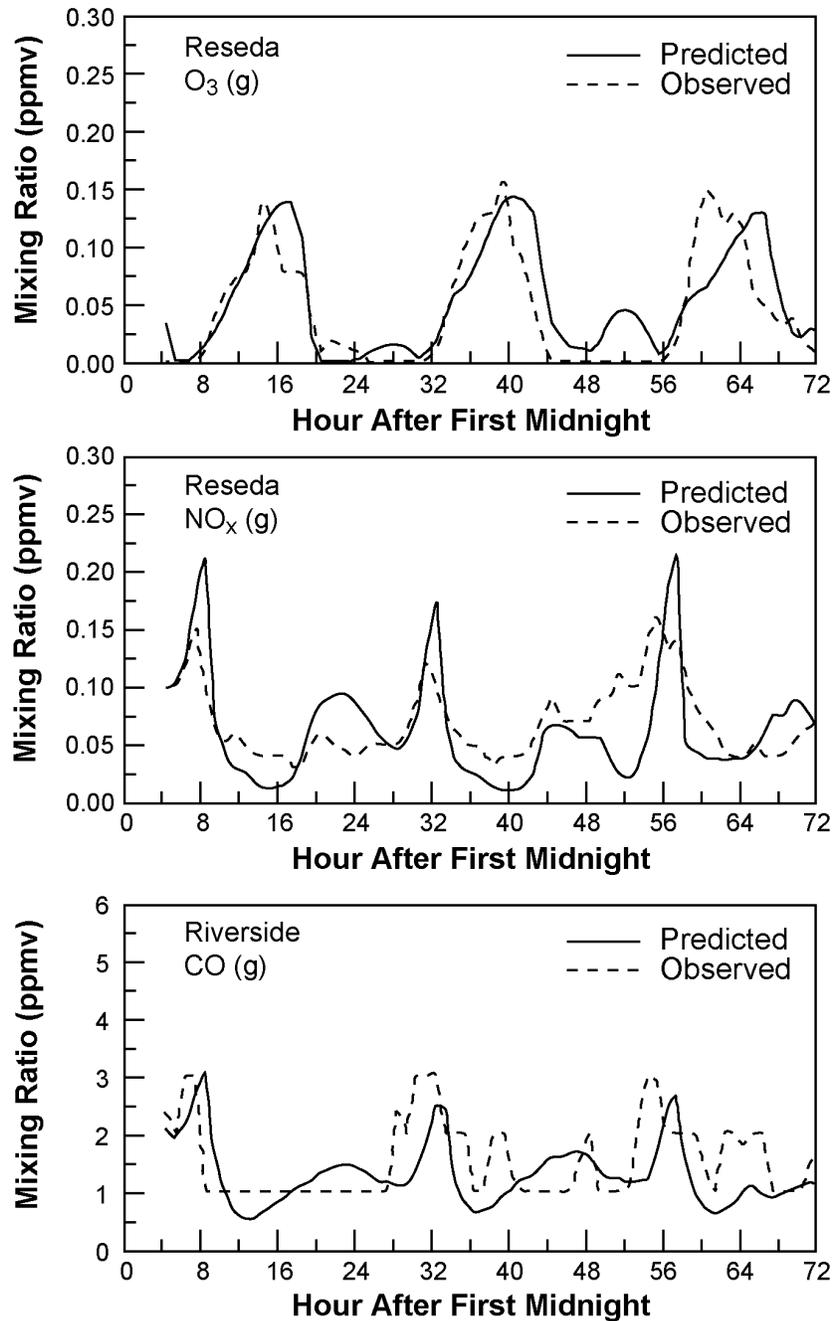


Figure AX2-23a. Time series for measured gas-phase species in comparison with results from a photochemical model. The dashed lines represent measurements, and solid lines represent model predictions (in parts per million, ppmv) for August 26–28, 1988 at sites in southern California. The horizontal axis represents hours past midnight, August 25. Results represent O₃ and NO_x at Reseda and CO at Riverside.

Source: Jacobson et al. (1996).

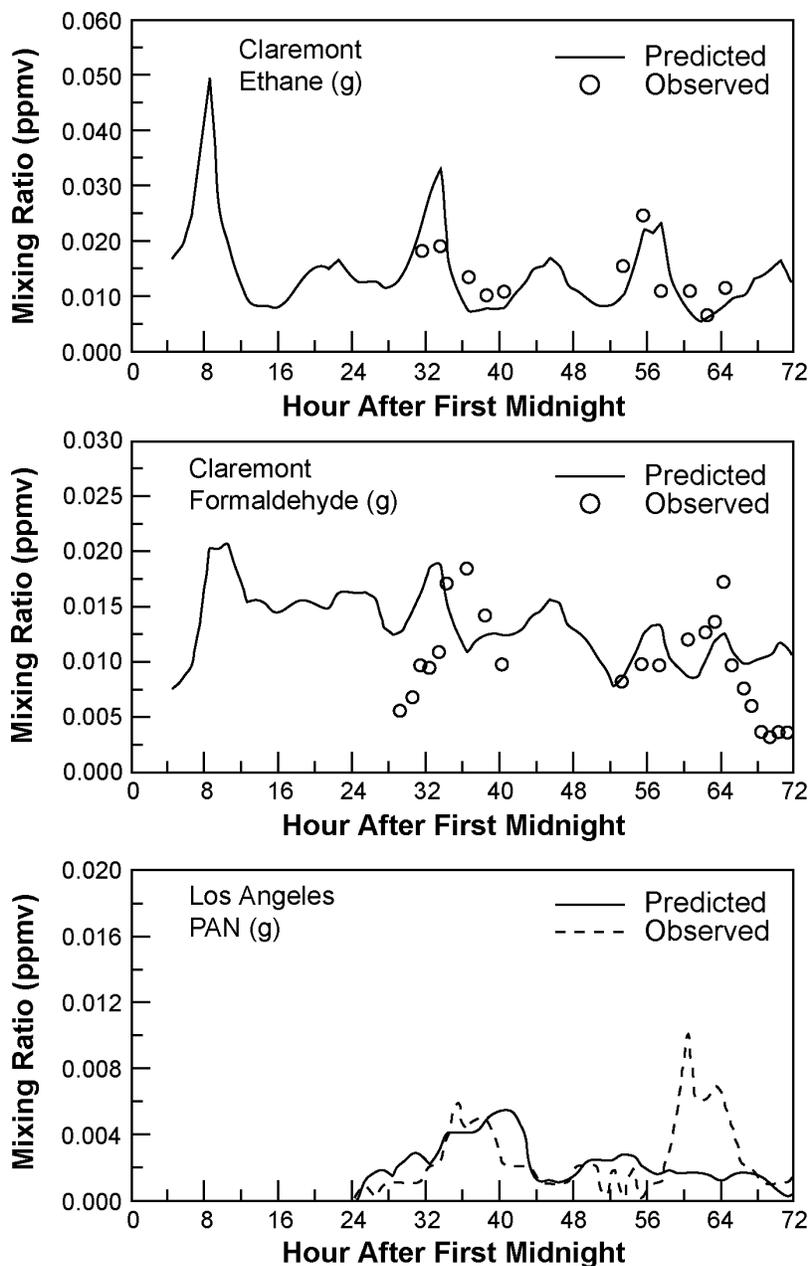


Figure AX2-23b. Time series for measured gas-phase species in comparison with results from a photochemical model. The circles represent measurements, and solid lines represent model predictions (in parts per million, ppmv) for August 26 – 28, 1988 at sites in southern California. The horizontal axis represents hours past midnight, August 25. Results represent ethane and formaldehyde at Claremont, and PAN at Los Angeles.

Source: Jacobson et al. (1996).

rural and remote sites (e.g., Daum et al., 1990, 1996; Martin et al., 1997; Young et al., 1997; Thompson et al., 2000; Hoell et al., 1996, 1997; Fehsenfeld et al., 1996a; Emmons et al., 2000; Hess, 2001; Carroll et al., 2001). The equivalent measurements are available for some polluted rural sites in the eastern United States but only at a few urban locations (Meagher et al., 1998; Hübler et al., 1998; Kleinman et al., 2000, 2001; Fast et al., 2002; new SCAQS-need reference). Extensive measurements have also been made in Vancouver (Steyn et al., 1997) and in several European cities (Staffelbach et al., 1997; Prévôt et al., 1997, Dommen et al., 1999; Geyer et al., 2001; Thielman et al., 2001; Martilli et al., 2002; Vautard et al., 2002).

The results of straightforward comparisons between observed and predicted concentrations of O₃ can be misleading because of compensating errors, although this possibility is diminished when a number of species are compared. Ideally, each of the main modules of a chemistry-transport model system (for example, the meteorological model and the chemistry and radiative transfer routines) should be evaluated separately. However, this is rarely done in practice. To better indicate how well physical and chemical processes are being represented in the model, comparisons of relations between concentrations measured in the field and concentrations predicted by the model can be made. These comparisons could involve ratios and correlations between species. For example, correlation coefficients could be calculated between primary species as a means of evaluating the accuracy of emission inventories; or between secondary species as a means of evaluating the treatment of photochemistry in the model. In addition, spatial relations involving individual species (correlations, gradients) can also be used as a means of evaluating the accuracy of transport parameterizations. Sillman and He (2002) examined differences in correlation patterns between O₃ and NO_z in Los Angeles, CA, Nashville, TN and various sites in the rural United States. Model calculations (Figure AX2-24) show differences in correlation patterns associated with differences in the sensitivity of O₃ to NO_x and VOCs. Primarily NO_x-sensitive (NO_x-limited) areas in models show a strong correlation between O₃ and NO_z with a relatively steep slope, while primarily VOC-sensitive (NO_x-saturated) areas in models show lower O₃ for a given NO_z and a lower O₃-NO_z slope. They found that differences found in measured data ensembles were matched by predictions from chemical transport models. Measurements in rural areas in the eastern U.S. show differences in the pattern of correlations for O₃ versus NO_z between summer and autumn (Jacob et al., 1995;

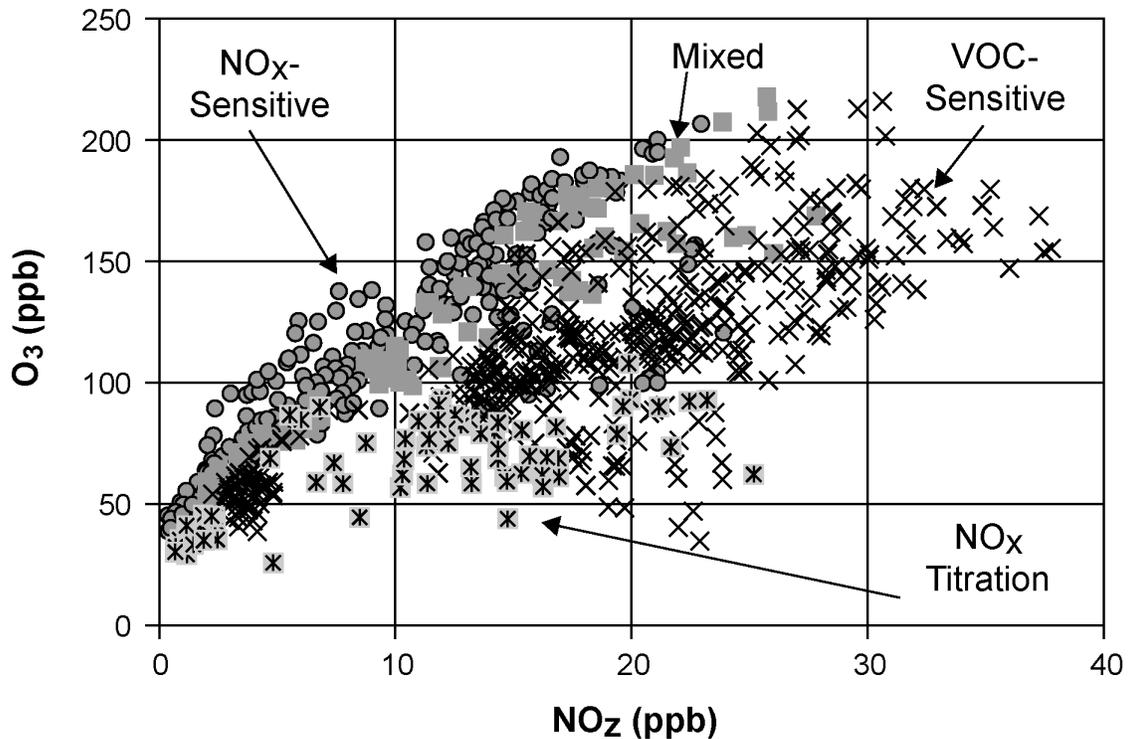


Figure AX2-24. Correlations for O₃ versus NO_z (NO_y-NO_x) in ppb from chemical transport models for the northeast corridor, Lake Michigan, Nashville, the San Joaquin Valley, and Los Angeles. Each location is classified as NO_x-limited or NO_x-sensitive (circles), NO_x-saturated or VOC-sensitive (crosses), mixed or with near-zero sensitivity (squares), and dominated by NO_x titration (asterisks) based on the model response to reduced NO_x and VOC.

Source: Sillman and He (2002).

Hirsch et al., 1996), corresponding to the transition from NO_x-limited to NO_x-saturated patterns, a feature which is also matched by chemistry-transport models.

The difference in correlations between secondary species in NO_x-limited to NO_x-saturated environments can also be used to evaluate the accuracy of model predictions in individual applications. Figures AX2-25a and AX2-25b show results for two different model scenarios for Atlanta. As shown in the figures, the first model scenario predicts an urban plume with high NO_y and O₃ formation apparently suppressed by high NO_y. Measurements show much lower

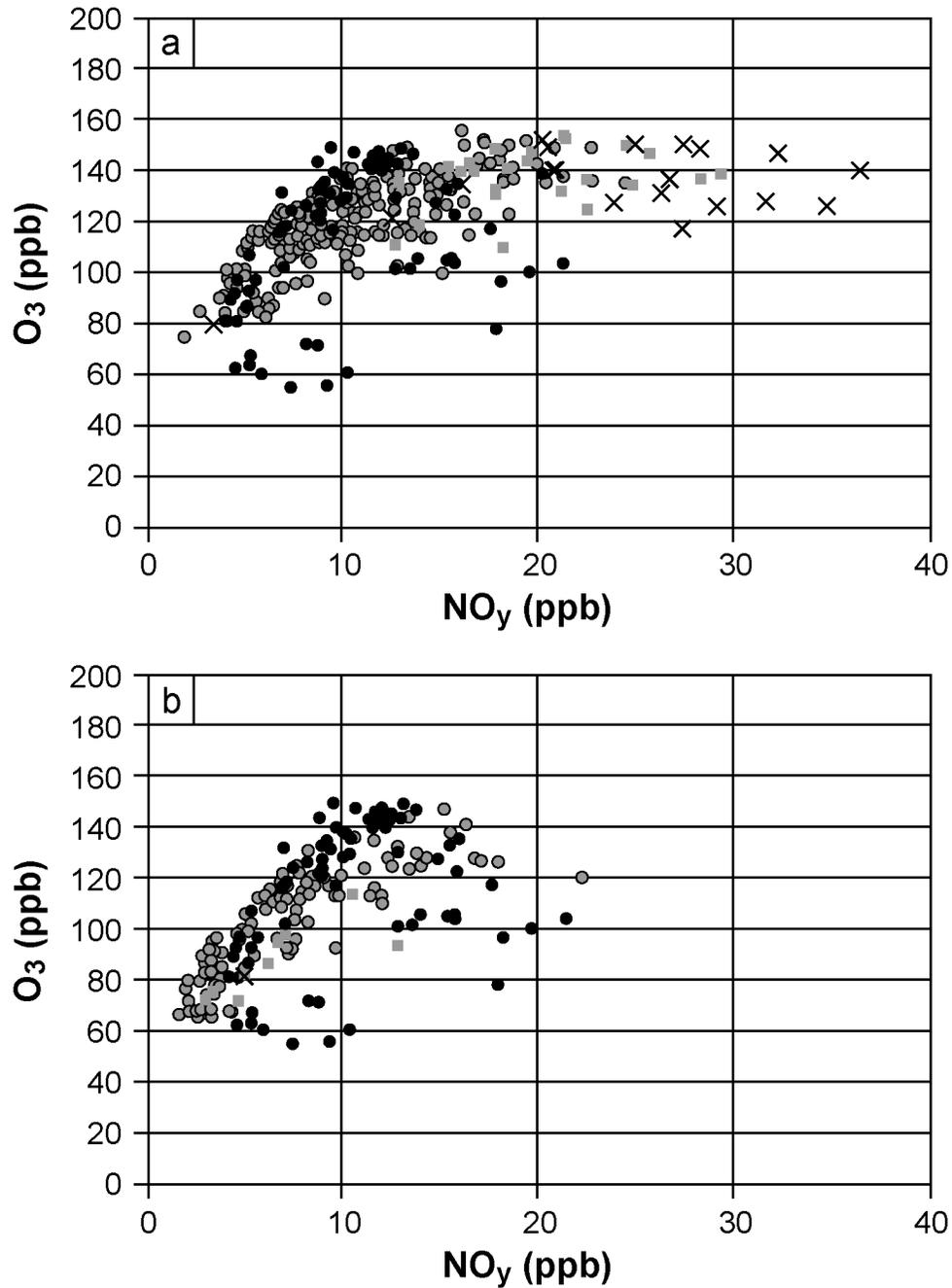


Figure AX2-25a,b. Evaluation of model versus measured O_3 versus NO_y for two model scenarios for Atlanta. The model values are classified as NO_x -limited (circles), NO_x -saturated (crosses), or mixed or with low sensitivity to NO_x (squares). Diamonds represent aircraft measurements.

Source: Sillman et al. (1997).

NO_y in the Atlanta plume. This error was especially significant because the model locations with high NO_y were not sensitive to NO_x, while locations with lower NO_y were primarily sensitive to NO_x. The second model scenario (with primarily NO_x-sensitive conditions) shows much better agreement with measured values. Figure AX2-26a,b shows model-measurement comparisons for secondary species in Nashville, showing better agreement with measured conditions. Greater confidence in the predictions made by chemistry-transport models will be gained by the application of techniques such as these on a more routine basis.

The ability of chemical mechanisms to calculate the concentrations of free radicals under atmospheric conditions was tested in the Berlin Ozone Experiment, BERLIOZ (Volz-Thomas et al., 2003) during July and early August at a site located about 50 km NW of Berlin. (This location was chosen as O₃ episodes in central Europe are often associated with SE winds.) Concentrations of major compounds such as O₃, hydrocarbons, etc., were fixed at observed values. In this regard, the protocol used in this evaluation is an example of an observationally based method. Figure AX2-27 compares the concentrations of RO₂ (organic peroxy), HO₂ (hydroperoxy) and OH (hydroxyl) radicals predicted by RACM (regional air chemistry mechanism; Stockwell et al., 1997) and MCM (master chemical mechanism; Jenkin et al, 1997 with updates) with observations made by the laser induced fluorescence (LIF) technique and by matrix isolation ESR spectroscopy (MIESR). Also shown are the production rates of O₃ calculated using radical concentrations predicted by the mechanisms and those obtained by measurements, and measurements of NO_x concentrations. As can be seen, there is good agreement between measurements of organic peroxy, hydroperoxy and hydroxyl radicals with values predicted by both mechanisms at high concentrations of NO_x (>10 ppb). However, at lower NO_x concentrations, both mechanisms substantially overestimate OH concentrations and moderately overestimate HO₂ concentrations. Agreement between models and measurements is generally better for organic peroxy radicals, although the MCM appears to overestimate their concentrations somewhat. In general, the mechanisms reproduced the HO₂ to OH and RO₂ to OH ratios better than the individual measurements. The production of O₃ was found to increase linearly with NO (for NO <0.3 ppb) and to decrease with NO (for NO >0.5 ppb).

OH and HO₂ concentrations measured during the PM_{2.5} Technology Assessment and Characterization Study conducted at Queens College in New York City in the summer of 2001 were also compared with those predicted by RACM (Ren et al., 2003). The ratio of observed to

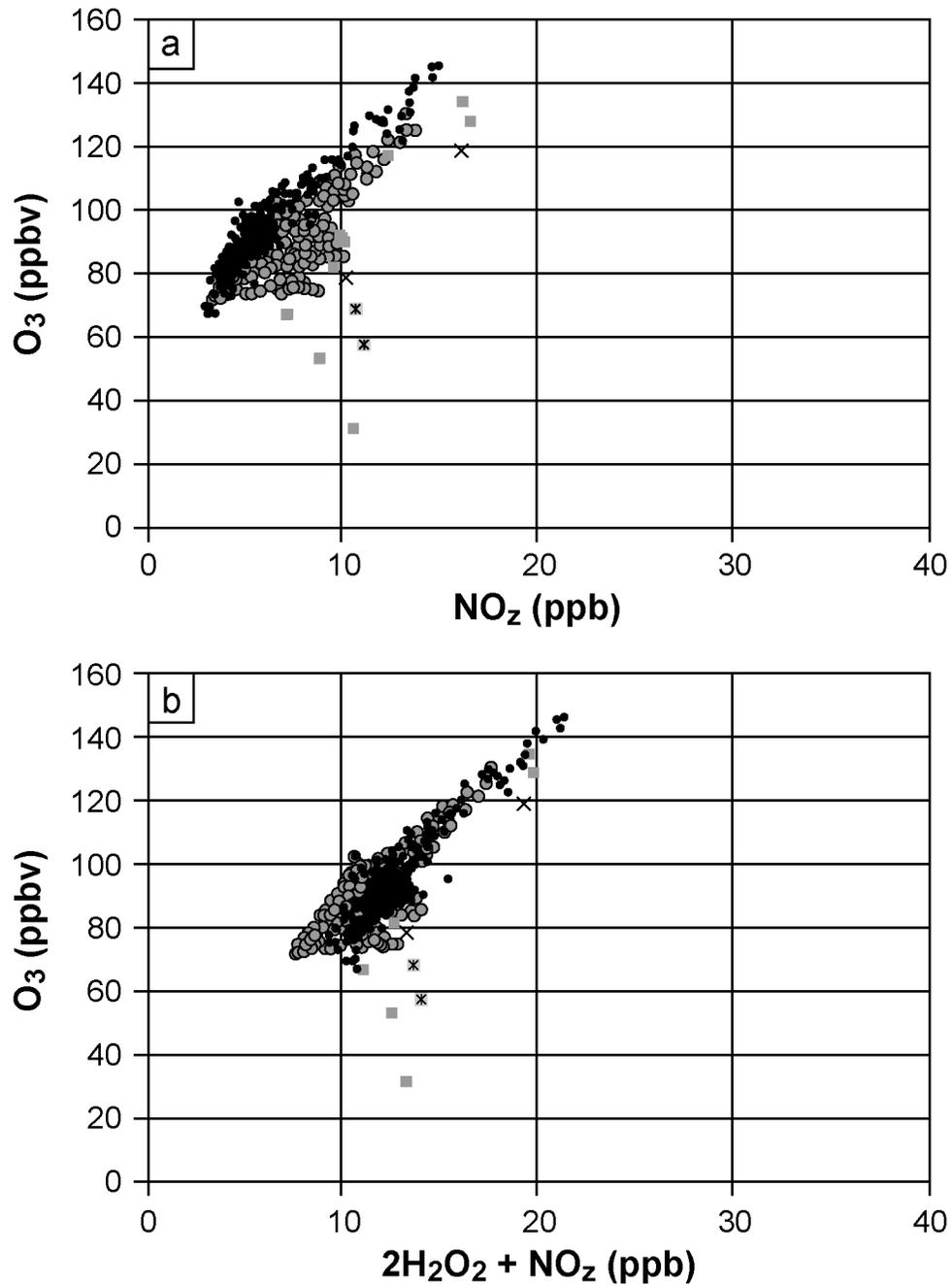


Figure AX2-26a,b. Evaluation of model versus: (a) measured O₃ versus NO_z and (b) O₃ versus the sum 2H₂O₂ + NO_z for Nashville, TN. The model values are classified as NO_x-limited (gray circles), NO_x-saturated (x), mixed or with near-zero sensitivity (squares), or dominated by NO_x titration (filled circles). Diamonds represent aircraft measurements.

Source: Sillman et al. (1998).

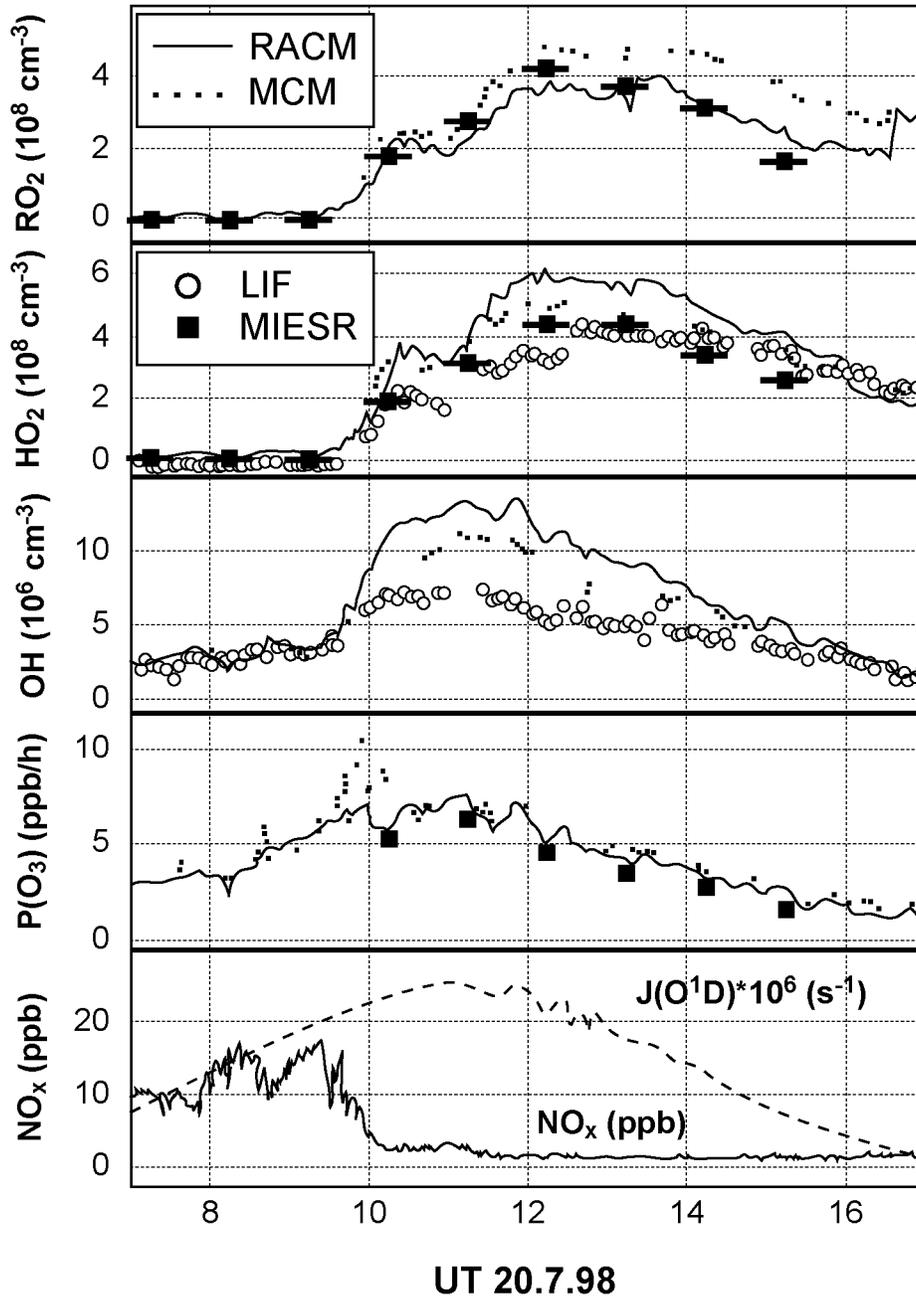


Figure AX2-27. Time series of concentrations of RO_2 , HO_2 , and OH radicals, local O_3 photochemical production rate and concentrations of NO_x from measurements made during BERLIOZ. Also shown are comparisons with results of photochemical box model calculations using the RACM and MCM chemical mechanisms.

Source: Volz-Thomas et al. (2003).

predicted HO₂ concentrations over a diurnal cycle was 1.24 and the ratio of observed to predicted OH concentrations was about 1.10 during the day, but the mechanism significantly underestimated OH concentrations during the night.

AX2.5.4.1 Evaluation of Emissions Inventories

Comparisons of emissions model predictions with observations have been performed in a number of environments. A number of studies of ratios of concentrations of CO to NO_x and NMOC to NO_x during the early 1990s in tunnels and ambient air (summarized in Air Quality Criteria for Carbon Monoxide [U.S. Environmental Protection Agency, 2000]) indicated that emissions of CO and NMOC were systematically underestimated in emissions inventories. However, the results of more recent studies have been mixed in this regard, with many studies showing agreement to within $\pm 50\%$ (U.S. Environmental Protection Agency, 2000). Improvements in many areas have resulted from the process of emissions model development, evaluation, and further refinement. It should be remembered that the conclusions from these reconciliation studies depend on the assumption that NO_x emissions are predicted correctly by emissions factor models. Road side remote sensing data indicate that over 50% of NMHC and CO emissions are produced by less than about 10% of the vehicles (Stedman et al., 1991). These “super-emitters” are typically poorly maintained vehicles. Vehicles of any age engaged in off-cycle operations (e.g., rapid accelerations) emit much more than if operated in normal driving modes. Bishop and Stedman (1996) found that the most important variables governing CO emissions are fleet age and owner maintenance.

Emissions inventories for North America can be evaluated with comparisons to measured long-term trends and or ratios of pollutants in ambient air. A decadal field study of ambient CO at a rural site in the Eastern U.S. (Hallock-Waters et al., 1999) indicates a downward trend consistent with the downward trend in estimated emissions over the period 1988 to 1999 (U.S. Environmental Protection Agency, 1997), even when a global downward trend is accounted for. Measurements at two urban areas in the United States confirmed the decrease in CO emissions (Parrish et al., 2002). That study also indicated that the ratio of CO to NO_x emissions decreased by almost a factor of three over 12 yr (such a downward trend was noted in AQCD 96). Emissions estimates (U.S. Environmental Protection Agency, 1997) indicate a much smaller decrease in this ratio, suggesting that NO_x emissions from mobile sources may be

underestimated and/or increasing. The authors conclude that O₃ photochemistry in U.S. urban areas may have become more NO_x-limited over the past decade.

Pokharel et al. (2002) employed remotely-sensed emissions from on-road vehicles and fuel use data to estimate emissions in Denver. Their calculations indicate a continual decrease in CO, HC, and NO emissions from mobile sources over the 6 yr study period. Inventories based on the ambient data were 30 to 70% lower for CO, 40% higher for HC, and 40 to 80% lower for NO than those predicted by the recent MOBILE6 model.

Stehr et al. (2000) reported simultaneous measurements of CO, SO₂ and NO_y at an East Coast site. By taking advantage of the nature of mobile sources (they emit NO_x and CO but little SO₂) and power plants (they emit NO_x and SO₂ but little CO), the authors evaluated emissions estimates for the eastern United States. Results indicated that coal combustion contributes 25 to 35% of the total NO_x emissions in agreement with emissions inventories (U.S. Environmental Protection Agency, 1997).

Parrish et al. (1998) and Parrish and Fehsenfeld (2000) proposed methods to derive emission rates by examining measured ambient ratios among individual VOC, NO_x and NO_y. There is typically a strong correlation among measured values for these species (e.g., Figure AX2-14) because emission sources are geographically collocated, even when individual sources are different. Correlations can be used to derive emissions ratios between species, including adjustments for the impact of photochemical aging. Investigations of this type include correlations between CO and NO_y (e.g., Parrish et al., 1991), between individual VOC species and NO_y (Goldan et al., 1995, 1997, 2000) and between various individual VOC (Goldan et al., 1995, 1997; McKeen and Liu, 1993; McKeen et al., 1996). Buhr et al. (1992) derived emission estimates from principal component analysis (PCA) and other statistical methods. Many of these studies are summarized in Trainer et al. (2000), Parrish et al. (1998), and Parrish and Fehsenfeld (2000). Goldstein and Schade (2000) also used species correlations to identify the relative impacts of anthropogenic and biogenic emissions. Chang et al. (1996, 1997) and Mendoza-Dominguez and Russell (2000, 2001) used the more formal techniques of inverse modeling to derive emission rates, in conjunction with results from chemistry-transport models. Another concern regarding the use of emissions inventories is that emissions from all significant sources have been included. This may not always be the case. As an example, hydrocarbon

seeps from offshore oil fields may represent a significant source of reactive organic compounds in near by coastal areas (Quigley et al., 1999).

AX2.5.4.2 Availability and Accuracy of Ambient Measurements

The use of methods such as observationally based methods or source apportionment models, either as stand-alone methods or as a basis for evaluating chemistry/transport models, is often limited by the availability and accuracy of measurements. Measured speciated VOC and NO_x are widely available in the United States through the PAMS network. However, challenges have been raised about both the accuracy of the measurements and their applicability.

Parrish et al. (1998) and Parrish and Fehsenfeld (2000) developed a series of quality assurance tests for speciated VOC measurements. Essentially these tests used ratios among individual VOC with common emission sources to identify whether the variations in species ratios were consistent with the relative photochemical lifetimes of individual species. These tests were based on a number of assumptions: the ratio between ambient concentrations of long-lived species should show relatively little variation among measurements affected by a common emissions sources; and the ratio between ambient concentrations of long-lived and short-lived species should vary in a way that reflects photochemical aging at sites more different from source regions. Parrish et al. used these expectations to establish criteria for rejecting apparent errors in measurements. They found that the ratios among alkenes at many PAMS sites did not show variations that would be expected due to photochemical aging.

The PAMs network currently includes measured NO and NO_x . However, Cardelino and Chameides (2000) reported that measured NO during the afternoon was frequently at or below the detection limit of the instruments (1 ppb), even in large metropolitan regions (Washington, DC; Houston, TX; New York, NY). NO_x measurements are made with commercial chemilluminiscent detectors with molybdenum converters. However these measurements typically include some organic nitrates in addition to NO_x , and cannot be interpreted as a “pure” NO_x measurement (see summary in Parrish and Fehsenfeld, 2000).

Total reactive nitrogen (NO_y) is included in the PAMS network only at a few sites. The possible expansion of PAMS to include more widespread NO_y measurements has been suggested (McClenny, 2000). A major issue concerning measured NO_y is the possibility that HNO_3 , a major component of NO_y , is sometimes lost in inlet tubes and not measured (Luke et al., 1998;

Parrish and Fehsenfeld, 2000). This problem is especially critical if measured NO_y is used to identify NO_x -limited versus NO_x -saturated conditions. The correlation between O_3 and NO_y differs for NO_x -limited versus NO_x -saturated locations, but this difference is driven primarily by differences in the ratio of O_3 to HNO_3 . If HNO_3 were omitted from the NO_y measurements, then the measurements would represent a biased estimate and their use would be problematic.

AX2.6 TECHNIQUES FOR MEASURING OZONE AND ITS PRECURSORS

AX2.6.1 Sampling and Analysis of Ozone

Numerous techniques have been developed for sampling and measurement of O_3 in the ambient atmosphere at ground level. As noted above, sparse surface networks tend to underestimate maximum O_3 concentrations. Today, monitoring is conducted almost exclusively with UV absorption spectrometry with commercial short path (0.15 to 0.3 m) instruments, a method that has been thoroughly evaluated in clean air. The ultimate reference method is a relatively long-path (3 m path length) UV absorption instrument maintained under carefully controlled conditions at NIST (e.g., Fried and Hodgeson, 1982). Episodic measurements are made with a variety of other techniques based on the principles of chemiluminescence, electrochemistry, DOAS, and LIDAR. The rationale, history, and calibration of O_3 measurements were summarized in AQCD 96, so this section will focus on the current state of ambient O_3 measurement, tests for artifacts, and on new developments.

Several reports in the reviewed scientific literature have investigated interferences in O_3 detection via UV radiation absorption. Kleindienst et al. (1993) investigated the effects of water vapor and VOCs on instruments based on both UV absorption and chemiluminescence. They concluded that water vapor had no significant impact on UV absorption-based instruments, but could cause a positive interference of up to 9% in chemiluminescence-based detectors at high humidities (dew point of 24 C). In smog chamber studies, aromatic compounds and their oxidation products were found to generate a positive but small interference in the UV absorption instruments. Kleindienst et al. concluded that “when the results are scaled back to ambient concentrations of toluene and NO_x , the effect appears to be very minor (ca. 3 percent under the study conditions).” Arshinov et al. (2002) reported a positive interference in UV absorption

instruments from ambient particles at high concentrations, but this interference is eliminated by use of particle filters less subject to absorption/adsorption artifacts such as used in the NAMS/SLAMS network along with replacement of these filters to avoid artifacts associated with particle loading on the filters. The possibility for substantive interferences in O₃ detection exists, but such interferences have not been observed even in urban plumes. Ryerson et al. (1998) measured O₃ with UV absorption and chemiluminescence instruments operated off a common inlet on the NOAA WP-3 research aircraft. As reported by Parrish and Fehsenfeld (2000) “Through five field missions over four years, excellent correlations were found between the measurements of the two instruments, although the chemiluminescence instrument was systematically low (5%) throughout some flights. The data sets include many passes through the Nashville urban plume. There was never any indication (<1%) that the UV instrument measured systematically higher in the urban plume.” The same group tested the air of Houston, El Paso, Nashville, Los Angeles, San Francisco, and the East Coast. They observed only one instance of substantive positive interference defined as the UV absorption technique showing more than a few ppb more than the CL. This occurred in Laporte, TX under heavily polluted conditions and a low inversion, at night (Jobson et al., 2004).

Leston et al. (2005) reported positive and negative interferences in UV absorption techniques for measuring O₃ (relative to the CL technique) in Mexico City and in a smog chamber study. They suggested that O₃ measured in ambient air could be too high by 20 to 40 ppb under specific conditions due to positive interference by a number of organic compounds, mainly those produced during the oxidation of aromatic hydrocarbons and some primary compounds such as styrene and naphthalene. However, the concentrations of these compounds were many times higher in both of these environments than are typically found at ambient air monitoring sites in the United States. Although Hg is also potentially a strong interfering agent, because the Hg resonance line is used in this technique, its concentration would also have to be many times higher than is typically found in ambient air, e.g., as might be found in power plant plumes. Thus, it seems unlikely that such interferences would amount to more than one or two ppb (within the design specifications of the FEM), except under conditions conducive to producing high concentrations of the substances they identified as causing interference. These conditions might be found next to a plant producing styrene, for example. Leston et al. (2005)

also noted that the use of alternative materials in the scrubber could alleviate many potential problems under these conditions.

Ozone can also be detected by differential optical absorption spectroscopy (DOAS) at a variety of wavelengths in the UV and visible parts of the spectrum. Prior comparisons of DOAS results to those from a UV absorption instrument showed good agreement, on the order of 10% (Stevens et al., 1993). Reisinger (2000) reported a positive interference due to an unidentified absorber in the 279 to 289 nm spectral region used by many commercial short-path DOAS systems for the measurement of O₃. Results of that study suggest that effluent from wood burning, used for domestic heating, may be responsible. Vandaele et al. (2002) reported good agreement with other methods in the detection of O₃ (and SO₂) over the course of several years in Brussels. While the DOAS method remains attractive due to its sensitivity and speed of response further intercomparisons and interference tests are recommended.

Electrochemical methods are commonly employed where sensor weight is a problem, such as in balloon borne sondes, and these techniques have been investigated for ambient monitoring. Recent developments include changes in the electrodes and electrolyte solution (Knake and Hauser, 2002) and selective removal of O₃ for a chemical zero (Penrose et al., 1995). Interferences from other oxidants such as NO₂ and HONO remain potential problems and further comparisons with UV absorption are necessary. Because of potential interferences from water vapor (ASTM, 2003a,b), all instruments should be either calibrated and zeroed with air humidity near ambient or demonstrated to be insensitive to humidity.

Change in the vibration frequency of a piezoelectric quartz crystal has been investigated as a means of detecting O₃. Ozone reacts with polybutadiene coated onto the surface of a crystal, and the resulting change in mass is detected as a frequency change (Black et al., 2000). While this sensor has advantages of reduced cost power consumption and weight, it lacks the lifetime and absolute accuracy for ambient monitoring.

AX2.6.2 Sampling and Analysis of Nitrogen Oxides

Reactive nitrogen is generally released as NO but quickly converted in ambient air to NO₂ and back again, thus these two species are often referred to together as NO_x (NO + NO₂). The photochemical interconversion of NO and NO₂ leads to O₃ formation. Because NO₂ is a health hazard at sufficiently high concentrations, it is itself a criteria pollutant. In EPA documents,

emissions of NO_x are expressed in units of mass of NO_2 per unit time, i.e., the total mass of NO_x that would be emitted if all the NO were converted to NO_2 . Ambient air monitors have been required to demonstrate compliance with the standard for NO_2 and thus have focused on measuring this gas or determining an upper limit for its concentration.

NO_x can be oxidized to species such as nitrous acid (HNO_2), nitric acid (HNO_3), aerosol nitrate (NO_3^-), and organo-nitrates such as alkyl nitrates (RONO_2) and peroxy acetyl nitrate, PAN, ($\text{CH}_3\text{C}(\text{O})\text{O}_2\text{NO}_2$). The sum of these species (explicitly excluding N_2 , N_2O , and reduced N such as NH_3 and HCN) is called NO_y . Nitrates play important roles in acid rain, and nutrient cycling including over nitrification of surface ecosystems and in the formation of fine particulate matter, but are generally inactive photochemically. Some studies refer specifically to the oxidized or processed NO_y species, $\text{NO}_y\text{-NO}_x$, as NO_z because this quantity is related to the degree of photochemical aging in the atmosphere. Several NO_z species such as PAN and HONO can be readily photolyzed or thermally dissociated to NO or NO_2 and thus act as reservoirs for NO_x . This discussion focuses on current methods and on promising new technologies, but no attempt is made here to cover the extensive development of these methods or of methods such as wet chemical techniques, no longer in widespread use. More detailed discussions of the histories of these methods may be found elsewhere (U.S. Environmental Protection Agency, 1993, 1996).

AX2.6.2.1 Calibration Standards

Calibration gas standards of NO , in nitrogen (certified at concentrations of approximately 5 to 40 ppm) are obtainable from the Standard Reference Material (SRM) Program of the National Institute of Standards and Technology (NIST), formerly the National Bureau of Standards (NBS), in Gaithersburg, MD. These SRMs are supplied as compressed gas mixtures at about 135 bar (1900 psi) in high-pressure aluminum cylinders containing 800 L of gas at standard temperature and pressure, dry (STPD; National Bureau of Standards, 1975; Guenther et al., 1996). Each cylinder is supplied with a certificate stating concentration and uncertainty. The concentrations are certified to be accurate to ± 1 percent relative to the stated values. Because of the resources required for their certification, SRMs are not intended for use as daily working standards, but rather as primary standards against which transfer standards can be calibrated.

Transfer stand-alone calibration gas standards of NO in N₂ (in the concentrations indicated above) are obtainable from specialty gas companies. Information as to whether a company supplies such mixtures is obtainable from the company, or from the SRM Program of NIST. These NIST Traceable Reference Materials (NTRMs) are purchased directly from industry and are supplied as compressed gas mixtures at approximately 135 bars (1,900 psi) in high-pressure aluminum cylinders containing 4,000 L of gas at STPD. Each cylinder is supplied with a certificate stating concentration and uncertainty. The concentrations are certified to be accurate to within ±1 percent of the stated values (Guenther et al., 1996). Additional details can be found in the previous AQCD for O₃ (U.S. Environmental Protection Agency, 1996).

AX2.6.2.2 Measurement of Nitric Oxide

Gas-Phase Chemiluminescence (CL) Methods

Nitric oxide, NO, can be measured reliably using the principle of gas-phase chemiluminescence induced by the reaction of NO with O₃ at low pressure. Modern commercial NO_x analyzers have sufficient sensitivity and specificity for adequate measurement in urban and many rural locations (U.S. Environmental Protection Agency, 1996). The physics of the method, detection limits, interferences, and comparisons under field comparisons have been thoroughly reviewed in the previous AQCD. Research grade CL instruments have been compared under realistic field conditions to spectroscopic instruments, and the results indicate that both methods are reliable (at concentrations relevant to smog studies) to better than 15 percent with 95 percent confidence. Response times are on the order of 1 minute. For measurements meaningful for understanding O₃ formation, emissions modeling, and N deposition, special care must be taken to frequently zero and calibrate the instrument. A chemical zero, by reacting the NO up stream and out of view of the PMT, is preferred because it accounts for unsaturated hydrocarbon or other interferences. Calibration should be performed with NIST-traceable reference material of compressed NO in N₂. Standard additions of NO at the inlet will account for NO loss or conversion to NO₂ in the lines. In summary CL methods, when operated in an appropriate manner, can be suitable for measuring or monitoring NO (e.g., Crosley, 1996).

Spectroscopic Methods for Nitric Oxide

Nitric oxide has also been successfully measured in ambient air with direct spectroscopic methods; these include two-photon laser-induced fluorescence (TPLIF), tunable diode laser absorption spectroscopy (TDLAS), and two-tone frequency-modulated spectroscopy (TTFMS). These were reviewed thoroughly in the previous AQCD and will be only briefly summarized here. The spectroscopic methods demonstrate excellent sensitivity and selectivity for NO with detection limits on the order of 10 ppt for integration times of 1 min. Spectroscopic methods compare well with the CL method for NO in controlled laboratory air, ambient air, and heavily polluted air (e.g., Walega et al., 1984; Gregory et al., 1990; Kireev et al., 1999). These spectroscopic methods remain in the research arena due to their complexity, size, and cost, but are essential for demonstrating that CL methods are reliable for monitoring NO concentrations involved in O₃ formation—from 100's of ppb to around 20 ppt.

Atmospheric pressure laser ionization followed by mass spectroscopy has also been reported for detection of NO and NO₂. Garnica et al. (2000) describe a technique involving selective excitation at one wavelength followed by ionization at a second wavelength. They report good selectivity and detection limits well below 1 ppb. The practicality of the instrument for ambient monitoring has yet to be demonstrated.

AX2.6.2.3 Measurements of Nitrogen Dioxide

Gas-Phase Chemiluminescence Methods

Since the previous AQCD, photolytic reduction followed by CL has been improved and the method of laser-induced fluorescence has been developed. Ryerson et al. (2000) developed a photolytic converter based on a Hg lamp with increased radiant intensity in the region of peak NO₂ photolysis (350 to 400 nm) and producing conversion efficiencies of 70% or more in less than 1 s. Because the converter produces little radiation at wavelengths less than 350 nm, interferences from HNO₃ and PAN are minimal.

Alternative methods to photolytic reduction followed by CL are desirable to test the reliability of this widely used technique. In any detector based on conversion to another species interferences can be a problem. Several atmospheric species, PAN and HO₂NO₂ for example, dissociate to NO₂ at higher temperatures.

Laser induced fluorescence for NO₂ detection involves excitation of atmospheric NO₂ with laser light emitted at wavelengths too long to induce photolysis. The resulting excited molecules relax in a photoemissive mode and the fluorescing photons are counted. Because collisions would rapidly quench electronically excited NO₂, the reactions are conducted at low pressure (Cohen, 1999; Thornton et al., 2000; Day et al., 2002). For example Cleary et al. (2002) describe field tests of a system that uses continuous, supersonic expansion followed by excitation at 640 nm with a commercial cw external-cavity tunable diode laser. Sensitivity is adequate for measurements in most continental environments (145 ppt in 1 min) and no interferences have been identified.

Matsumi et al. (2001) describe a comparison of laser-induced fluorescence with a photofragmentation chemiluminescence instrument. The laser-induced fluorescence system involves excitation at 440 nm with a multiple laser system. They report sensitivity of 30 ppt in 10 s and good agreement between the two methods under laboratory conditions at mixing ratios up to 1.0 ppb. This high-sensitivity laser-induced fluorescence system has yet to undergo long-term field tests.

NO₂ can be detected by differential optical absorption spectroscopy (DOAS) in an open, long-path system (Kim and Kim, 2001). Vandaele et al. (2002) reported that the DOAS technique measured higher NO₂ concentrations than were reported by other techniques in a three-year study conducted in Brussels. Harder et al. (1997b) conducted an experiment in rural Colorado involving simultaneous measurements of NO₂ with DOAS and photolysis followed by chemiluminescence. They found differences of as much as 110% in clean air from the west, but for NO₂ mixing ratios in excess of 300 ppt, the two methods agreed to better than 10%. Stutz and Platt (1996) report less uncertainty.

AX2.6.2.4 Monitoring for NO₂ Compliance Versus Monitoring for Ozone Formation

Observations of NO₂ have been focused on demonstrating compliance with the NAAQS for NO₂. Today, few locations violate that standard, but NO₂ and related NO_y compounds remain among the most important atmospheric trace gases to measure and understand. Commercial instruments for NO/NO_x detection are generally constructed with an internal converter for reduction of NO₂ to NO, and generate a signal referred to as NO_x. These converters, generally constructed of molybdenum oxides (MoO_x), reduce not only NO₂ but also most other NO_y

species (Fehsenfeld et al., 1987; Crosley, 1996; Nunnermacker et al., 1998). Thus the NO_x signal is more accurately referred to as NO_y . Unfortunately with an internal converter, the instruments may not give a faithful indication of NO_y either — reactive species such as HNO_3 will adhere to the walls of the inlet system. Most recently, commercial vendors such as Thermo Environmental (Franklin, MA) have offered NO/NO_y detectors with external Mo converters. If such instruments are calibrated through the inlet with a reactive nitrogen species such as propyl nitrate, they should give accurate measurements of total NO_y , suitable for evaluation of photochemical models. States should be encouraged to make these NO_y measurements where ever possible.

AX2.6.3 Measurements of Nitric Acid Vapor, HNO_3

Accurate measurement of nitric acid vapor, HNO_3 , has presented a long-standing analytical challenge to the atmospheric chemistry community. In this context, it is useful to consider the major factors that control HNO_3 partitioning between the gas and deliquesced-particulate phases in ambient air. In equation form,



where K_H is the Henry's Law constant in M atm^{-1} and K_a is the acid dissociation constant in M .

Thus, the primary controls on HNO_3 phase partitioning are its thermodynamic properties (K_H , K_a , and associated temperature corrections), aerosol liquid water content (LWC), solution pH, and kinetics. Aerosol LWC and pH are controlled by the relative mix of different acids and bases in the system, hygroscopic properties of condensed compounds, and meteorological conditions (RH, temperature, and pressure). It is evident from relationship XX that, in the presence of chemically distinct aerosols of varying acidities (e.g., super- μm predominantly sea salt and sub- μm predominantly S aerosol), HNO_3 will partition preferentially with the less-acidic particles, which is consistent with observations (e.g., Huebert et al., 1996; Keene and Savoie, 1998; Keene et al., 2002). Kinetics are controlled by atmospheric concentrations of HNO_3 vapor and particulate NO_3^- and the size distribution and corresponding atmospheric lifetimes of particles against deposition. Sub- μm -diameter aerosols typically equilibrate with the gas phase

in seconds to minutes while super-um aerosols require hours to a day or more (e.g., Meng and Seinfeld, 1996; Erickson et al., 1999). Consequently, smaller aerosol size fractions are typically close to thermodynamic equilibrium with respect to HNO₃ whereas larger size fractions (for which atmospheric lifetimes against deposition range from hours to a few days) are often undersaturated (e.g., Erickson et al., 1999; Keene and Savoie, 1998).

Many sampling techniques for HNO₃ (e.g., standard filterpack and mist-chamber samplers) employ upstream prefilters to remove particulate species from sample air. However, when chemically distinct aerosols with different pHs (e.g., sea salt and S aerosols) mix together on a bulk filter, the acidity of the bulk mixture will be greater than that of the less acidic aerosols with which most NO₃⁻ is associated. This change in pH may cause the bulk mix to be supersaturated with respect to HNO₃ leading to volatilization and, thus, positive measurement bias in HNO₃ sampled downstream. Alternatively, when undersaturated super-um size fractions (e.g., sea salt) accumulate on a bulk filter and chemically interacts over time with HNO₃ in the sample air stream, scavenging may lead to negative bias in HNO₃ sampled downstream. Because the magnitude of both effects will vary as functions of the overall composition and thermodynamic state of the multiphase system, the combined influence can cause net positive or net negative measurement bias in resulting data. Pressure drops across particle filters can also lead to artifact volatilization and associated positive bias in HNO₃ measured downstream.

Widely used methods for measuring HNO₃ include standard filterpacks configured with nylon or alkaline-impregnated filters (e.g., Goldan et al., 1983; Bardwell et al., 1990; respectively) and standard mist chambers (Talbot et al., 1990). Samples are typically analyzed by ion chromatography. Intercomparisons of these measurement techniques (e.g., Hering et al., 1988; Tanner et al., 1989; Talbot et al., 1990) report differences of a factor of two or more.

More recently, sensitive HNO₃ measurements based on the principle of Chemical Ionization Mass Spectroscopy (CIMS) have been reported (e.g., Huey et al., 1998; Mauldin et al., 1998; Furutani and Akimoto, 2002; Neuman et al., 2002). CIMS relies on selective formation of ions such as SiF₅⁻·HNO₃ or HSO₄⁻·HNO₃ followed by detection via mass spectroscopy. Two CIMS techniques and a filter pack technique were intercompared in Boulder, CO (Fehsenfeld et al., 1998). Results indicated excellent agreement (within 15%) between the two CIMS instruments and between the CIMS and filterpack methods under relatively clean conditions with HNO₃ mixing ratios between 50 and 400 pptv. In more polluted air, the

filterpack technique generally yielded higher values than the CIMS suggesting that interactions between chemically distinct particles on bulk filters is a more important source of bias in polluted continental air. Differences were also greater at lower temperature when particulate NO_3^- corresponded to relatively greater fractions of total NO_3^- .

AX2.6.4 Sampling and Analysis of Volatile Organic Compounds

Hydrocarbons can be measured with gas chromatography followed by flame ionization detection (GC-FID). Detection by mass spectroscopy is sometimes used to confirm species identified by retention time (Westberg and Zimmerman, 1993; Dewulf and Van Langenhove, 1997). Preconcentration is typically required for less abundant species. Details are available in AQCD 96.

Because of their variety, nonmethane hydrocarbons pose special analytical problems, and several laboratory and field studies have recently addresses the uncertainty of VOC measurements. An intercomparison conducted with 16 components among 28 laboratories, showed agreement on the order of 10s of percents (Apel et al., 1994). In a more recent intercomparison (Apel et al., 1999) 36 investigators from around the world were asked to identify and quantify C_2 to C_{10} hydrocarbons (HCs) in a mixture in synthetic air. Calibration was based on gas standards of individual compounds, such as propane in air, and a 16-compound mixture of C_2 to C_{16} -alkanes, all prepared by NIST and certified to ± 3 percent. The top-performing laboratories, including several in the United States, identified all the compounds correctly, and obtained agreement of generally better than 20 percent for the 60 compounds. Intercomparison of NMHCs in ambient air has only recently been reported by a European group of 12 – 14 laboratories (Slemr et al., 2002). Some compounds gave several groups difficulties, including isobutene, butadiene, methyl pentanes, and trimethyl benzenes. These intercomparisons illustrated the need for reliable, multicomponent calibration standards.

AX2.6.4.1 Polar Volatile Organic Compounds

Many of the more reactive oxygen- and nitrogen-containing organic compounds play a role in O_3 formation and are included among the list of 189 hazardous air pollutants specified in the 1990 CAAA (U.S. Congress, 1990). These compounds are emitted directly from a variety of sources including biogenic processes, biomass burning, industry, vehicles, and consumer

products. Some can also be formed in the atmosphere by photochemical oxidation of hydrocarbons. Although these compounds have been referred to collectively as PVOCs, their reactivity and water solubility, rather than just polarity, make sampling and measurement challenging. As indicated in the earlier AQCD, few ambient data exist for these species, but that database has grown. The previous AQCD discusses two analytical methods for PVOCs—cryogenic trapping techniques similar to those used for the nonpolar hydrocarbon species, and adsorbent material for sample preconcentration. Here we discuss recently developed methods.

Several techniques for sampling, preconcentrating and detecting oxygenated volatile organic compounds were inter-compared during the 1995 Southern Oxidants Study Nashville Intensive (Apel et al., 1998). Both chemical traps and derivatization followed by HPLC and preconcentration and gas chromatography followed by mass spectrometric or flame ionization were investigated. Both laboratory and field tests were conducted for formaldehyde, acetaldehyde, acetone, and propanal. Substantial differences were observed indicating that reliable sampling and measurement of PVOCs remains an analytical challenge and high research priority.

Chemical ionization-mass spectroscopy, such as proton-transfer-reaction mass spectroscopy (PTR-MS) can also be used for fast-response measurement of volatile organic compounds including acetonitrile (CH_3CN), methanol (CH_3OH), acetone (CH_3COCH_3), acetaldehyde (CH_3CHO), benzene (C_6H_6) and toluene ($\text{C}_6\text{H}_5\text{CH}_3$) (e.g., Hansel et al., 1995a,b; Lindinger et al., 1998; Leibrock and Huey, 2000; Warneke et al., 2001). The method relies on gas phase proton transfer reactions between H_3O^+ primary ions and volatile trace gases with a proton affinity higher than that of water. Into a flow drift tube continuously flushed with ambient air, H_3O^+ ions (from a hollow cathode ion source) are injected. On collisions between H_3O^+ ions and organic molecules protons H^+ are transferred thus charging the reagent. Both primary and product ions are analyzed in a quadrupole mass spectrometer and detected by a secondary electron multiplier/pulse counting system. The instrument has been successfully employed in several field campaigns and compared to other techniques including gas chromatography and Atmospheric Pressure Chemical Ionization Mass Spectrometer (AP-CIMS) (Crutzen et al., 2000; Sprung et al., 2001). Sufficient sensitivity was observed for urban and rural measurements; no interferences were discovered, although care must be exercised to avoid

sampling losses. Commercial instruments are becoming available, but their price still precludes widespread monitoring.

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ANNEX AX3. ENVIRONMENTAL CONCENTRATIONS, PATTERNS, AND EXPOSURE ESTIMATES

AX3.1 INTRODUCTION

Identification and Use of Existing Air Quality Data

Topics discussed in this annex include the characterization of ambient air quality data for ozone (O_3), the uses of these data in assessing the exposure of vegetation to O_3 , concentrations of O_3 in microenvironments, and a discussion of the currently available human exposure data and exposure model development. The information contained in this chapter pertaining to ambient concentrations is taken primarily from the U.S. Environmental Protection Agency (EPA) Air Quality System (AQS; formerly the AIRS database). The AQS contains readily accessible detailed, hourly data that has been subject to EPA quality control and assurance procedures. Data available in AQS were collected from 1979 to 2001. As discussed in previous versions of the O_3 Air Quality Criteria Document or AQCD (U.S. Environmental Protection Agency, 1986, 1996a), the data available prior to 1979 may be unreliable due to calibration problems and measurement uncertainties.

As indicated in the 1996 O_3 AQCD (U.S. Environmental Protection Agency, 1996a), O_3 is the only photochemical oxidant other than nitrogen dioxide (NO_2) that is routinely monitored and for which a comprehensive database exists. Data for peroxyacetyl nitrate (PAN), hydrogen peroxide (H_2O_2), and other oxidants either in the gas phase or particle phase typically have been obtained only as part of special field studies. Consequently, no data on nationwide patterns of occurrence are available for these non- O_3 oxidants; nor are extensive data available on the relationships of levels and patterns of these oxidants to those of O_3 . However, available data for gas-phase and particle-phase oxidants will be discussed.

Characterizing Ambient Ozone Concentrations

The “concentration” of a specific air pollutant is typically defined as the amount (mass) of that material per unit volume of air. However, most of the data presented in this annex are expressed as “mixing ratios” in terms of a volume-to-volume ratio (parts per million [ppm] or parts per billion [ppb]). Data expressed this way are often referred to as concentrations, both in

the literature and in the text, following common usage. Human exposures are expressed in units of mixing ratio times time.

Several different types of indicators are used for evaluating exposures of vegetation to O₃. The peak-weighted, cumulative exposure indicators used in this chapter for characterizing vegetation exposures are SUM06 and SUM08 (the sums of all hourly average concentrations ≥ 0.06 and 0.08 ppm, respectively) and W126 (the sum of the hourly average concentrations that have been weighted according to a sigmoid function that is based on a hypothetical vegetation response [see Lefohn and Runeckles, 1987]). Further discussion of these exposure indices is presented in Chapter 9.

The U.S. Environmental Protection Agency (U.S. EPA) has established “ozone seasons” for the required monitoring of ambient O₃ concentrations for different locations within the United States and U.S. territories (CFR, 2000). Table AX3-1 shows the O₃ seasons during which continuous, hourly averaged O₃ concentrations must be monitored. Note that O₃ monitoring is optional outside of the “ozone season” and is monitored in many locations throughout the year.

In Section AX3.2, surface O₃ concentrations are characterized and the difficulties of characterizing background O₃ concentrations for controlled exposure studies and for assessing the health benefits associated with setting the NAAQS are discussed. In addition, hourly averaged concentrations obtained by several monitoring networks have been characterized for urban and rural areas. Spatial variations that occur within urban areas, between rural and urban areas, as well as variations with elevation are discussed in Section AX3.3. The diurnal variations for the various urban and rural locations are found in Section AX3.4, where urban and rural patterns are described. In Section AX3.5 seasonal variations in 1-h and 8-h average concentrations are discussed. Section AX3.6 of this annex summarizes the historical trends for 1980 to 2001 on a national scale and for selected cities. The most recent U.S. EPA trends results are also presented. Section AX3.7 describes available information for the concentrations and patterns of related photochemical oxidants. Section AX3.8 describes the co-occurrence patterns of O₃ with NO₂, sulfur dioxide (SO₂), and 24-h PM_{2.5}. Indoor O₃ concentrations, including sources and factors affecting indoor O₃ concentrations, are described in Section AX3.9. Section AX3.10 describes human population exposure measurement methods, factors influencing exposure, and exposure models.

Table AX3-1. Ozone Monitoring Seasons by State

State	Start Month — End	State	Start Month — End
Alabama	March — October	Nevada	January — December
Alaska	April — October	New Hampshire	April — September
Arizona	January — December	New Jersey	April — October
Arkansas	March — November	New Mexico	January — December
California	January — December	New York	April — October
Colorado	March - September	North Carolina	April — October
Connecticut	April — September	North Dakota	May — September
Delaware	April — October	Ohio	April — October
District of Columbia	April — October	Oklahoma	March — November
Florida	March — October	Oregon	May — September
Georgia	March — October	Pennsylvania	April — October
Hawaii	January — December	Puerto Rico	January — December
Idaho	April — October	Rhode Island	April — September
Illinois	April — October	South Carolina	April — October
Indiana	April — September	South Dakota	June — September
Iowa	April — October	Tennessee	March — October
Kansas	April — October	Texas ¹	January — December
Kentucky	March — October	Texas ¹	March — October
Louisiana	January — December	Utah	May — September
Maine	April — September	Vermont	April — September
Maryland	April — October	Virginia	April — October
Massachusetts	April — September	Washington	May — September
Michigan	April — September	West Virginia	April — October
Minnesota	April — October	Wisconsin	April 15 — October 15
Mississippi	March — October	Wyoming	April — October
Missouri	April — October	American Samoa	January — December
Montana	June — September	Guam	January — December
Nebraska	April — October	Virgin Islands	January — December

¹The ozone season is defined differently in different sections of Texas.

Source: CFR (2000).

AX3.2 SURFACE OZONE CONCENTRATIONS

Data for O₃ concentrations in a number of different environments, ranging from urban to remote, are summarized and characterized in this section. The main emphasis is placed on the characterization of the variability of O₃ concentrations in these different environments. Another important issue relates to the determination of background concentrations. There are a number of different uses of the term background depending on the context in which it is used. Various definitions of background have been covered in the 1996 O₃ AQCD (U.S. Environmental Protection Agency, 1996a) and in Air Quality Criteria for Particulate Matter (PM AQCD; U.S. Environmental Protection Agency, 1996b). This section deals with the characterization of background O₃ concentrations that are used for two main purposes: (1) performing experiments relating the effects of exposure to O₃ on humans, animals, and vegetation; and (2) assessing the health benefits associated with setting different levels of the NAAQS for O₃. Ozone background concentrations used for NAAQS setting purposes are referred to as policy relevant background (PRB) concentrations. PRB concentrations are defined by the U.S. EPA Office of Air Quality Programs and Standards (OAQPS) as those concentrations that would be observed in the United States if anthropogenic sources of O₃ precursors were turned off in continental North America (the United States, Canada and Mexico), i.e., the definition includes O₃ formed from natural sources everywhere in the world and from anthropogenic O₃ precursors outside of North America. The 1996 O₃ AQCD considered two possible methods for quantifying background O₃ concentrations for the two purposes mentioned above. The first method relied on mathematical models and historical data. The second method used the distribution of hourly average O₃ concentrations observed at clean, relatively remote monitoring sites (RRMS) in the United States (i.e., those which experience low maximum hourly concentrations). At the time of the 1996 O₃ AQCD, simulations of mathematical models were limited; therefore, the second method was employed to quantify background O₃ concentrations.

Sections AX3.2.1 and AX3.2.2 review data for O₃ concentrations in urban and nonurban (but influenced by urban emissions) environments. Section AX3.2.3 reviews the data from relatively clean remote sites, addresses the issue of how to use these data to help set background levels for controlled exposure studies, and presents evidence of trends in O₃ concentrations at these sites. The characterization of PRB O₃ concentrations will be the subject of Section AX3.2.4. Two alternative approaches for establishing PRB concentrations are

presented: the first uses data from relatively clean, remote monitoring sites and the second uses numerical models. The strengths and weaknesses of each approach are presented in the hopes of stimulating discussion that will resolve issues related to the use of either of these alternative methods.

Ozone Air Quality at Urban, Suburban, and Nonurban Sites

Figure AX3-1 shows the mean daily maximum 8-h O₃ concentrations and Figure AX3-2 shows the 95th percentile values of the daily maximum 8-h O₃ concentrations, based on countywide site-wise averages across the United States from May to September 2000 to 2004. The locations of the monitoring sites, whose data were used in the calculation of background O₃ concentrations, are shown in Figure AX3-3. The period from May to September was chosen because, although O₃ was monitored for different lengths of time across the country, all O₃ monitors should be operational during these months. Data flagged because of quality control issues were removed with concurrence of the local monitoring agency. Only days for which there were 75% complete data (i.e., 18 of 24 hours) were kept, and a minimum of 115 of 153 days were required in each year. Cut points for the tertile distributions on each map were chosen at the median and 95th percentile values. These cut points were chosen as they represent standard metrics for characterizing important aspects of human exposure used by the EPA. Any other percentiles or statistics that are believed to be helpful for characterizing human exposures could also be used. Blank areas on the maps indicate no data coverage. It should be noted that county areas can be much larger in the West than in the East, but monitors are not spread evenly within a county. As a result, the assigned concentration range might not represent conditions throughout a particular county and so large areas in western counties where there are not any monitors were blanked out.

As shown in Figure AX3-1, the median of the countywide, mean daily maximum 8-h O₃ concentration across the United States is 49 ppb, and 5% of these site-wise means exceeded 57 ppb. Although the median and 95th percentile value of the countywide means are fairly close, these results cannot be taken to imply that mean O₃ concentrations lie in a relatively narrow range throughout the United States, because data coverage is not as complete in the West as it is in the East. High mean daily maximum 8-h O₃ concentrations are found in California and states in the Southwest as well as in several counties in the East. As shown in Figure AX3-2, the

Seasonal (May-September) Mean of Daily Maximum 8-Hour Values, 2002-2004

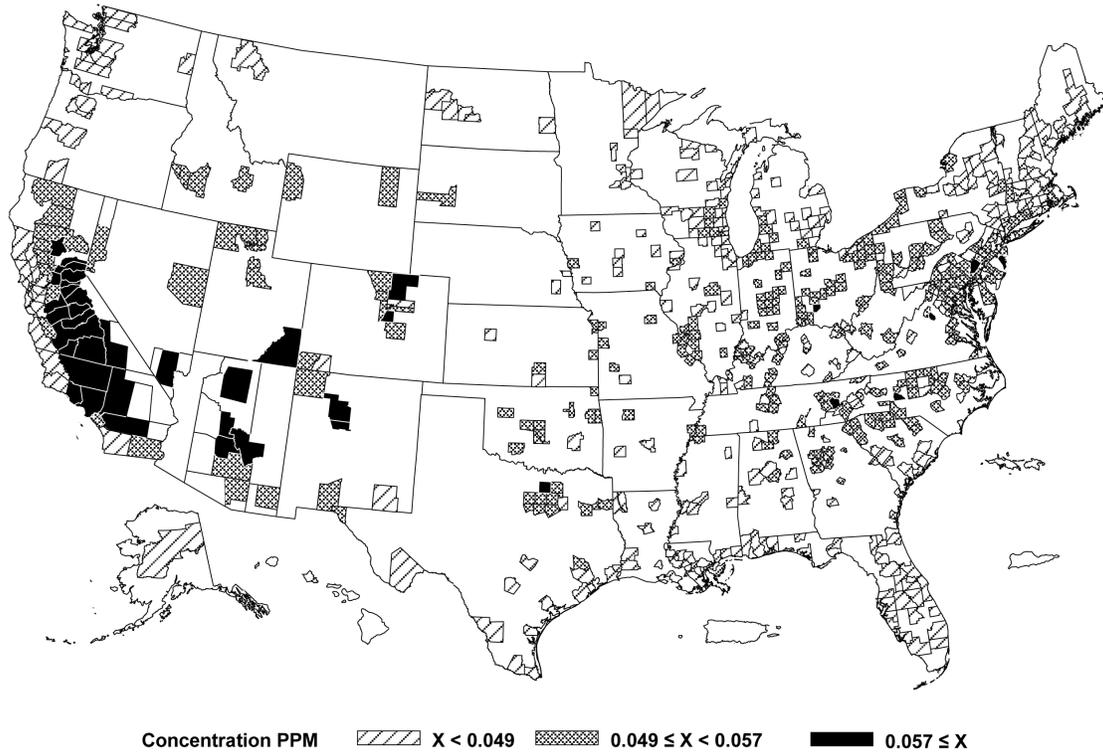


Figure AX3-1. Countywise mean daily maximum 8-h O₃ concentrations, May to September 2002 to 2004.

Source: Fitz-Simons et al. (2005).

nationwide median of the countywise, 95th percentile value of the daily maximum 8-h O₃ concentration is 73 ppb and 5% of these values are above 85 ppb. High values for the 95th percentiles are found in California, Texas, and in the East, but not necessarily in the same counties as shown for the mean daily maximum 8-h concentrations in Figure AX3-1.

Although mean O₃ concentrations in Houston, TX were below the nationwide median, its 95th percentile value ranks in the highest 5% nationwide. Conversely, mean O₃ concentrations in southwestern states are among the highest in the United States, but peak values (i.e., 95th or 98th percentile values) in those counties are not among the highest peak values in the United States. In other areas where the highest mean O₃ concentrations occurred, such as California; Dallas-Fort Worth, TX; and the Northeast Corridor, the highest peak values also were observed.

Seasonal (May-September) 95th Percentile of Daily Maximum 8-Hour Values, 2002-2004

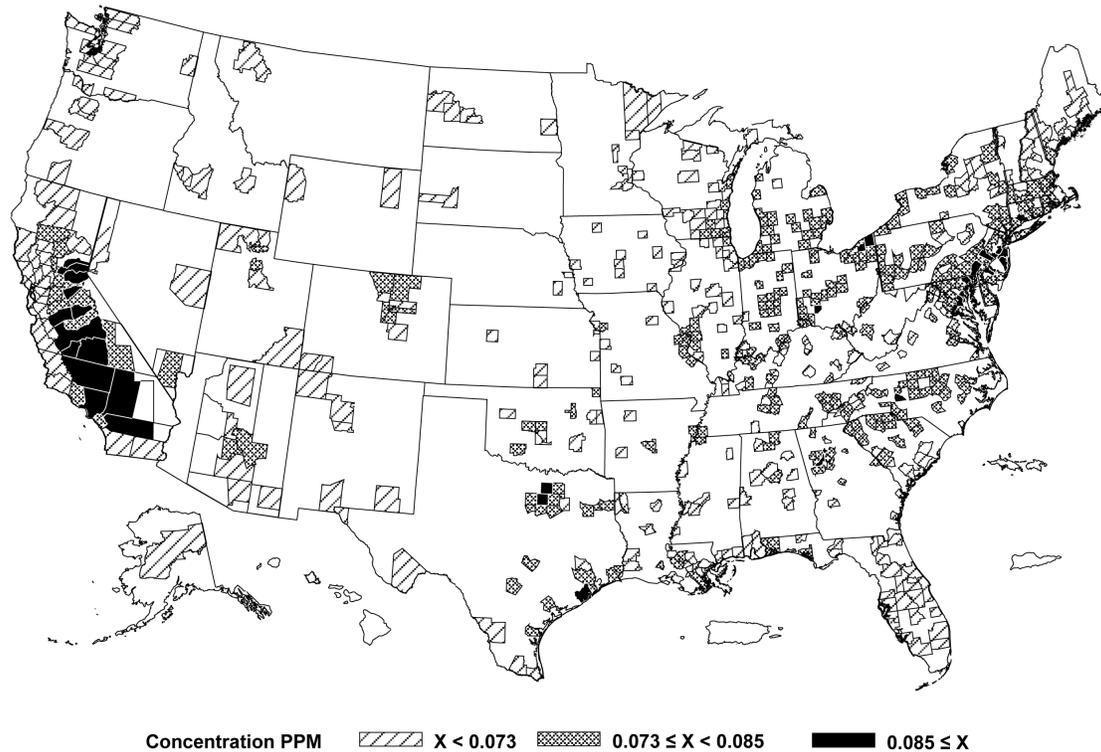


Figure AX3-2. Countywide 95th percentile value of daily maximum 8-h O₃ concentrations, May to September 2002 to 2004.

Source: Fitz-Simons et al. (2005).

Although countywide averages are shown, it should be noted that considerable spatial variability can exist within a county, especially within urban areas as described in Section AX3.3. In addition, there can also be differences in the diurnal profile of O₃ among monitors within counties.

Box plots showing the percentile distribution of nationwide O₃ concentrations for different averaging periods (1-h daily maximum, 8-h daily maximum and 24-h daily average) are given in Figures AX3-4 to AX3-6 and the numerical values are given in Table AX3-2. The differences between the 50th and 95th percentile values indicate the range of O₃ levels between “typical” O₃ days and “high” O₃ days. These differences are approximately 40, 30, and 25 ppb

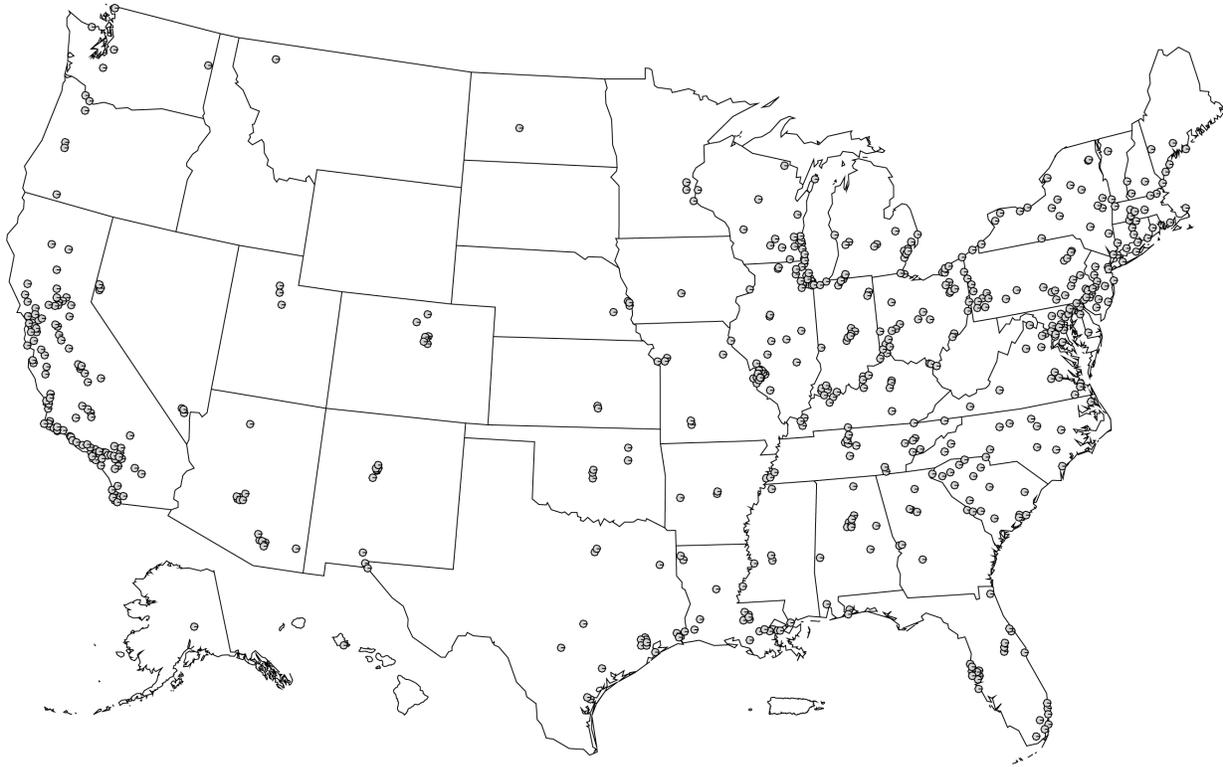


Figure AX3-3. Locations of monitoring sites used for calculating countywide averages across the United States.

Source: Fitz-Simons et al. (2005).

for the daily 1-h, 8-h, maxima and daily averaged O_3 concentrations. As might be expected, the daily maximum 1-h and 8-h O_3 concentrations are highly correlated.

Lehman et al. (2004) have shown that the eastern United States can be divided into five regions, each of which exhibit spatial, relatively coherent spatial patterns of O_3 at nonurban sites. Only sites classified as being rural or suburban and with land usage of forest, agriculture, or residential were included in the analyses. These criteria were chosen to avoid sites where O_3 is scavenged by NO that can be found in high concentrations near major sources, such as traffic in urban cores. The five regions, shown in Figure AX3-7, are characterized by different patterns of O_3 properties such as temporal persistence and seasonal variability. Figure AX3-7 shows nonurban, monthly average, daily maximum 8-h O_3 concentrations in the five regions in the eastern United States from April to October 1993 to 2002.

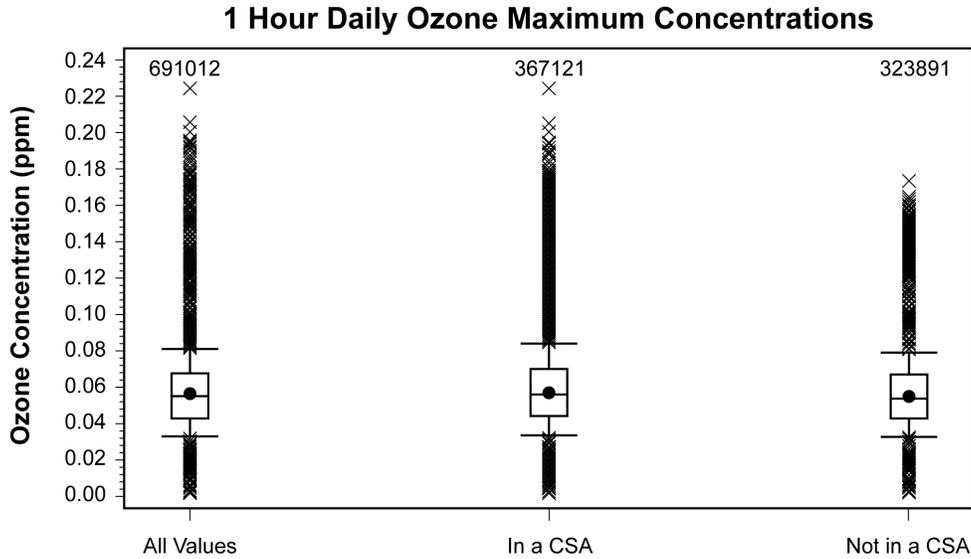


Figure AX3-4. Distribution of nationwide daily maximum 1-h average O₃ concentrations from May to September 2000 to 2004. Medians, interquartile ranges, minima and maxima and means (as dots) are shown. Numbers above the boxes are the number of observations.

Source: Fitz-Simons et al. (2005).

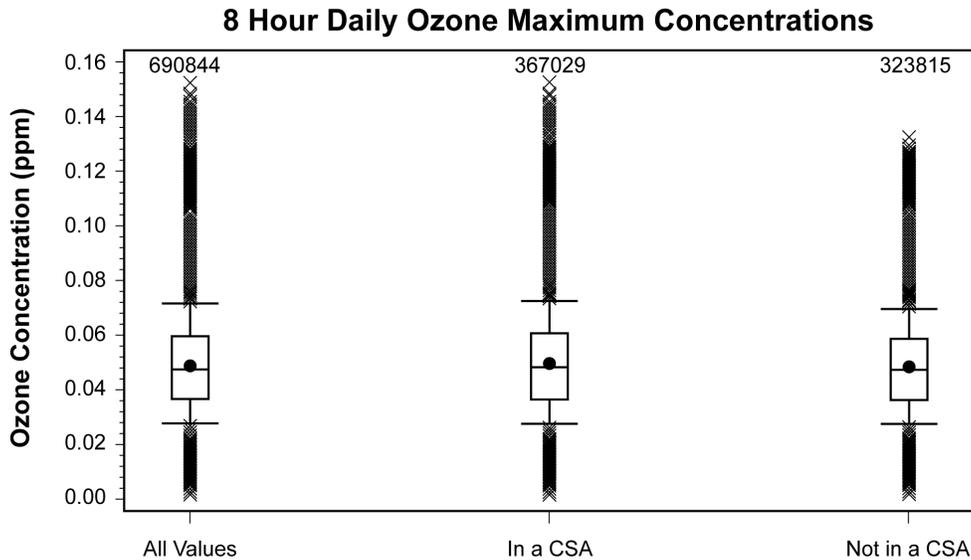


Figure AX3-5. Distribution of nationwide daily maximum 8-h average O₃ concentrations from May to September 2000 to 2004. Medians, interquartile ranges, minima and maxima and means (as dots) are shown. Numbers above the boxes are the number of observations.

Source: Fitz-Simons et al. (2005).

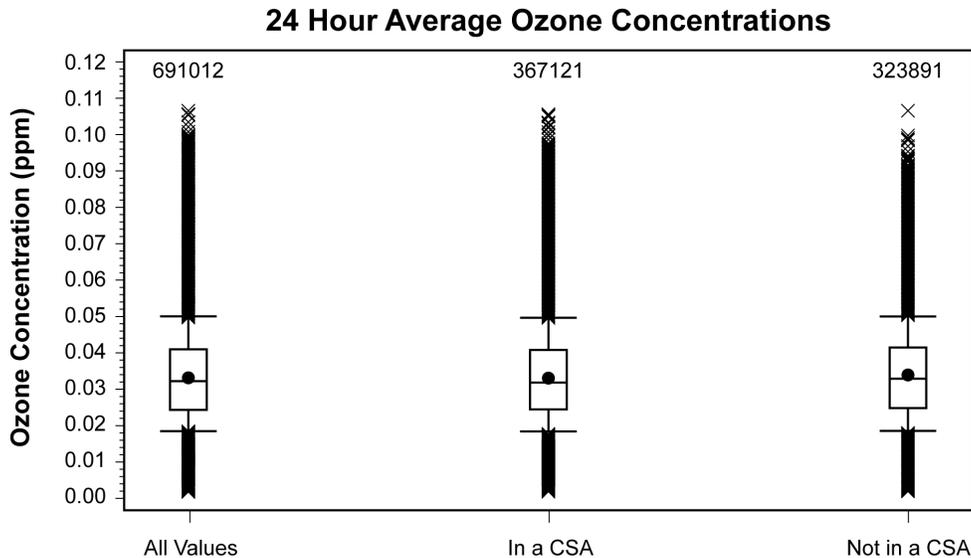


Figure AX3-6. Distribution of nationwide 24-h average O₃ concentrations from May to September 2000 to 2004. Medians, interquartile ranges, minima and maxima and means (as dots) are shown. Numbers above the boxes are the number of observations.

Source: Fitz-Simons et al. (2005).

Regional differences are immediately apparent. Highest concentrations among all the regions are generally found in the Mid-Atlantic region (mean of 52 ppb) with highest values throughout the ozone concentration distribution except for the overall maximum. Lowest mean concentrations (42 ppb) are found in Florida. In the northern regions (the Northeast, Great Lakes) and the Mid-Atlantic region, highest median and peak concentrations are found in July, whereas in the Southwest, highest median concentrations are found in August, with highest peaks in June and September, i.e., outside the warmest summer months. In Florida, highest monthly averaged median and peak concentrations are found during the spring. High O₃ concentrations tend to be most persistent (3-4 days of persistence) in the southern regions, less persistent in the Mid-Atlantic region (2-3 days) and least persistent in the northern regions (1 or 2 days). Such analyses could not be made for the western United States, in part because of the presence of more extensive mountain ranges.

Box plots showing the distributions of hourly average O₃ concentrations for different types of rural sites for 2001 are given in Figures AX3-8 (rural-agricultural), AX3-9 (rural-forest),

Table AX3-2. Summary of Percentiles of Data Pooled Across Monitoring Sites for May to September 2000-2004

Concentrations are in ppb.

Pooled Group/ Avg. Time	Number of Values	Mean	Percentiles										
			1	5	10	25	30	50	70	75	90	95	99
Daily 1-h Maximum Concentrations													
Monitors in CSAs	367,121	58	20	29	34	44	46	56	66	70	84	94	116
Monitors not in CSAs	323,891	55	20	28	33	43	45	54	64	67	79	87	104
8-h Daily Maximum Concentrations													
Monitors in CSAs	367,029	50	16	23	28	37	40	49	58	61	73	81	98
Monitors not in CSAs	323,815	49	16	23	28	37	39	48	57	59	70	77	91
24-h Average Concentrations													
Monitors in CSAs	367,121	33	10	15	18	24	26	32	39	41	50	56	68
Monitors not in CSAs	323,891	34	10	15	18	25	27	33	39	41	50	56	68

AX3-11

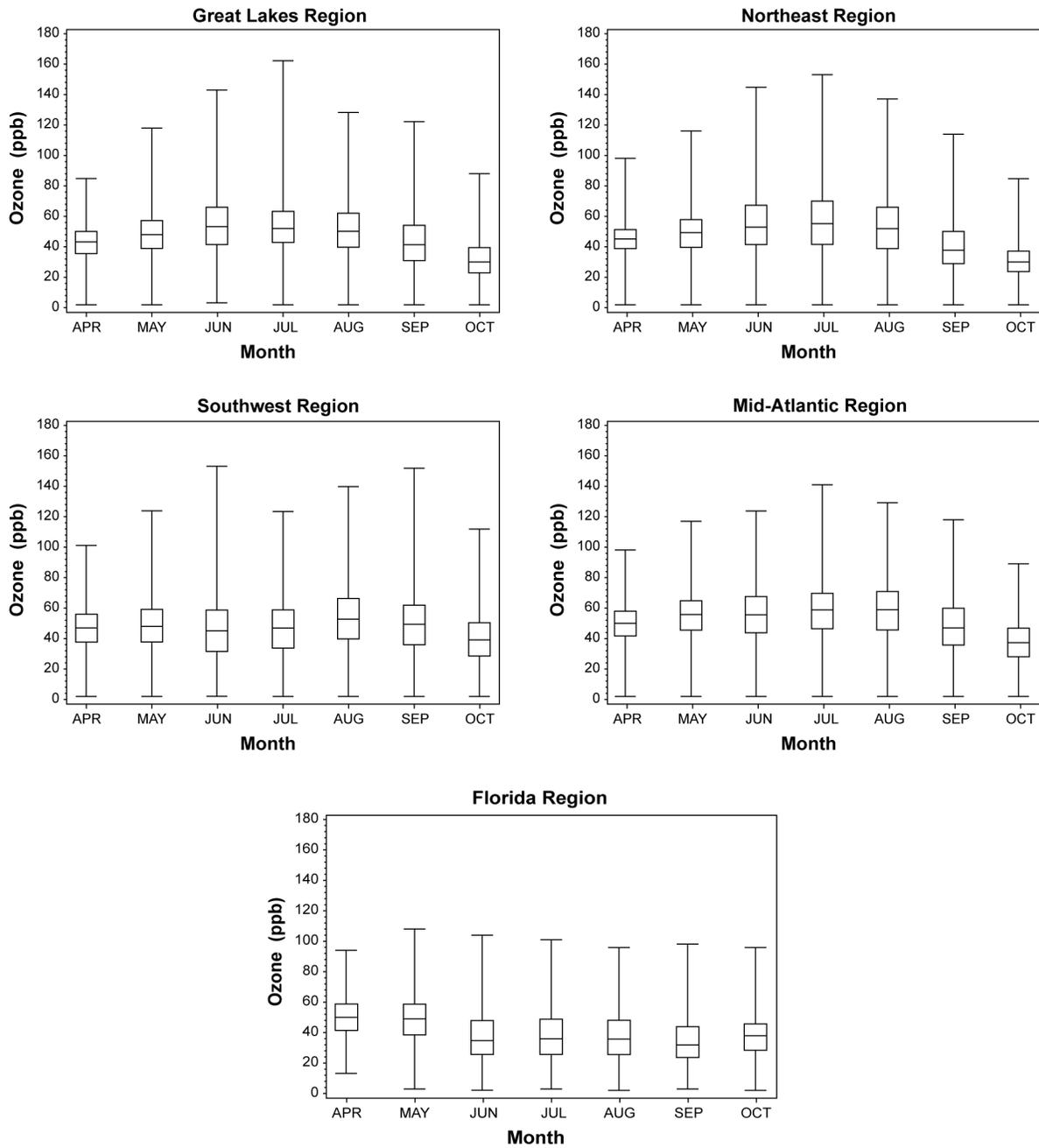


Figure AX3-7. Box plots showing O₃ averaged by month from 1993 to 2002 in the five regions in the eastern United States derived by Lehman et al. (2004). The boxes define the interquartile range and the whiskers, the extreme values.

Source: Lehman et al. (2004).

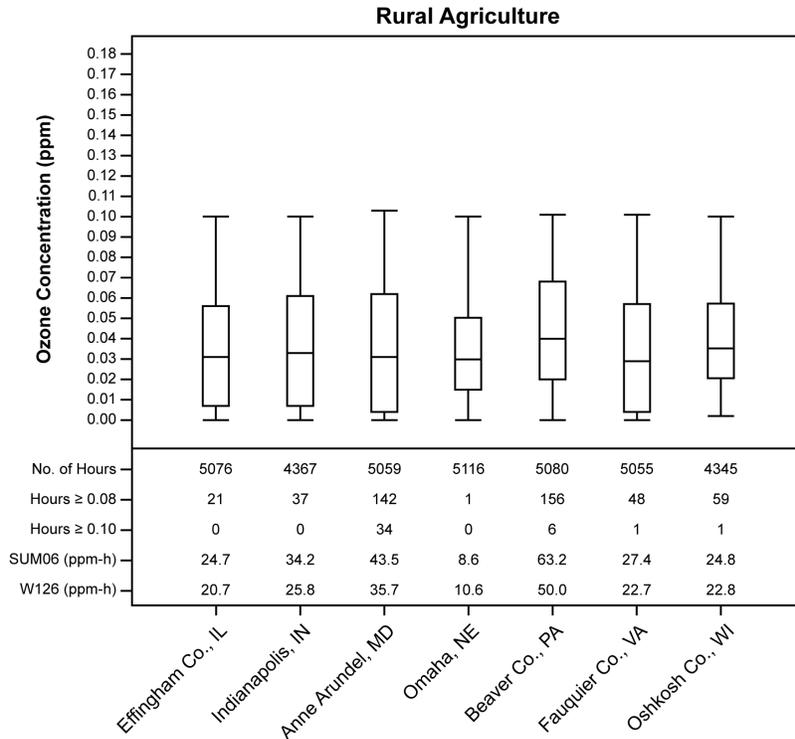


Figure AX3-8. Hourly average O₃ concentrations observed at selected rural-agricultural sites from April to October 2001. The whiskers represent minimum and maximum concentrations. The boxes represent the 10th and 90th percentile concentrations.

Source: Fitz-Simons et al. (2005).

and AX3-10 (rural-residential or commercial). Shown below the figures are the number of observations and various metrics for characterizing vegetation exposures. Note that high O₃ concentrations are found at sites that are classified as rural, as in Anne Arundel Co., MD; Yosemite NP, CA; and Crestline, CA. Land use designations might not give an accurate picture of exposure regimes in rural areas, because the land use characterization of “rural” does not necessarily mean that a specific location is isolated from anthropogenic influences. Rather, the characterization refers only to the current use of the land, not to the presence of sources. Since O₃ produced from emissions in urban areas is transported to more rural downwind locations, elevated O₃ concentrations can occur at considerable distances from urban centers. In addition, major sources of O₃ precursors such as power plants and highways are located in nonurban areas and also produce O₃ in these areas. Due to lower rates of chemical scavenging in

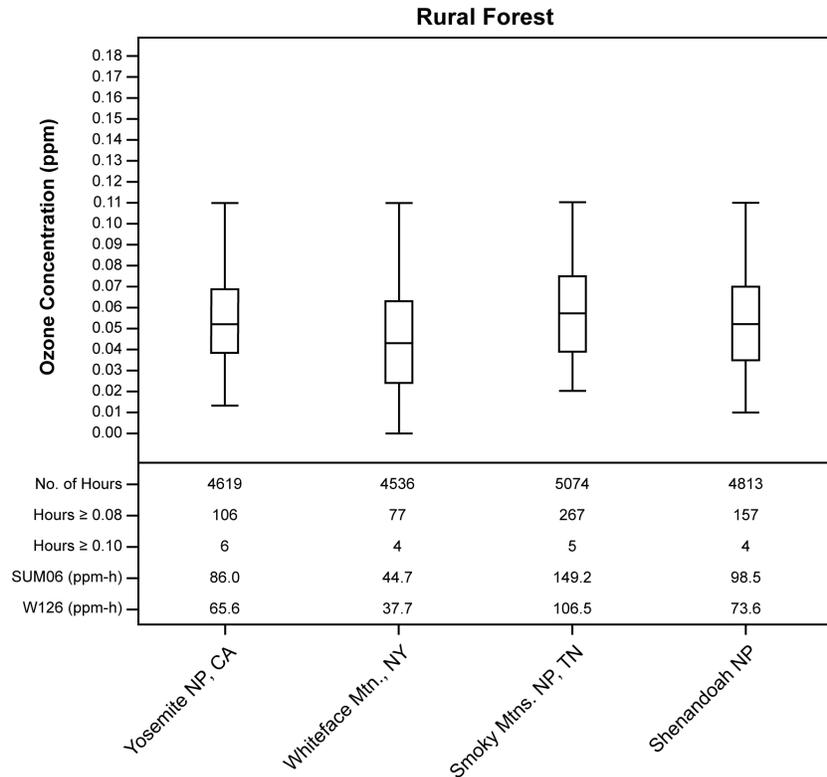


Figure AX3-9. Hourly average O₃ concentrations observed at selected rural-forest sites from April to October 2001. The whiskers represent minimum and maximum concentrations. The boxes represent the 10th and 90th percentile concentrations.

Source: Fitz-Simons et al. (2005).

nonurban areas, O₃ tends to persist longer in nonurban than in urban areas, also tending to lead to higher exposures in nonurban areas influenced by anthropogenic precursor emissions.

Ozone Air Quality Data at Relatively Remote Monitoring Sites (RRMS)

RRMS are sites that are located in the national parks that tend to be less affected by obvious pollution sources than other sites. This does not mean that they are completely unaffected by local pollution, because of the large number of visitors to these national parks. It is important to characterize hourly average O₃ concentrations at RRMS so that assessments of the possible effects of O₃ on human health and vegetation, use concentration ranges that mimic the range found in the United States. Hourly average concentrations used as controls in studies

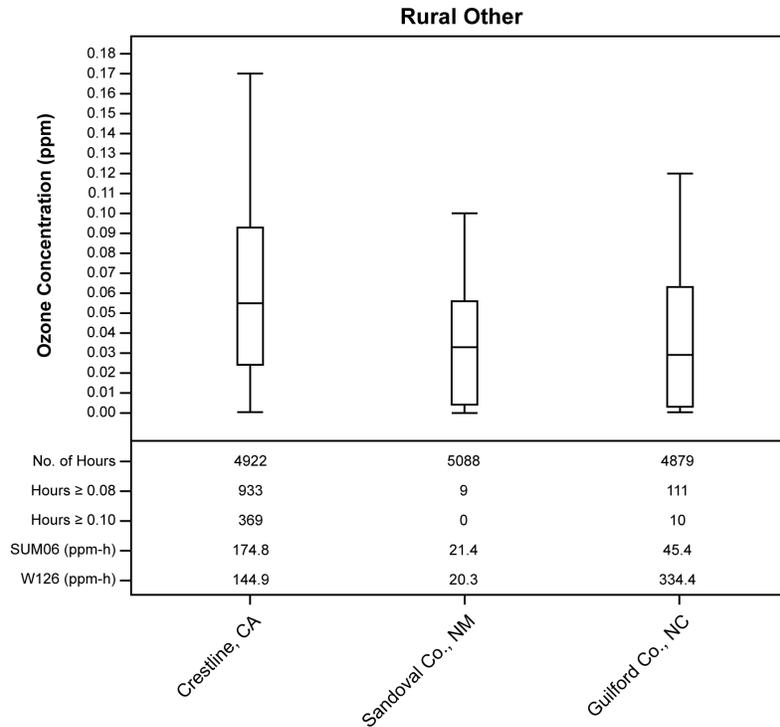


Figure AX3-10. Hourly average O₃ concentrations observed at selected rural-commercial or -residential sites from April to October 2001. The whiskers represent minimum and maximum concentrations. The boxes represent the 10th and 90th percentile concentrations.

Source: Fitz-Simons et al. (2005).

of human health and vegetation exposures to O₃ appear to be lower than those experienced at RRMS in the United States or in other parts of the world (see Chapter 9). Typically, ambient air is filtered to remove O₃ before being admitted into the exposure chambers. As a result, O₃ concentrations might only be a few ppb within these chambers.

Box plots in Figures AX3-11a-d depicting the distributions of annual hourly average measured O₃ concentrations at four relatively remote monitoring sites (RRMS), show that annual mean values of the daily 8-h maximum O₃ concentration have not changed much over the past 10 years of available data. Mean values range typically from about 0.020 ppm to about 0.040 ppm. Concentrations only rarely exceed 0.080 ppm, in contrast to observations at other “rural” sites shown in Figures AX3-8 to AX3-10.

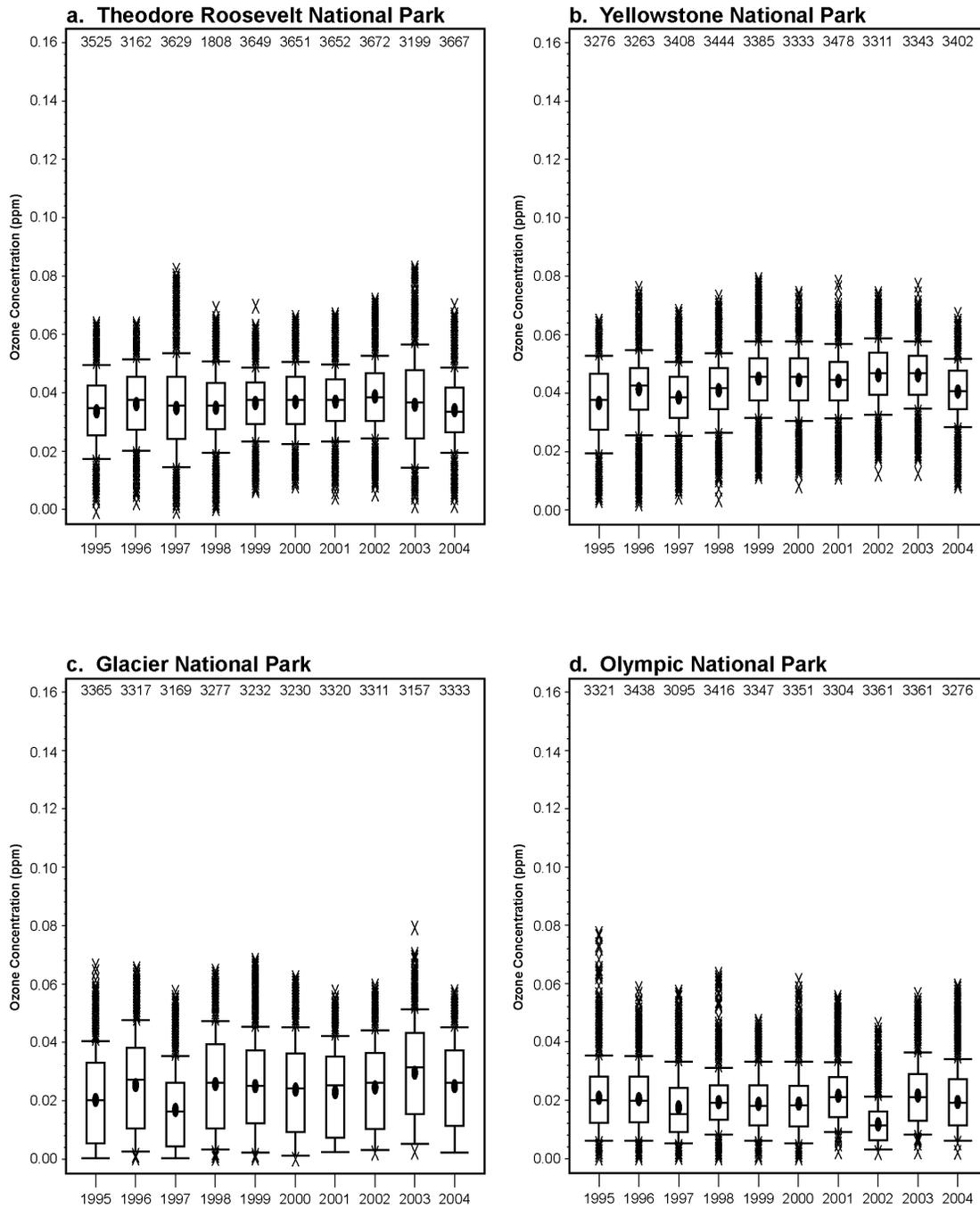


Figure AX3-11a-d. Daily 8-h maximum O₃ concentrations observed at selected national park sites. The whiskers on the box plot represent the 10th and 90th percentile concentrations. The “X”s above and below the whiskers are the values that fall below and above the 10th and 90th percentile concentrations. The dots inside the box represent the mean. The number of observations is shown above each box plot.

Source: Fitz-Simons et al. (2005).

It is unlikely that distributions found at sites with low maximum hourly average concentrations in the western United States represent those at sites in the eastern and midwestern United States because of regional differences in sources of precursors and transport patterns. Given the high density of sources in the eastern and midwestern United States, it is unclear whether a site could be found in either of these regions that would not be influenced by the transport of O₃ from nearby urban areas. Thus, with the exception of the Voyageurs NP site in Minnesota, observations at RRMS are limited to those obtained in the western United States. However, not all national park sites in the West can be considered to be free of strong regional pollution influences, e.g., Yosemite NP (CA), as can be seen from Figure AX3-9.

The 1996 O₃ AQCD (U.S. Environmental Protection Agency, 1996a) concluded that the annual average “background” concentration of O₃ near sea level ranged from 0.020 to 0.035 ppm and that, during the summer, the 1-h daily maximum ranged from 0.03 to 0.05 ppm. The 1996 O₃ AQCD also included O₃ hourly average concentrations measured at several clean, RRMS mostly located in the western United States. Table AX3-3 provides a summary of the characterization of the hourly average concentrations recorded from 1988 to 2001 at some of the monitoring sites previously analyzed. The percentile distribution of the hourly average concentrations (April to October), number of hourly average occurrences ≥ 0.08 and ≥ 0.10 ppm, seasonal 7-h average concentrations, the SUM06, and W126 values were characterized for those site years with a data capture of $\geq 75\%$. From 1988 to 2001, no hourly average concentrations ≥ 0.08 ppm were observed at monitoring sites in Redwood NP (CA), Olympic NP (WA), Glacier NP (MT), Denali NP (AK), Badlands (SD), and Custer NF (MT) during the months of April to October. There were eight occurrences of hourly average O₃ concentrations ≥ 0.08 ppm from April to October of 1997 at the monitoring site in Theodore Roosevelt NP (ND). However, no hourly average concentrations ≥ 0.08 ppm were observed from April to October in any other year at this site. Except for 1988, the year in which there were major forest fires at Yellowstone NP (WY), the monitoring site located there experienced no hourly average concentrations ≥ 0.08 ppm. Logan (1989) noted that O₃ hourly average concentrations rarely exceed 0.08 ppm at remote monitoring sites in the western United States. In almost all cases for the above sites, the maximum hourly average concentration was ≤ 0.075 ppm. The top 10 daily maximum 8-h average concentrations for sites experiencing low maximum hourly average concentrations with

Table AX3-3. Seasonal (April to October) Percentile Distribution of Hourly Ozone Concentrations (ppm), Number of Hourly Mean Ozone Occurrences ≥ 0.08 and ≥ 0.10 , Seasonal 7-h Average Concentrations, SUM06, and W126 Values for Sites Experiencing Low Maximum Hourly Average Concentrations with Data Capture of $\geq 75\%$

Site	Year	Min.	Percentiles							Max.	No. of Obs.	Hours		Seasonal 7-h	SUM06 (ppm-h)	W126 (ppm-h)
			10	30	50	70	90	95	99			≥ 0.08	≥ 0.10			
Redwood NP 060150002 (California) 235 m	1988	0.002	0.011	0.018	0.023	0.029	0.038	0.041	0.046	0.06	4825	0	0	0.026	1.8	0.1
	1989	0.000	0.010	0.017	0.022	0.027	0.034	0.038	0.042	0.047	4624	0	0	0.024	1.0	0.0
	1990	0.000	0.011	0.018	0.023	0.028	0.035	0.038	0.043	0.053	4742	0	0	0.025	1.2	0.0
	1991	0.001	0.012	0.019	0.025	0.031	0.038	0.041	0.045	0.054	4666	0	0	0.027	1.7	0.0
	1992	0.000	0.010	0.017	0.021	0.026	0.035	0.039	0.045	0.055	4679	0	0	0.023	1.1	0.0
	1993	0.000	0.010	0.017	0.022	0.027	0.035	0.038	0.042	0.054	4666	0	0	0.025	1.1	0.0
	1994	0.001	0.011	0.018	0.024	0.028	0.035	0.038	0.043	0.050	4846	0	0	0.026	0.0	1.2
Olympic NP (Washington) 530090012 125 m	1989	0.000	0.003	0.010	0.015	0.022	0.030	0.035	0.046	0.065	4220	0	0	0.021	0.7	0.1
	1990	0.000	0.005	0.012	0.018	0.023	0.030	0.034	0.043	0.064	4584	0	0	0.022	0.8	0.3
	1991	0.000	0.006	0.014	0.019	0.024	0.033	0.036	0.044	0.056	4677	0	0	0.025	0.9	0.0
	1993	0.000	0.004	0.010	0.016	0.021	0.029	0.034	0.041	0.064	4595	0	0	0.022	0.7	0.3
	1994	0.000	0.006	0.013	0.019	0.025	0.033	0.038	0.043	0.062	4044	0	0	0.025	0.2	0.8
	1995	0.000	0.006	0.014	0.020	0.027	0.037	0.040	0.048	0.077	4667	0	0	0.027	0.8	1.9
	1996	0.000	0.006	0.013	0.019	0.025	0.034	0.038	0.043	0.058	4811	0	0	0.025	0.0	1.0
	1997	0.000	0.005	0.010	0.015	0.022	0.035	0.040	0.046	0.057	4403					
	1998	0.000	0.008	0.014	0.019	0.025	0.033	0.037	0.044	0.063	4792	0	0	0.024	0.3	1.1
	1999	0.000	0.006	0.014	0.019	0.026	0.036	0.039	0.044	0.050	4656	0	0	0.024	0.0	1.1
	2000	0.000	0.006	0.013	0.019	0.025	0.035	0.039	0.045	0.061	4676	0	0	0.024	0.1	1.2
2001	0.002	0.009	0.017	0.023	0.028	0.036	0.041	0.046	0.055	4643	0	0	0.027	0.0	1.4	

Table AX3-3 (cont'd). Seasonal (April to October) Percentile Distribution of Hourly Ozone Concentrations (ppm), Number of Hourly Mean Ozone Occurrences ≥ 0.08 and ≥ 0.10 , Seasonal 7-h Average Concentrations, SUM06, and W126 Values for Sites Experiencing Low Maximum Hourly Average Concentrations with Data Capture of $\geq 75\%$

Site	Year	Min.	Percentiles							Max.	No. of Obs.	Hours		Seasonal 7-h	SUM06 (ppm-h)	W126 (ppm-h)
			10	30	50	70	90	95	99			≥ 0.08	≥ 0.10			
Glacier NP 300298001 (Montana) 963 m	1989	0.000	0.003	0.015	0.026	0.036	0.046	0.050	0.058	0.067	4770	0	0	0.036	5.9	1.8
	1990	0.000	0.003	0.014	0.026	0.035	0.044	0.047	0.052	0.066	5092	0	0	0.036	4.1	1.3
	1991	0.000	0.001	0.014	0.027	0.036	0.046	0.049	0.056	0.062	5060	0	0	0.036	5.3	0.7
	1992	0.000	0.001	0.013	0.025	0.033	0.043	0.048	0.055	0.077	4909	0	0	0.033	4.1	1
	1993	0.000	0.000	0.010	0.020	0.029	0.040	0.044	0.050	0.058	5071	0	0	0.029	0.0	2.3
	1994	0.000	0.001	0.014	0.026	0.036	0.046	0.050	0.056	0.061	5072	0	0	0.036	0.1	5.4
	1995	0.000	0.000	0.010	0.022	0.031	0.041	0.045	0.051	0.066	4744	0	0	0.023	0.3	2.3
	1996	0.000	0.002	0.013	0.025	0.035	0.046	0.051	0.058	0.065	4666	0	0	0.035	1.9	5.4
	1997	0.000	0.000	0.008	0.017	0.026	0.041	0.045	0.053	0.058	4378	0	0	0.027	0.0	2.3
	1998	0.000	0.003	0.013	0.025	0.035	0.047	0.051	0.058	0.064	4649	0	0	0.036	1.4	5.6
	1999	0.000	0.002	0.015	0.026	0.035	0.046	0.051	0.058	0.068	4540	0	0	0.035	1.3	5.4
	2000	0.000	0.001	0.011	0.023	0.033	0.044	0.048	0.055	0.062	4551	0	0	0.033	0.7	3.8
2001	0.000	0.000	0.013	0.025	0.033	0.042	0.044	0.049	0.057	4643	0	0	0.033	0.0	2.7	
Yellowstone NP (Wyoming) 560391010 2484 m	1988	0.002	0.020	0.029	0.037	0.044	0.054	0.058	0.070	0.098	4257	17	0	0.043	14.0	8.9
	1989	0.002	0.018	0.027	0.036	0.044	0.052	0.057	0.063	0.071	4079	0	0	0.042	11.0	6.7
	1990	0.000	0.015	0.023	0.029	0.036	0.043	0.046	0.053	0.061	4663	0	0	0.034	3.8	0.5
	1991	0.004	0.020	0.030	0.037	0.042	0.048	0.051	0.057	0.064	4453	0	0	0.042	7.7	1.2
	1992	0.001	0.018	0.029	0.036	0.042	0.051	0.056	0.064	0.075	4384	0	0	0.042	10.7	6.3
	1993	0.000	0.018	0.028	0.036	0.042	0.047	0.050	0.054	0.060	4399	0	0	0.041	6.5	0.2
	1994	0.003	0.022	0.033	0.040	0.046	0.053	0.056	0.062	0.072	4825	0	0	0.046	6.0	15.2
1995	0.004	0.022	0.033	0.040	0.045	0.052	0.055	0.059	0.065	4650	0	0	0.045	2.8	12.5	

AX3-19

Table AX3-3 (cont'd). Seasonal (April to October) Percentile Distribution of Hourly Ozone Concentrations (ppm), Number of Hourly Mean Ozone Occurrences ≥ 0.08 and ≥ 0.10 , Seasonal 7-h Average Concentrations, SUM06, and W126 Values for Sites Experiencing Low Maximum Hourly Average Concentrations with Data Capture of $\geq 75\%$

Site	Year	Min.	Percentiles							Max.	No. of Obs.	Hours		Seasonal 7-h	SUM06 (ppm-h)	W126 (ppm-h)
			10	30	50	70	90	95	99			≥ 0.08	≥ 0.10			
Yellowstone NP (Wyoming) 560391011 2468 m	1997	0.005	0.026	0.035	0.040	0.045	0.051	0.054	0.060	0.068	4626	0	0	0.043	3.3	12.4
	1998	0.004	0.029	0.038	0.043	0.048	0.055	0.058	0.064	0.073	4827	0	0	0.046	9.9	20.0
	1999	0.012	0.033	0.040	0.046	0.051	0.059	0.062	0.069	0.079	4733	0	0	0.049	27.1	29.8
	2000	0.009	0.031	0.039	0.045	0.050	0.057	0.060	0.065	0.074	4678	0	0	0.047	17.0	23.4
	2001	0.012	0.034	0.041	0.046	0.050	0.057	0.060	0.065	0.078	4869	0	0	0.048	16.9	25.6
Denali NP (Alaska) 022900003 640 m	1988	0.003	0.018	0.024	0.028	0.033	0.044	0.050	0.053	0.056	4726	0	0	0.031	0.0	4.0
	1990	0.003	0.017	0.024	0.029	0.034	0.040	0.043	0.048	0.050	3978	0	0	0.030	2.1	0.0
	1991	0.005	0.018	0.024	0.028	0.034	0.041	0.043	0.047	0.057	4809	0	0	0.030	2.7	0.0
	1992	0.003	0.016	0.023	0.028	0.034	0.044	0.047	0.050	0.054	4800	0	0	0.031	3.7	0.0
	1993	0.002	0.017	0.023	0.028	0.033	0.041	0.043	0.048	0.055	4773	0	0	0.030	2.6	0.0
	1994	0.003	0.017	0.022	0.027	0.033	0.042	0.045	0.049	0.053	4807	0	0	0.030	0.0	2.9
	1995	0.001	0.013	0.019	0.025	0.032	0.042	0.044	0.052	0.059	4825	0	0	0.028	0.0	3.0
	1996	0.002	0.015	0.022	0.028	0.035	0.044	0.047	0.052	0.063	4831	0	0	0.031	0.1	4.1
	1997	0.001	0.015	0.023	0.030	0.038	0.045	0.048	0.051	0.084	4053	1	0	0.032	0.2	4.0
	1998	0.004	0.018	0.023	0.030	0.036	0.048	0.050	0.055	0.058	4782	0	0	0.032	0.0	6.0
	1999	0.002	0.016	0.024	0.029	0.036	0.045	0.048	0.054	0.058	4868	0	0	0.032	0.0	4.7
2000	0.003	0.014	0.019	0.025	0.029	0.034	0.036	0.038	0.049	4641	0	0	0.025	0.0	1.0	
2001	0.002	0.016	0.023	0.029	0.036	0.048	0.051	0.055	0.068	4868	0	0	0.032	0.7	11.1	
Badlands NP 460711001 (South Dakota) 730 m	1989	0.006	0.020	0.027	0.034	0.041	0.049	0.053	0.060	0.071	4840	0	0	0.040	9.2	3.1
	1990	0.006	0.019	0.027	0.032	0.037	0.044	0.048	0.054	0.063	4783	0	0	0.037	4.8	0.8
	1991	0.005	0.020	0.028	0.033	0.040	0.047	0.050	0.056	0.066	4584	0	0	0.038	6.2	0.7

AX3-20

Table AX3-3 (cont'd). Seasonal (April to October) Percentile Distribution of Hourly Ozone Concentrations (ppm), Number of Hourly Mean Ozone Occurrences ≥ 0.08 and ≥ 0.10 , Seasonal 7-h Average Concentrations, SUM06, and W126 Values for Sites Experiencing Low Maximum Hourly Average Concentrations with Data Capture of $\geq 75\%$

Site	Year	Min.	Percentiles							Max.	No. of Obs.	Hours		Seasonal 7-h	SUM06 (ppm-h)	W126 (ppm-h)
			10	30	50	70	90	95	99			≥ 0.08	≥ 0.10			
Theod. Roos. NP 380530002 (North Dakota) 730 m	1984	0.000	0.017	0.025	0.032	0.039	0.047	0.050	0.059	0.068	4923	0	0	0.038	7.0	2.8
	1985	0.000	0.019	0.026	0.032	0.038	0.046	0.049	0.054	0.061	4211	0	0	0.038	5.0	0.1
	1986	0.004	0.017	0.027	0.033	0.039	0.047	0.050	0.056	0.062	4332	0	0	0.039	5.5	0.4
	1989	0.004	0.023	0.032	0.039	0.045	0.054	0.058	0.065	0.073	4206	0	0	0.046	14.2	11.0
	1992	0.005	0.019	0.027	0.033	0.039	0.047	0.050	0.056	0.063	4332	0	0	0.040	6.1	0.8
	1993	0.004	0.018	0.025	0.031	0.037	0.045	0.048	0.055	0.064	4281	0	0	0.038	4.6	0.7
	1994	0.000	0.018	0.028	0.035	0.041	0.049	0.052	0.058	0.079	4644	0	0	0.041	1.1	8.4
	1995	0.000	0.018	0.028	0.035	0.041	0.050	0.053	0.058	0.064	4242	0	0	0.042	1.2	7.7
	1996	0.003	0.022	0.031	0.037	0.043	0.051	0.054	0.059	0.064	3651	0	0	0.044	1.8	8.5
1997	0.000	0.016	0.029	0.037	0.044	0.053	0.058	0.069	0.082	4344	8	0	0.046	11.8	14.6	
Theod. Roos. NP 380070002 (North Dakota) 808 m	1999	0.007	0.024	0.031	0.037	0.042	0.049	0.052	0.058	0.070	5105	0	0	0.041	1.6	10
	2000	0.002	0.021	0.031	0.036	0.043	0.050	0.053	0.058	0.066	5105	0	0	0.041	2.3	10.5
	2001	0.002	0.023	0.031	0.036	0.042	0.049	0.052	0.058	0.064	5099	0	0	0.041	1.9	9.2
Custer NF, MT 300870101 (Montana) 1006 m	1978	0.000	0.010	0.020	0.035	0.040	0.050	0.055	0.060	0.070	4759	0	0	0.033	3.0	8.3
	1979	0.010	0.025	0.035	0.040	0.045	0.050	0.055	0.060	0.075	5014	0	0	0.043	7.3	13.2
	1980	0.010	0.025	0.035	0.040	0.050	0.055	0.060	0.065	0.070	4574	0	0	0.043	22.4	19.7
	1983	0.010	0.025	0.035	0.040	0.045	0.05	0.055	0.060	0.065	4835	0	0	0.042	4.2	10.7

AX3-21

a data capture of $\geq 75\%$ are summarized in Table AX3-4. The highest 8-h daily maximum concentrations do not necessarily all occur during the summer months. For example, at the Yellowstone National Park site, the three highest 8-h daily maximum concentrations occurred in April and May in 1998, and the fourth highest, 8-h daily maximum concentration did not occur until July of that year. In 1999, the three highest, 8-h daily maximum concentrations were observed in March and May, and the fourth highest value occurred in April. In 2000, the four highest values occurred in May, June, July, and August.

The 1996 O₃ AQCD (U.S. Environmental Protection Agency, 1996a) noted that the 7-month (April to October) average of the 7-h daily average concentrations (0900 to 1559 hours) observed at the Theodore Roosevelt National Park monitoring site in North Dakota were 0.038, 0.039, and 0.039 ppm, respectively, for 1984, 1985, and 1986 and concluded that the range of 7-h seasonal averages for the Theodore Roosevelt National Park site was representative of the range of maximum daily 8-h average O₃ concentrations that may occur at other fairly clean sites in the United States and other locations in the Northern Hemisphere. However, as shown in Table AX3-4, the representative (as given by the fourth highest) daily maximum 8-h average O₃ concentrations at fairly clean sites in the United States are higher than the 0.038 and 0.039 ppm values cited in the 1996 O₃ AQCD, and these updated values should be used to characterize O₃ at these sites.

As described in the 1996 O₃ AQCD, the O₃ monitoring site in the Ouachita National Forest, AR experienced distributions of hourly average concentrations similar to some of the western sites. However, since 1993, this site has seen significant shifts, both increases and decreases, in hourly average concentrations. Figure AX3-12 shows the changes that have occurred from 1991 to 2001. The large changes in hourly average O₃ concentrations observed at the Ouachita National Forest may indicate that this rural site is influenced by the transport of pollution. Given the high density of sources in the eastern and midwestern United States, it is unclear whether a site could be found in either of these regions that would not be influenced by the transport of O₃ from urban areas. Thus, with the exception of the Voyageurs National Park site, observations in this section are limited to those obtained at relatively clean, remote sites in western North America.

Table AX3-4. The Top 10 Daily Maximum 8-h Average Concentrations (ppm) for Sites Experiencing Low Maximum Hourly Average Concentrations with Data Capture of $\geq 75\%$

Site	Year	1	2	3	4	5	6	7	8	9	10
Redwood NP 060150002 (California) 235 m	1988	0.061	0.058	0.053	0.052	0.049	0.047	0.046	0.046	0.045	0.045
	1989	0.044	0.043	0.043	0.043	0.042	0.042	0.042	0.042	0.041	0.041
	1990	0.051	0.048	0.048	0.047	0.047	0.046	0.045	0.044	0.043	0.043
	1991	0.048	0.047	0.046	0.045	0.045	0.045	0.044	0.044	0.043	0.043
	1992	0.060	0.053	0.045	0.045	0.045	0.044	0.044	0.043	0.043	0.042
	1993	0.049	0.046	0.043	0.043	0.043	0.042	0.042	0.042	0.041	0.041
	1994	0.048	0.048	0.046	0.046	0.045	0.044	0.044	0.043	0.043	0.043
Olympic NP 530090012 (Washington) 125 m	1989	0.054	0.052	0.047	0.044	0.044	0.044	0.042	0.042	0.038	0.038
	1990	0.056	0.048	0.046	0.046	0.043	0.040	0.040	0.039	0.038	0.038
	1991	0.050	0.048	0.045	0.043	0.042	0.041	0.041	0.041	0.041	0.041
	1993	0.055	0.052	0.044	0.042	0.040	0.039	0.038	0.038	0.037	0.037
	1994	0.050	0.046	0.042	0.042	0.042	0.042	0.041	0.041	0.040	0.040
	1995	0.064	0.063	0.050	0.049	0.045	0.045	0.044	0.044	0.044	0.044
	1996	0.046	0.046	0.046	0.046	0.043	0.042	0.041	0.041	0.041	0.040
	1997	0.052	0.051	0.046	0.045	0.045	0.045	0.044	0.043	0.042	0.042
	1998	0.051	0.050	0.049	0.046	0.044	0.043	0.042	0.041	0.041	0.041
	1999	0.045	0.044	0.044	0.043	0.043	0.042	0.042	0.042	0.042	0.041
	2000	0.051	0.051	0.048	0.047	0.045	0.044	0.043	0.042	0.042	0.042
	2001	0.051	0.050	0.047	0.045	0.045	0.044	0.044	0.044	0.043	0.043

Table AX3-4 (cont'd). The Top 10 Daily Maximum 8-h Average Concentrations (ppm) for Sites Experiencing Low Maximum Hourly Average Concentrations with Data Capture of $\geq 75\%$

Site	Year	1	2	3	4	5	6	7	8	9	10	
Glacier NP 300298001 (Montana) 963 m	1989	0.062	0.061	0.060	0.059	0.058	0.057	0.056	0.056	0.056	0.056	
	1990	0.058	0.057	0.055	0.054	0.053	0.053	0.052	0.052	0.052	0.052	
	1991	0.060	0.057	0.057	0.057	0.056	0.055	0.055	0.054	0.054	0.053	
	1992	0.062	0.056	0.055	0.054	0.054	0.054	0.053	0.053	0.053	0.053	
	1993	0.055	0.052	0.051	0.051	0.050	0.050	0.049	0.049	0.049	0.048	
	1994	0.057	0.057	0.056	0.056	0.055	0.055	0.055	0.055	0.055	0.054	0.053
	1995	0.061	0.055	0.053	0.052	0.052	0.052	0.051	0.051	0.051	0.051	0.050
	1996	0.059	0.059	0.058	0.058	0.057	0.057	0.055	0.055	0.056	0.055	0.055
	1997	0.056	0.054	0.052	0.052	0.052	0.051	0.050	0.050	0.050	0.050	0.050
	1998	0.060	0.059	0.058	0.058	0.056	0.056	0.055	0.055	0.055	0.055	0.054
	1999	0.065	0.065	0.060	0.058	0.056	0.055	0.055	0.055	0.055	0.055	0.054
	2000	0.059	0.058	0.058	0.056	0.054	0.052	0.051	0.050	0.050	0.050	0.050
2001	0.054	0.052	0.049	0.049	0.049	0.048	0.047	0.047	0.047	0.047	0.047	
Yellowstone NP 560391010 (Wyoming) 2484 m	1988	0.068	0.068	0.067	0.066	0.066	0.066	0.064	0.064	0.063	0.061	
	1989	0.067	0.065	0.064	0.063	0.063	0.061	0.061	0.061	0.061	0.060	
	1990	0.057	0.056	0.054	0.054	0.053	0.052	0.050	0.050	0.049	0.048	
	1991	0.059	0.058	0.058	0.057	0.056	0.056	0.056	0.055	0.055	0.055	
	1992	0.066	0.064	0.064	0.063	0.063	0.061	0.061	0.059	0.059	0.058	
	1993	0.057	0.054	0.054	0.054	0.053	0.053	0.053	0.052	0.052	0.052	
	1994	0.067	0.063	0.063	0.061	0.061	0.061	0.061	0.061	0.059	0.059	
	1995	0.064	0.062	0.061	0.060	0.059	0.059	0.059	0.059	0.059	0.058	

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Table AX3-4 (cont'd). The Top 10 Daily Maximum 8-h Average Concentrations (ppm) for Sites Experiencing Low Maximum Hourly Average Concentrations with Data Capture of $\geq 75\%$

Site	Year	1	2	3	4	5	6	7	8	9	10
Yellowstone NP 560391011 (Wyoming) 2468 m	1997	0.065	0.065	0.062	0.061	0.061	0.060	0.057	0.056	0.056	0.056
	1998	0.069	0.068	0.066	0.066	0.063	0.063	0.061	0.061	0.061	0.060
	1999	0.078	0.074	0.073	0.071	0.070	0.070	0.070	0.069	0.068	0.067
	2000	0.070	0.069	0.067	0.065	0.065	0.065	0.064	0.064	0.064	0.063
	2001	0.068	0.068	0.066	0.066	0.065	0.064	0.064	0.064	0.064	0.063
Denali NP 022900003 (Alaska) 640 m	1988	0.055	0.054	0.054	0.053	0.053	0.053	0.052	0.052	0.052	0.052
	1990	0.049	0.048	0.048	0.048	0.048	0.047	0.047	0.046	0.046	0.046
	1991	0.054	0.054	0.050	0.050	0.047	0.046	0.046	0.046	0.045	0.044
	1992	0.053	0.052	0.052	0.051	0.050	0.050	0.049	0.049	0.049	0.049
	1993	0.053	0.053	0.051	0.048	0.048	0.047	0.047	0.046	0.046	0.046
	1994	0.053	0.051	0.049	0.049	0.049	0.048	0.048	0.048	0.048	0.048
	1995	0.058	0.056	0.056	0.054	0.051	0.050	0.049	0.046	0.046	0.046
	1996	0.058	0.053	0.053	0.053	0.052	0.052	0.052	0.052	0.051	0.051
	1997	0.054	0.053	0.052	0.051	0.051	0.050	0.050	0.049	0.049	0.049
	1998	0.057	0.056	0.056	0.055	0.054	0.054	0.054	0.054	0.053	0.053
	1999	0.056	0.056	0.054	0.054	0.054	0.053	0.053	0.053	0.052	0.051
	2000	0.046	0.046	0.044	0.044	0.044	0.043	0.043	0.042	0.042	0.042
2001	0.061	0.058	0.057	0.055	0.055	0.055	0.053	0.053	0.053	0.053	
Badlands NP 460711001 (South Dakota) 730 m	1989	0.069	0.066	0.064	0.063	0.060	0.058	0.057	0.057	0.057	0.057
	1990	0.061	0.059	0.055	0.055	0.054	0.052	0.052	0.051	0.051	0.050
	1991	0.058	0.058	0.056	0.056	0.056	0.055	0.055	0.054	0.054	0.053

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Table AX3-4 (cont'd). The Top 10 Daily Maximum 8-h Average Concentrations (ppm) for Sites Experiencing Low Maximum Hourly Average Concentrations with Data Capture of $\geq 75\%$

Site	Year	1	2	3	4	5	6	7	8	9	10
Theod. Roos. NP 380530002 (North Dakota) 730 m	1984	0.064	0.062	0.062	0.062	0.059	0.058	0.057	0.057	0.057	0.057
	1985	0.058	0.055	0.055	0.054	0.054	0.054	0.053	0.053	0.053	0.052
	1986	0.059	0.058	0.057	0.056	0.055	0.055	0.054	0.053	0.053	0.052
	1989	0.073	0.069	0.066	0.065	0.065	0.064	0.063	0.063	0.063	0.063
	1992	0.060	0.059	0.058	0.058	0.056	0.056	0.056	0.054	0.054	0.054
	1993	0.062	0.059	0.056	0.056	0.055	0.053	0.052	0.052	0.052	0.052
	1994	0.066	0.064	0.058	0.058	0.057	0.056	0.056	0.056	0.056	0.055
	1995	0.060	0.059	0.058	0.058	0.058	0.058	0.057	0.057	0.056	0.055
	1996	0.060	0.059	0.059	0.059	0.058	0.058	0.057	0.057	0.057	0.056
	1997	0.080	0.073	0.072	0.071	0.069	0.068	0.066	0.066	0.063	0.063
Theod. Roos. NP 380070002 (North Dakota) 808 m	1999	0.063	0.060	0.059	0.058	0.057	0.057	0.057	0.056	0.056	0.056
	2000	0.062	0.061	0.060	0.059	0.059	0.057	0.057	0.057	0.057	0.057
	2001	0.060	0.059	0.059	0.058	0.058	0.057	0.057	0.056	0.055	0.055
Custer NF, MT 300870101 (Montana) 1006 m	1978	0.069	0.065	0.063	0.062	0.061	0.061	0.060	0.060	0.060	0.058
	1979	0.073	0.066	0.066	0.065	0.063	0.060	0.060	0.060	0.059	0.059
	1980	0.069	0.069	0.069	0.068	0.067	0.067	0.066	0.066	0.064	0.064
	1983	0.064	0.061	0.060	0.060	0.059	0.058	0.058	0.058	0.056	0.056

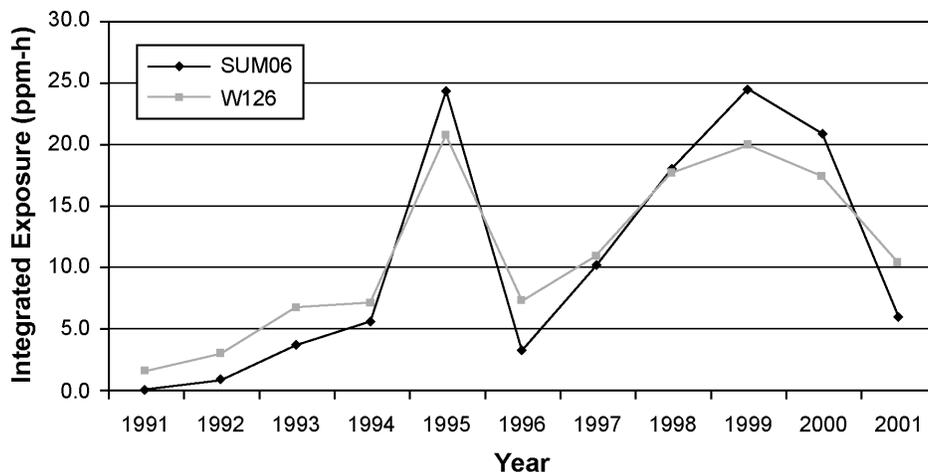


Figure AX3-12. Seasonal SUM06 and W126 exposure indices for the Ouachita National Forest for the period of 1991 to 2001.

AX3.2.1 Nationwide Distribution of Metrics for Characterizing Exposures of Vegetation to Ozone

The previous O₃ AQCD (U.S. Environmental Protection Agency, 1996a) concluded that higher hourly average concentrations (≥ 0.10 ppm) should be given greater weight than mid-level (0.06 to 0.099 ppm) and lower hourly average concentrations in predicting injury and yield reduction for agricultural crops and forests. The most recent findings concerning the importance of the higher hourly average concentrations in comparison to the mid-level and lower values will be discussed in Chapter 9. Because of a lack of air quality data collected at rural and remote locations, interpolation techniques, such as kriging, have been applied to the estimation of O₃ exposures across the United States (Reagan, 1984; Lefohn et al., 1987; Knudsen and Lefohn, 1988). “Kriging” (Matheron, 1963) has been used in the analyses of air quality data (Grivet, 1980; Faith and Sheshinski, 1979) and was used to provide estimates of seasonal O₃ values for the National Crop Loss Assessment Network (NCLAN) for 1978 through 1982 (May to September of each year) (Reagan, 1984). These values, along with updated values, coupled with exposure-response models, were used to predict agriculturally related economic benefits anticipated by lower O₃ levels in the United States (Adams et al., 1985, 1989). It should be noted that although kriging has been used here to map unmeasured ozone concentrations, it has shortcomings. In particular, the kriging variance underestimates the uncertainty in spatial

prediction and relies on the assumption of spatial covariance isotropy. Newer methods overcome many of these shortcomings (e.g., Le et al., 1992, 1997, 2001). These methodologies have been tested by Sun et al. (1998), who also show that the uncertainties in spatial fields can be substantially underestimated using kriging.

Spatiotemporal distributions of O₃ concentrations have alternatively been obtained using methods of the “Spatio-Temporal Random Field” (STRF) theory (Christakos and Vyas, 1998a,b). The STRF approach interpolates monitoring data in both space and time simultaneously. This method can analyze information on “temporal trends,” which cannot be incorporated directly in purely spatial interpolation methods such as standard kriging. Further, the STRF method can optimize the use of data that are not uniformly sampled in either space or time. The STRF theory was further extended in the Bayesian Maximum Entropy (BME) framework and applied to O₃ interpolation studies (Christakos and Hristopulos, 1998; Christakos and Kolovos, 1999; Christakos, 2000). The BME framework can use prior information in the form of “hard data” (measurements), probability law descriptors (type of distribution, mean and variance), interval estimation (maximum and minimum values) and even constraint from physical laws. According to these researchers, both STRF and BME were found to successfully reproduce O₃ fields when adequate monitor data are available.

For 2001, ordinary kriging was used to estimate the seasonal W126, SUM06, and number of hours ≥ 0.10 ppm (N100), using hourly average concentrations accumulated over a 24-h period. As discussed in Chapter 9, the correlation between the number of occurrences of hourly average concentrations ≥ 0.10 ppm and the magnitude of the W126 and SUM06 values is not strong. Because of this, the N100 was also estimated, along with the W126 and SUM06 exposure indices. For the period of April through September, the estimates of the seasonal W126, SUM06, and N100 exposure index values were made for each 0.5° by 0.5° cell in the continuous United States. The kriged values, the variance, and the 95% error bound for each 0.5° by 0.5° cell were estimated. Because of the concern for inner-city depletion caused by NO_x scavenging, data from specific monitoring stations located in large metropolitan areas were not included in the analysis.

Figure AX3-13 shows the kriged values for the 24-h cumulative seasonal W126 exposure index and the N100 index for 2001 for the eastern United States. Note that for some of the areas with elevated W126 values (e.g., >35 ppm-h), the number of hourly average concentrations was

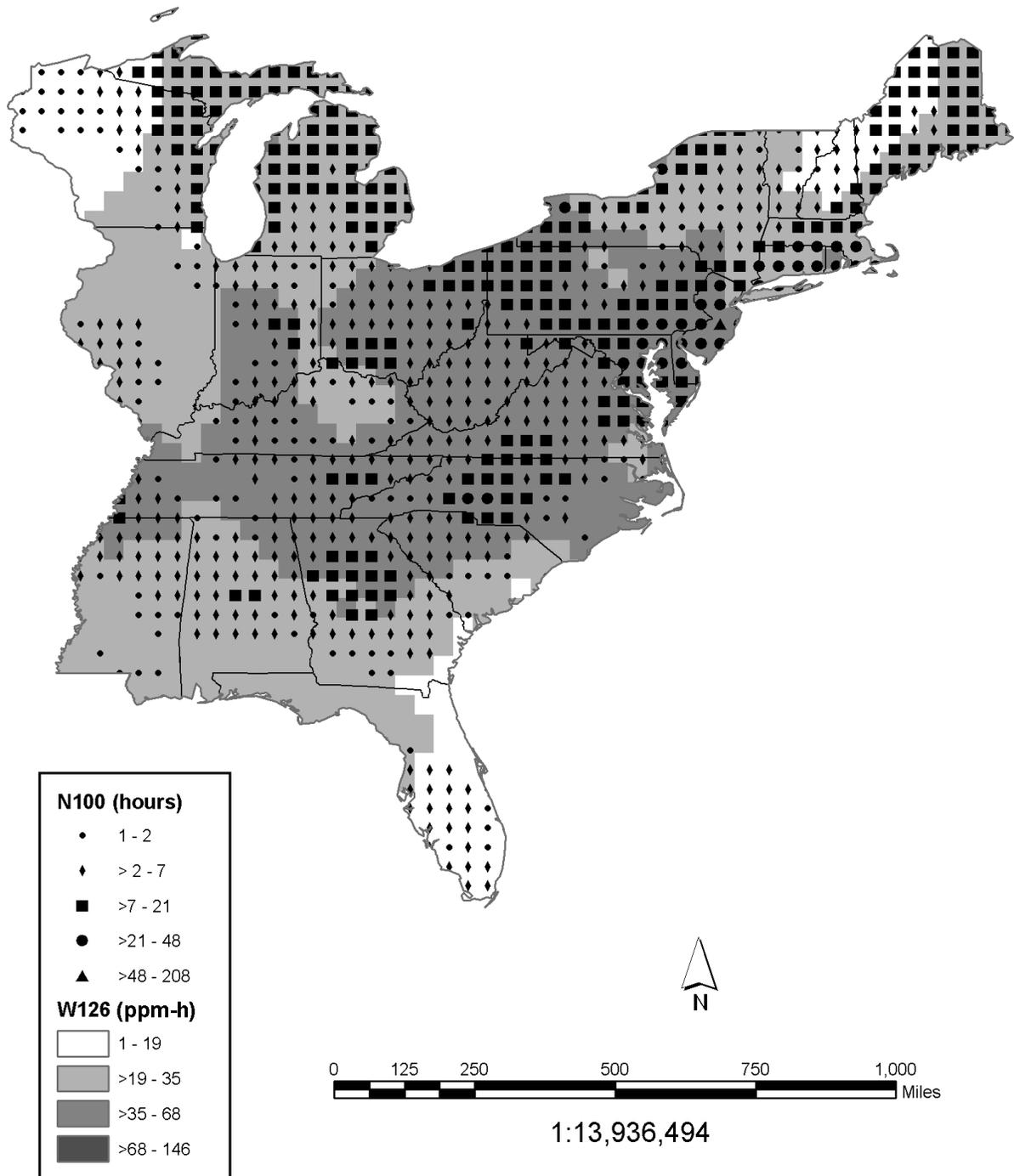


Figure AX3-13. Six-month (April to September) 24-h cumulative W126 exposure index with the number of hourly average concentrations ≥ 0.10 ppm (N100) occurring during 2001 for the eastern United States.

estimated to be <22. Figure AX3-14 illustrates the kriged values using the 24-h cumulative seasonal SUM06 exposure index and the N100 index for 2001 for the eastern United States. Figures AX3-15 and AX3-16 show the W126 and SUM06 values, respectively, with the N100 values for the central United States region. For 2001, the number of hourly average concentrations ≥ 0.10 ppm was usually <22 for the 6-month period. Figures AX3-17 and AX3-18 illustrate the W126 and SUM06 values, respectively, for the western United States region. Note that in the Southern California and Central California areas, the number of hourly average concentrations ≥ 0.10 ppm was in the range of 48 to 208 for the 6-month period. This is considerably greater than the frequency of occurrences for the higher hourly average concentrations observed in the eastern and central United States.

Due to the scarcity of monitoring sites across the United States, especially in the Rocky Mountain region, the uncertainty in the estimates for the various exposure indices vary. Figures AX3-19 through AX3-27 illustrate the 95% confidence intervals associated with the indices by region.

AX3.3 SPATIAL VARIABILITY IN OZONE CONCENTRATIONS

The spatial variability of O₃ concentrations in different environments in the United States occurring across a variety of spatial scales is characterized in this section. This information will be useful for understanding the influence of regional or altitudinal differences in O₃ exposure on vegetation and for establishing the spatial variations in O₃ concentrations as they are used in epidemiologic studies. Intracity variations in O₃ concentrations are described in Section AX3.3.1. Small scale horizontal and vertical variations in O₃ concentrations are discussed in Section AX3.3.2. Ozone concentrations at high elevations are characterized in Section AX3.3.3.

AX3.3.1 Spatial Variability of Ozone Concentrations in Urban Areas

Many processes contribute to spatial variability in O₃ concentrations in urban areas. Ozone formation occurs more or less continuously downwind of sources of precursors, producing a gradient in O₃ concentrations. Ozone “titration” by reaction with NO can deplete O₃ levels near NO sources such as highways and busy streets. Differences in surface characteristics affect the

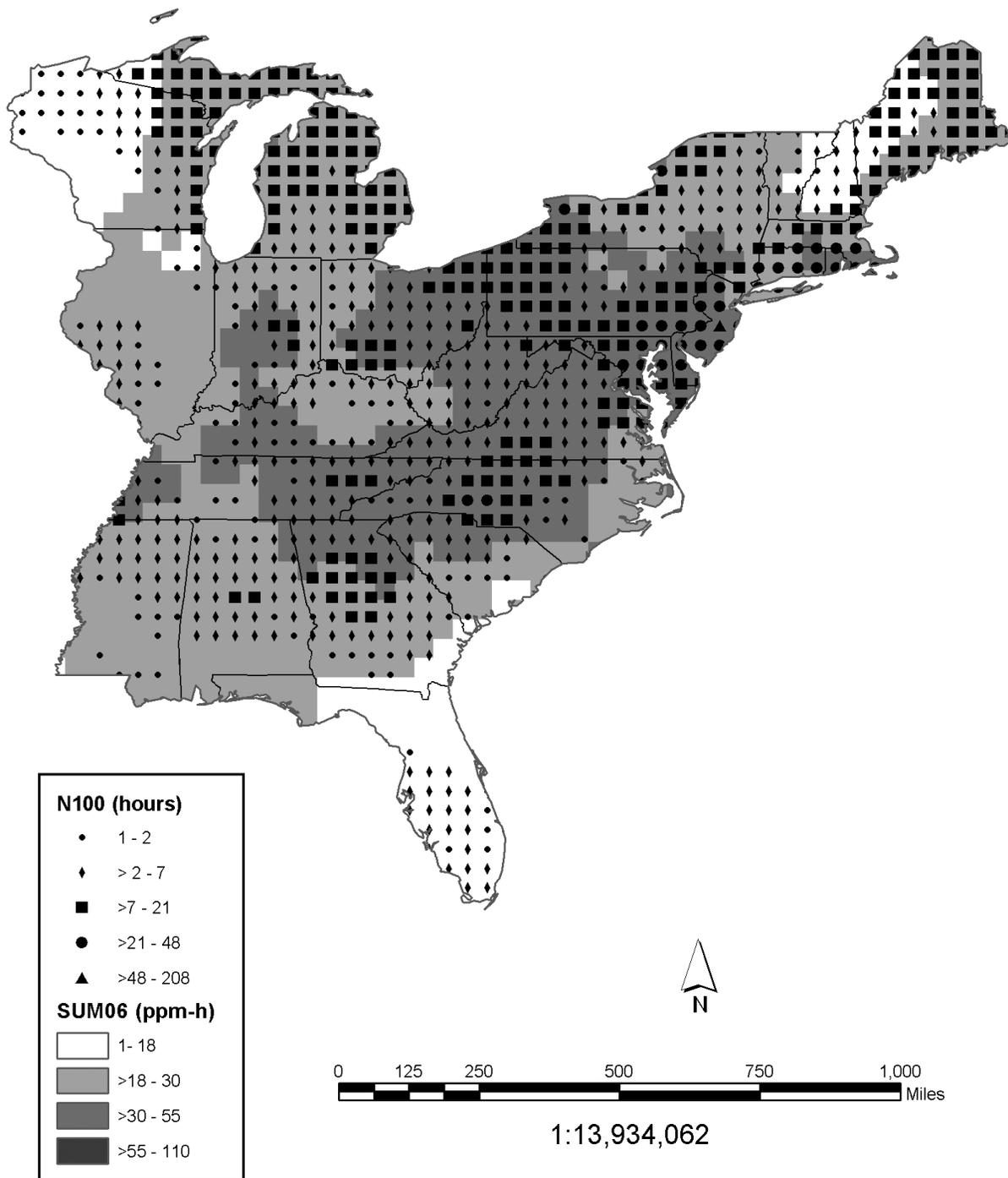


Figure AX3-14. Six-month (April to September) 24-h cumulative SUM06 exposure index with the number of hourly average concentrations ≥ 0.10 ppm (N100) occurring during 2001 for the eastern United States.

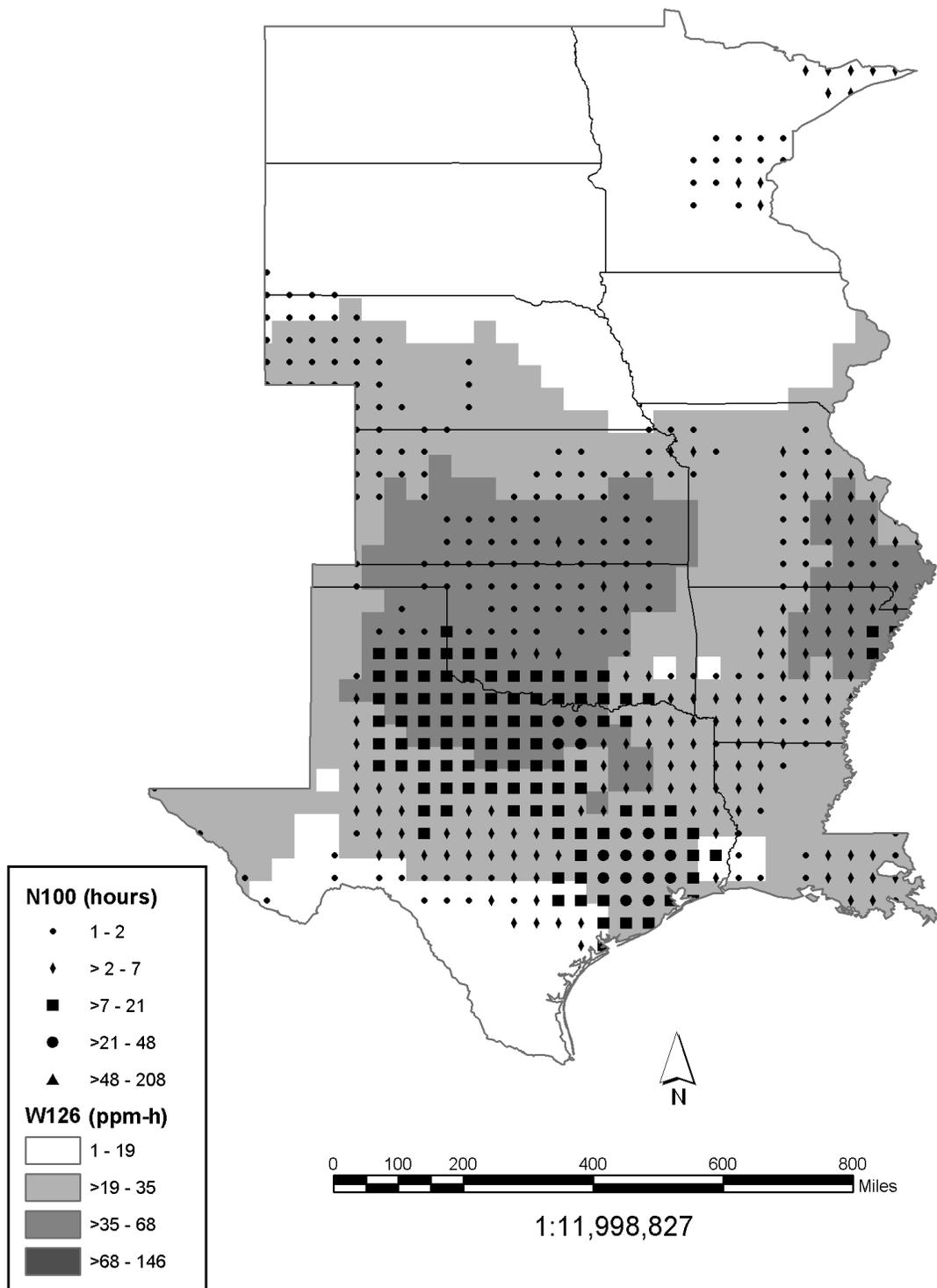


Figure AX3-15. Six-month (April to September) 24-h cumulative W126 exposure index with the number of hourly average concentrations ≥ 0.10 ppm (N100) occurring during 2001 for the central United States.

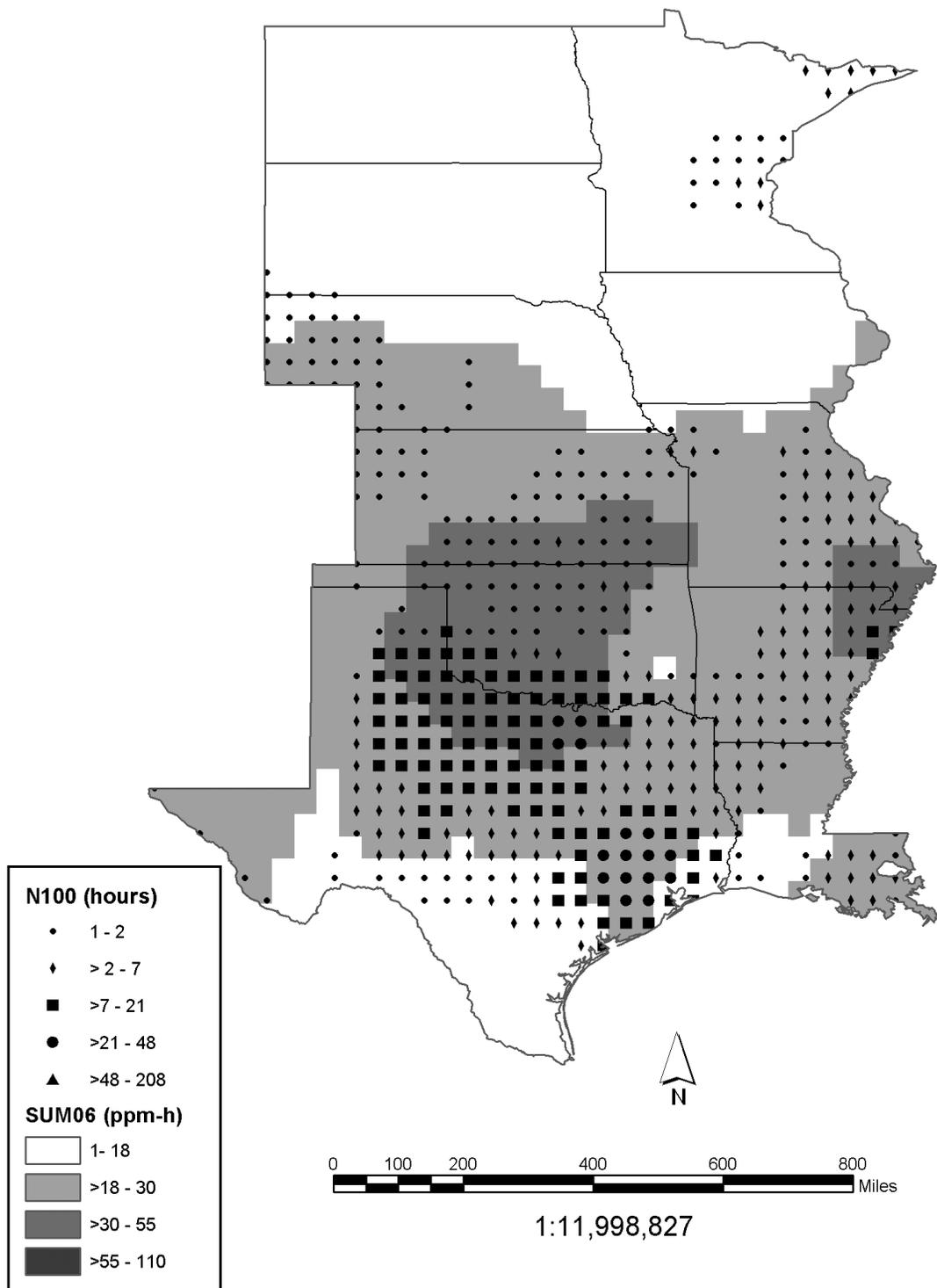


Figure AX3-16. Six-month (April to September) 24-h cumulative SUM06 exposure index with the number of hourly average concentrations ≥ 0.10 ppm (N100) occurring during 2001 for the central United States.

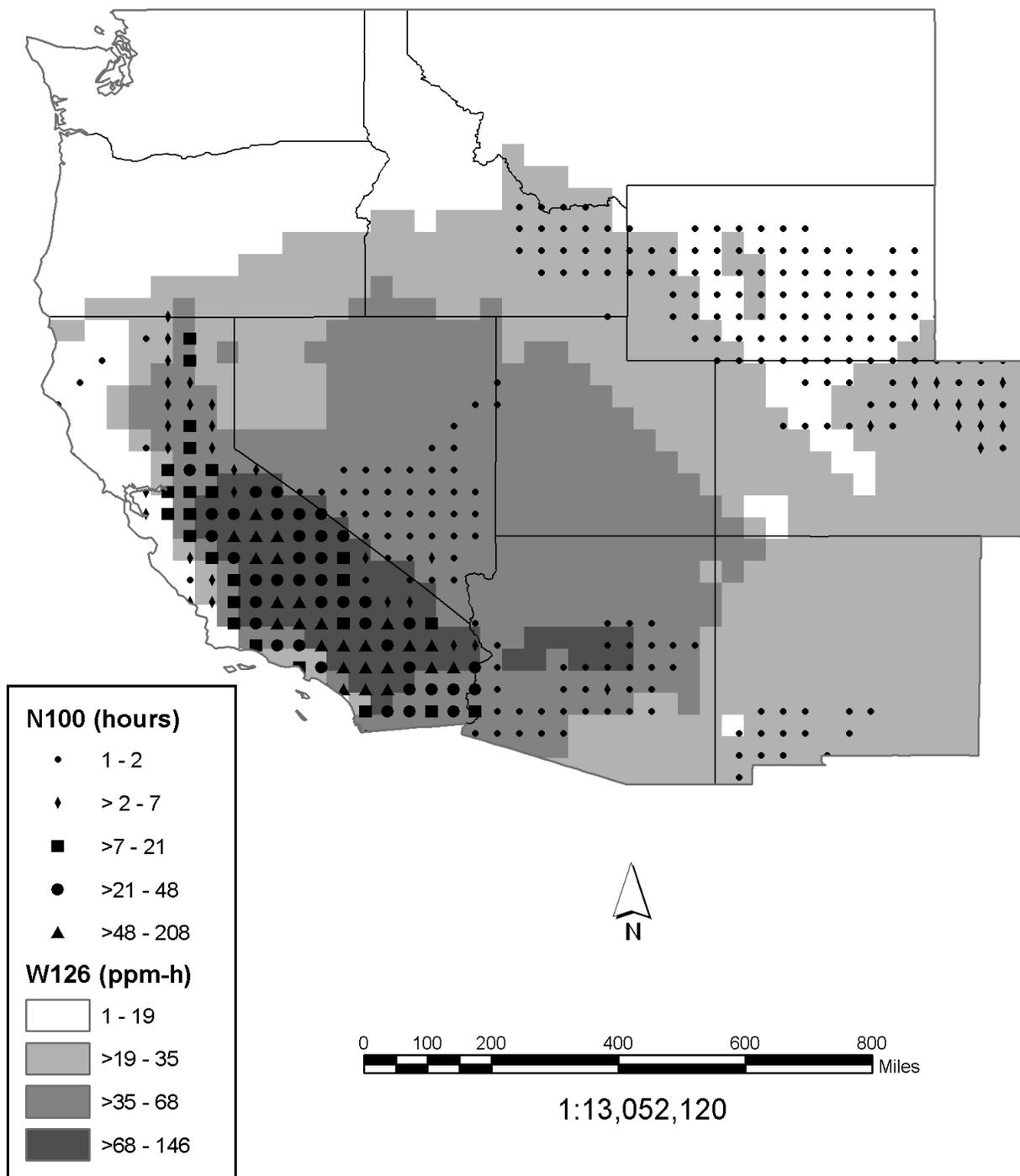


Figure AX3-17. Six-month (April to September) 24-h cumulative W126 exposure index with the number of hourly average concentrations ≥ 0.10 ppm (N100) occurring during 2001 for the western United States.

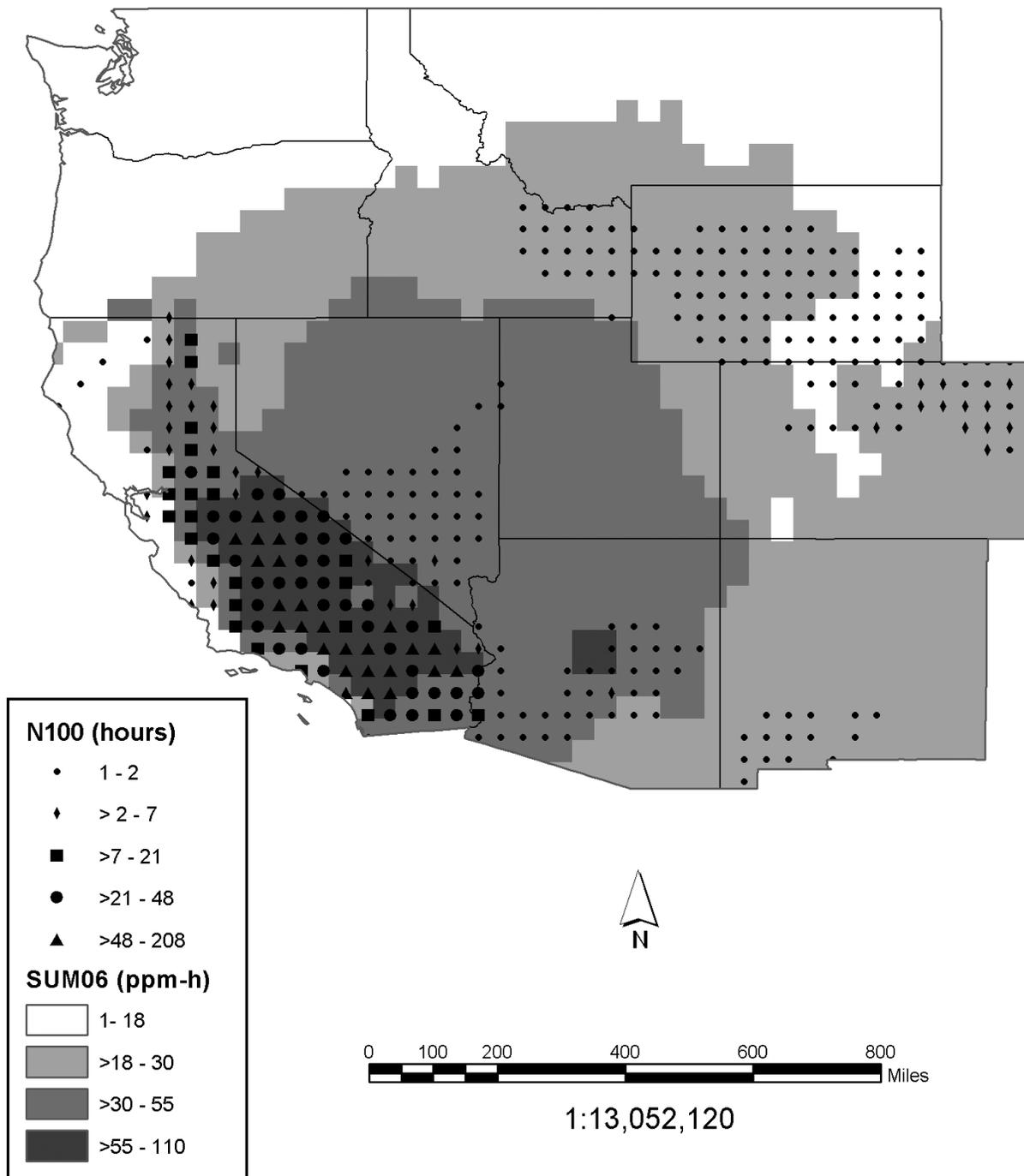


Figure AX3-18. Six-month (April to September) 24-h cumulative SUM06 exposure index with the number of hourly average concentrations ≥ 0.10 ppm (N100) occurring during 2001 for the western United States.

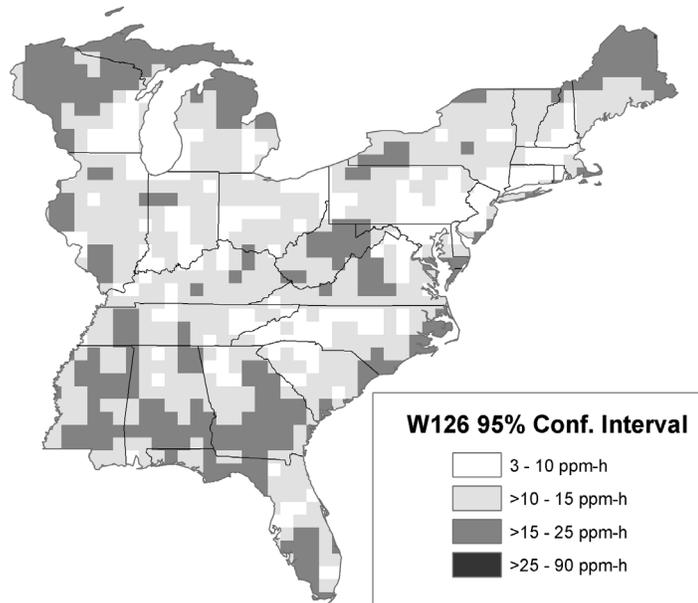


Figure AX3-19. The 95% confidence interval for the 6-month (April to September) 24-h cumulative W126 exposure index for 2001 for the eastern United States.

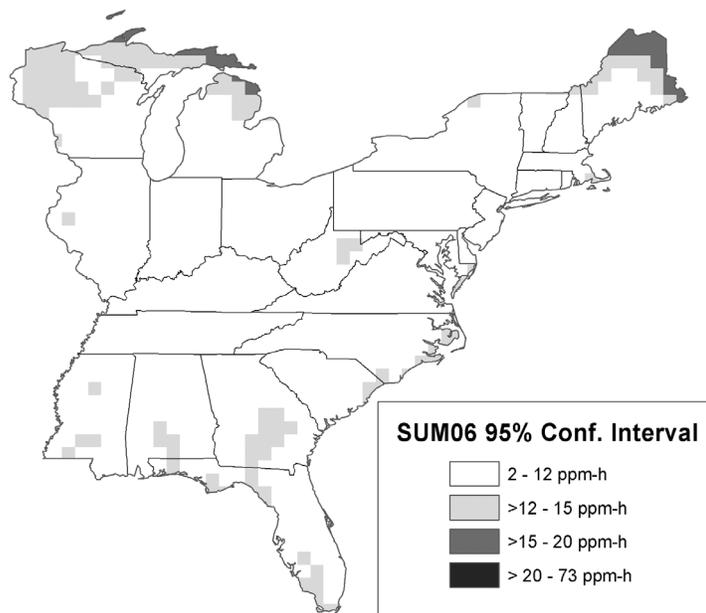


Figure AX3-20. The 95% confidence interval for the 6-month (April to September) 24-h cumulative SUM06 exposure index for 2001 for the eastern United States.

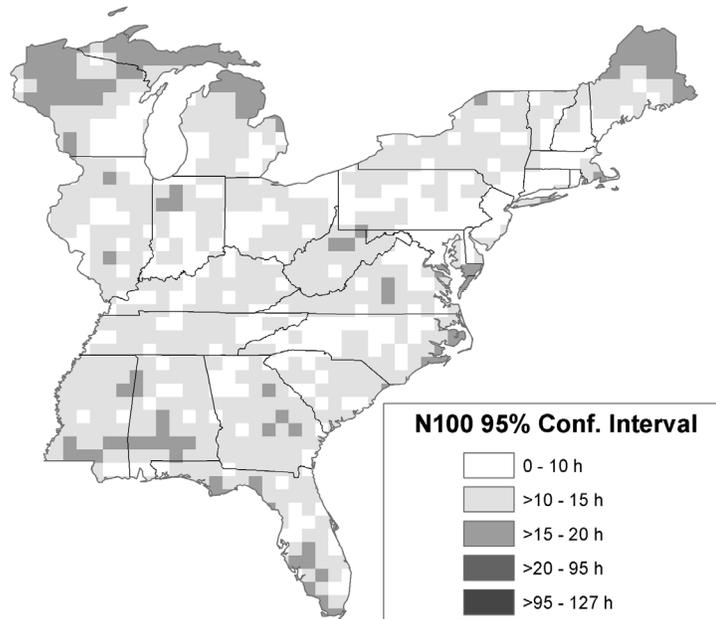


Figure AX3-21. The 95% confidence interval for the 6-month (April to September) 24-h cumulative N100 exposure index for 2001 for the eastern United States.

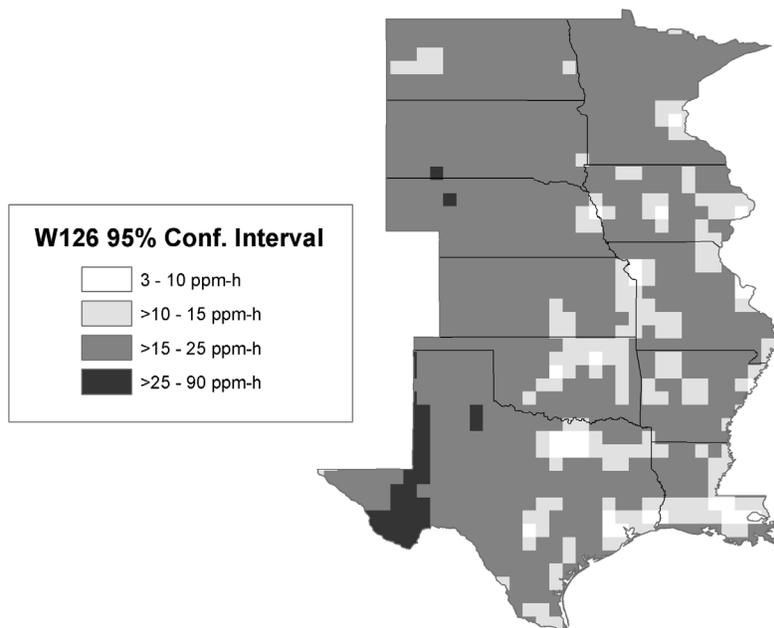


Figure AX3-22. The 95% confidence interval for the 6-month (April to September) 24-h cumulative W126 exposure index for 2001 for the central United States.

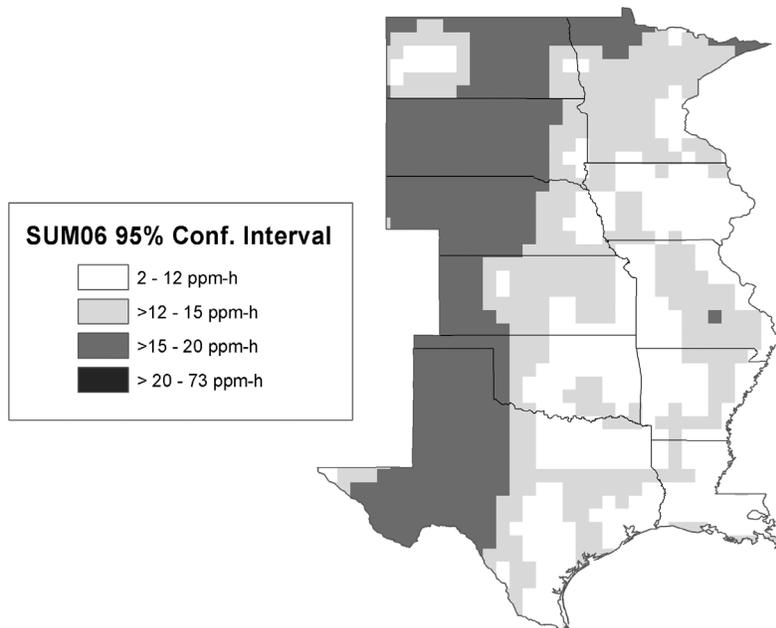


Figure AX3-23. The 95% confidence interval for the 6-month (April to September) 24-h cumulative SUM06 exposure index for 2001 for the central United States.

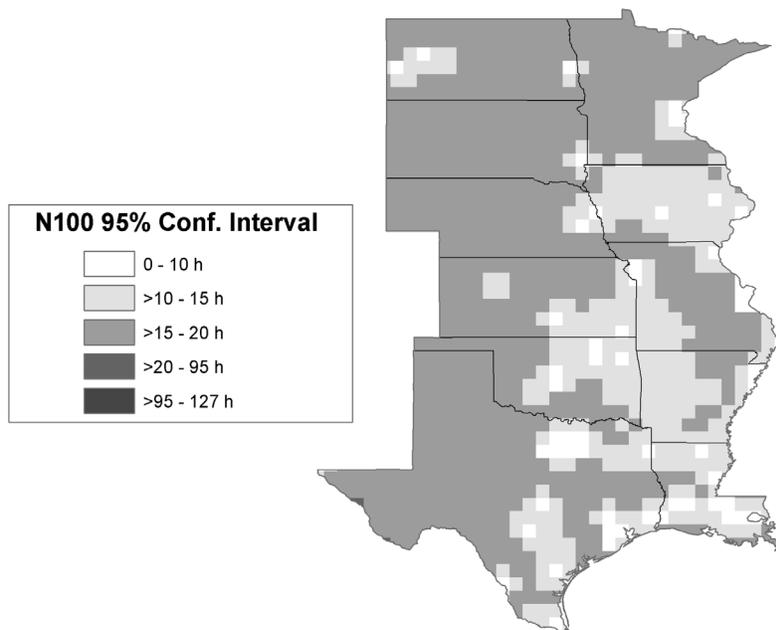


Figure AX3-24. The 95% confidence interval for the 6-month (April to September) 24-h cumulative N100 exposure index for 2001 for the central United States.

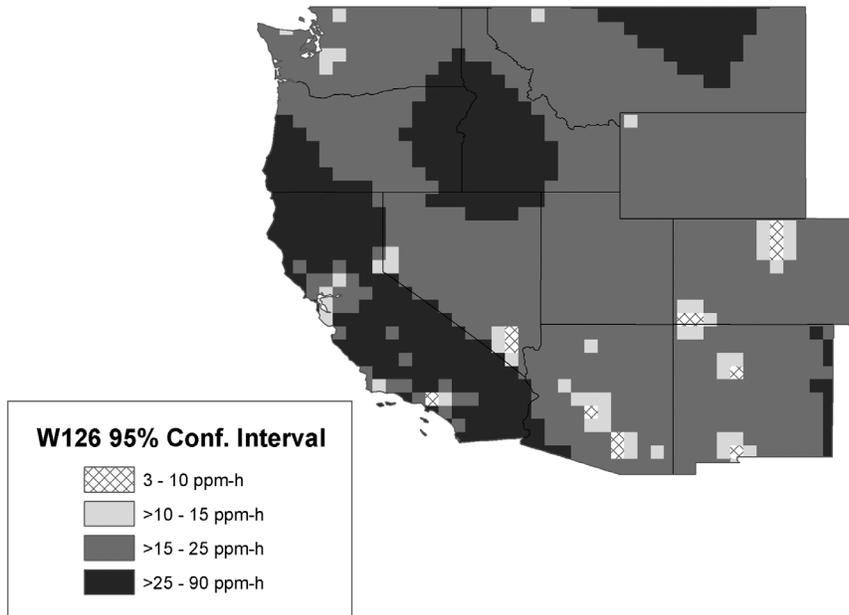


Figure AX3-25. The 95% confidence interval for the 6-month (April to September) 24-h cumulative W126 exposure index for 2001 for the western United States.

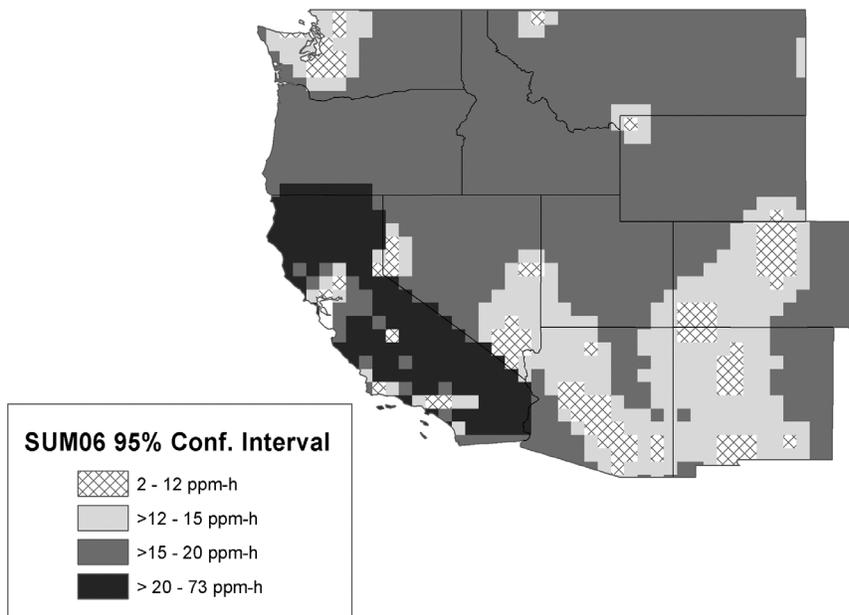


Figure AX3-26. The 95% confidence interval for the 6-month (April to September) 24-h cumulative SUM06 exposure index for 2001 for the western United States.

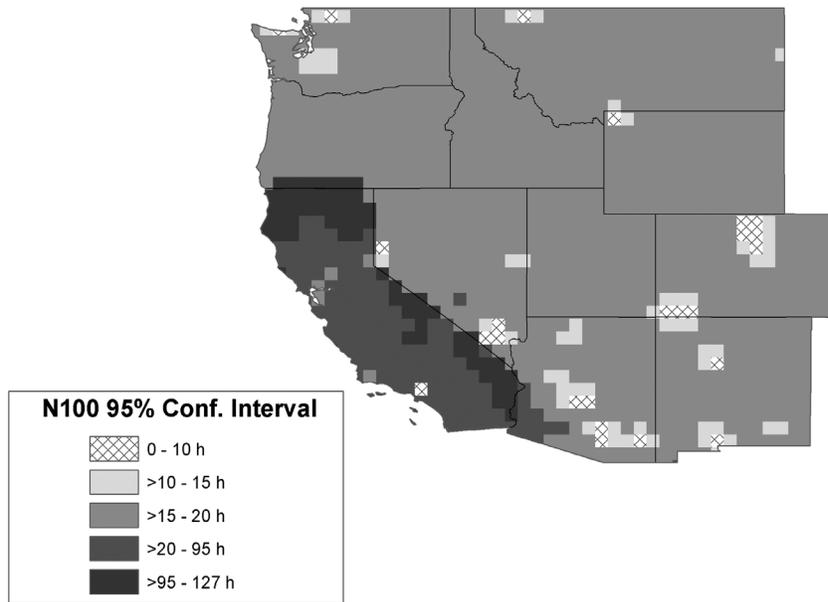


Figure AX3-27. The 95% confidence interval for the 6-month (April to September) 24-h cumulative N100 exposure index for 2001 for the western United States.

rate of deposition of O_3 . Mixing of O_3 from aloft can also lead to local increases in O_3 concentration.

The spatial variability in O_3 concentrations in 24 MSAs across the United States is characterized in this section. These areas were chosen to provide analyses to help guide risk assessment, to provide a general overview of the spatial variability of O_3 over different regions of the country, and also to provide insight into the spatial distribution of O_3 in cities where health outcome studies have been conducted. Statistical analyses of the human health effects of airborne pollutants based on aggregate population time-series data have often relied on ambient concentrations of pollutants measured at one or more central sites in a given metropolitan area. In the particular case of ground-level O_3 pollution, central-site monitoring has been justified as a regional measure of exposure partly on grounds that correlations between concentrations at neighboring sites measured over time are usually high (U.S. Environmental Protection Agency, 1996a). In analyses where multiple monitoring sites provide ambient O_3 concentrations, a

summary measure such as an averaged concentration has often been regarded as adequately characterizing the exposure distribution. Indeed, a number of studies have referred to multiple-site averaging as the method for estimating O₃ exposure (U.S. Environmental Protection Agency, 1996a). It is hoped that the analyses presented here will shed some light on the suitability of this practice. Earlier analyses were reported in the previous O₃ AQCD (U.S. Environmental Protection Agency, 1996a). The analyses presented there concluded that the extent of spatial homogeneity varies with the MSA under study. In particular, cities with low traffic densities that are located downwind of major sources of precursors are heavily influenced by long range transport and tend to show smaller spatial variability (e.g., New Haven, CT) than those source areas with high traffic densities located upwind (e.g., New York, NY).

Metrics for characterizing spatial variability include the use of Pearson correlation coefficients (*r*), values of the 90th percentile (*P*₉₀) of the absolute difference in concentrations, and coefficients of divergence (COD)¹. These methods of analysis follow those used for characterizing PM_{2.5} and PM_{10-2.5} concentrations in Pinto et al. (2004) and in the latest edition of the PM AQCD (U.S. Environmental Protection Agency, 2004a). Data were aggregated over local O₃ seasons, whose length varies from state to state. In several southwestern states, it lasts all year long. However, it typically lasts for 6 months in other areas, such as New England, the mid-Atlantic states, the Midwest, and the Northwest (see Table AX3-1).

Table AX3-5 shows the chosen urban areas, the range of 24-h average O₃ concentrations over the local O₃ season from 1999 to 2001, the range of intersite correlation coefficients, the range of *P*₉₀ differences in O₃ concentrations between site pairs, and the range in COD values. A COD of zero implies that values in both data sets are identical, and a COD of one indicates that the two data sets are uncorrelated with no identical values from either data set. In general, statistics were calculated for partial MSAs. This was done so as to obtain reasonable lower estimates of the spatial variability that is present, as opposed to examining the consolidated MSAs. In Boston, MA and New York, NY, this could not be readily done, and so statistics were

¹ The COD is defined as follows:

$$COD_{jk} = \sqrt{\frac{1}{p} \sum_{i=1}^p \left(\frac{x_{ij} - x_{ik}}{x_{ij} + x_{ik}} \right)^2} \quad (AX3-1)$$

where *x*_{*j*} and *x*_{*k*} represent the 24-h average PM_{2.5} concentration for day *i* at site *j* and site *k* and *p* is the number of observations.

Table AX3-5. Summary Statistics for Ozone (in ppm) Spatial Variability in Selected U.S. Urban Areas

Urban Area	Number of Sites	Minimum Mean Conc.	Maximum Mean Conc.	Minimum Corr. Coeff.	Maximum Corr. Coeff.	Minimum P ₉₀ ^a	Maximum P ₉₀	Minimum COD ^b	Maximum COD
Boston, MA	18	0.021	0.033	0.46	0.93	0.012	0.041	0.17	0.45
New York, NY	29	0.015	0.041	0.45	0.96	0.0080	0.044	0.17	0.55
Philadelphia, PA	12	0.020	0.041	0.79	0.95	0.011	0.036	0.23	0.46
Washington, DC	20	0.022	0.041	0.72	0.97	0.010	0.032	0.17	0.45
Charlotte, NC	8	0.031	0.043	0.48	0.95	0.012	0.038	0.17	0.32
Atlanta, GA	12	0.023	0.047	0.63	0.94	0.013	0.045	0.24	0.55
Tampa, FL	9	0.024	0.035	0.74	0.94	0.011	0.025	0.20	0.35
Detroit, MI	7	0.022	0.037	0.74	0.96	0.0090	0.027	0.19	0.36
Chicago, IL	24	0.015	0.039	0.38	0.96	0.0080	0.043	0.16	0.50
Milwaukee, WI	9	0.027	0.038	0.73	0.96	0.0090	0.025	0.18	0.33
St. Louis, MO	17	0.022	0.038	0.78	0.96	0.0090	0.031	0.15	0.41
Baton Rouge, LA	7	0.018	0.031	0.81	0.95	0.0090	0.029	0.23	0.41
Dallas, TX	10	0.028	0.043	0.67	0.95	0.011	0.033	0.16	0.36
Houston, TX	13	0.016	0.036	0.73	0.96	0.0090	0.027	0.20	0.38
Denver, CO	8	0.022	0.044	0.60	0.92	0.013	0.044	0.16	0.46
El Paso, TX	4	0.022	0.032	0.81	0.94	0.012	0.023	0.24	0.31
Salt Lake City, UT	8	0.029	0.048	0.52	0.92	0.012	0.043	0.13	0.51
Phoenix, AZ	15	0.021	0.058	0.29	0.95	0.011	0.057	0.15	0.61
Seattle, WA	5	0.015	0.038	0.63	0.94	0.0080	0.024	0.16	0.46
Portland, OR	5	0.015	0.036	0.73	0.91	0.011	0.025	0.20	0.50
Fresno, CA	6	0.030	0.047	0.90	0.97	0.0090	0.027	0.17	0.40
Bakersfield, CA	8	0.028	0.047	0.23	0.96	0.013	0.052	0.20	0.58
Los Angeles, CA	14	0.010	0.042	0.42	0.95	0.010	0.053	0.22	0.59
Riverside, CA	18	0.018	0.054	0.38	0.95	0.013	0.057	0.15	0.64

^aP90 = 90th percentile absolute difference in concentrations.

^bCOD = coefficient of divergence for different site pairs.

calculated for the consolidated MSAs. More detailed calculations for a subset of nine MSAs are given in Figures AX3-28 through AX3-36.

As can be seen, there are no clearly discernible regional trends in the ranges of parameters shown. Additional urban areas would need to be examined to discern broadscale patterns. The data indicate considerable variability in the concentration fields. Mean O₃ concentrations vary within individual urban areas from factors of 1.4 to 4.0.

The highest annual mean O₃ concentration (0.058 ppm) is found in the Phoenix, AZ MSA at a site which is located in the mountains well downwind of the main urban area. The lowest annual mean O₃ concentration (0.010 ppm) was found in Lynwood in the urban core of the Los Angeles MSA. CO and NO_x monitors at this site recorded the highest concentrations in California, indicating that titration of O₃ by NO freshly emitted from tail pipes of motor vehicles is responsible for the low O₃ values that are found. Ratios of highest to lowest mean O₃ concentrations in these two MSAs are among the highest shown in Table AX3-5. Both of these MSAs are characterized by sunny, warm climates; sources of precursors that are associated with O₃ titration to varying degrees in their urban centers; and with maximum O₃ found well downwind of the urban centers. Intersite correlation coefficients show mixed patterns, i.e., in some urban areas all pairs of sites are moderately to highly correlated, while other areas show a very large range of values. As may be expected, those areas which show smaller ratios of seasonal mean concentrations also exhibit a smaller range of intersite correlation coefficients. Within the examined urban areas, P₉₀ values were evenly distributed between all site pairs considered. The CODs indicate variability among site pairs. However, there are a number of cases where sites in an urban area may be moderately to highly correlated but showed substantial differences in absolute concentrations. In many cases, values for P₉₀ equaled or exceeded seasonal mean O₃ concentrations. This was reflected in both values for P₉₀ and for the COD.

It is instructive to compare the metrics for spatial variability shown in Table AX3-5 to those calculated for PM_{2.5} and PM_{10-2.5} in the PM AQCD (U.S. Environmental Protection Agency, 2004a). The values for concentrations and concentration differences are unique to the individual species, but the intersite correlation coefficients and the COD values can be directly compared.

Charlotte - Gastonia - Rock Hill, NC - SC MSA

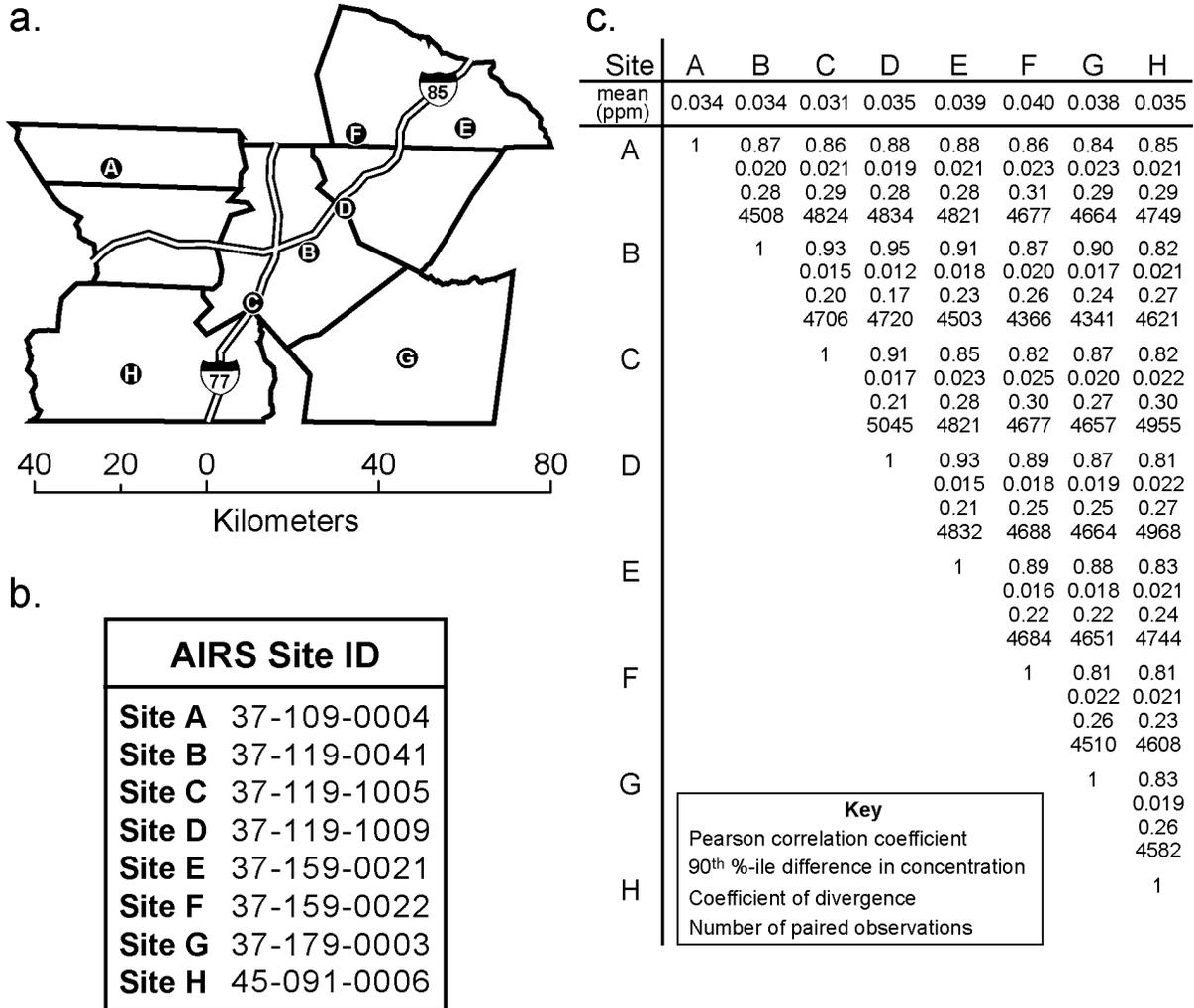


Figure AX3-28. Locations of O₃ sampling sites (a) by AQS ID# (b) and intersite correlation statistics (c) for the Charlotte, NC-Gastonia-Rock Hill, SC MSA. The mean hourly measured O₃ concentration at each site is given above its letter code. For each data pair, the Pearson correlation coefficient, 90th percentile difference in absolute concentrations, the coefficient of divergence, and number of observations are given.

Baton Rouge, LA MSA

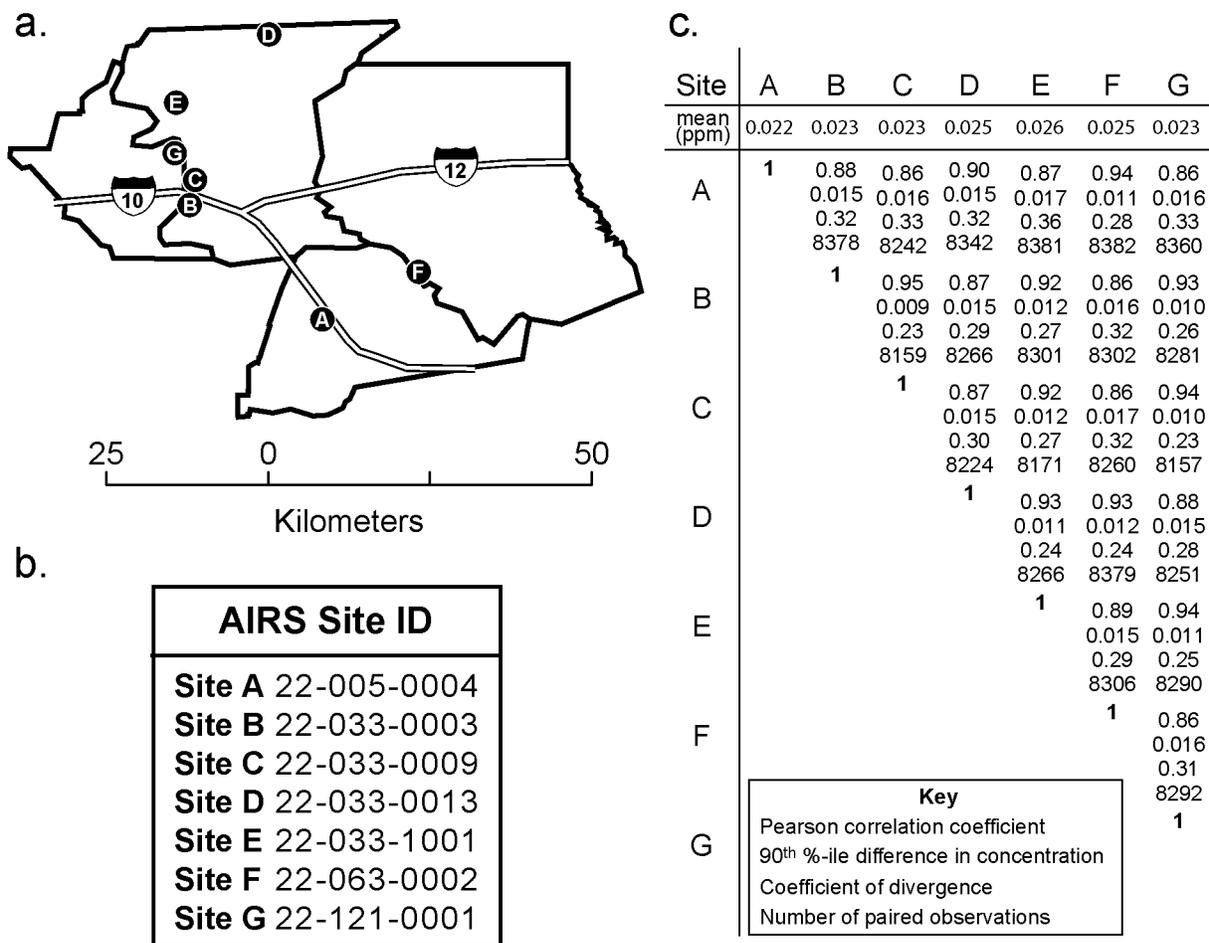


Figure AX3-29. Locations of O₃ sampling sites (a) by AQS ID# (b) and intersite correlation statistics (c) for the Baton Rouge, LA MSA. The mean hourly measured O₃ concentration at each site is given above its letter code. For each data pair, the Pearson correlation coefficient, 90th percentile difference in absolute concentrations, the coefficient of divergence, and number of observations are given.

Detroit - Ann Arbor - Flint, MI CMSA

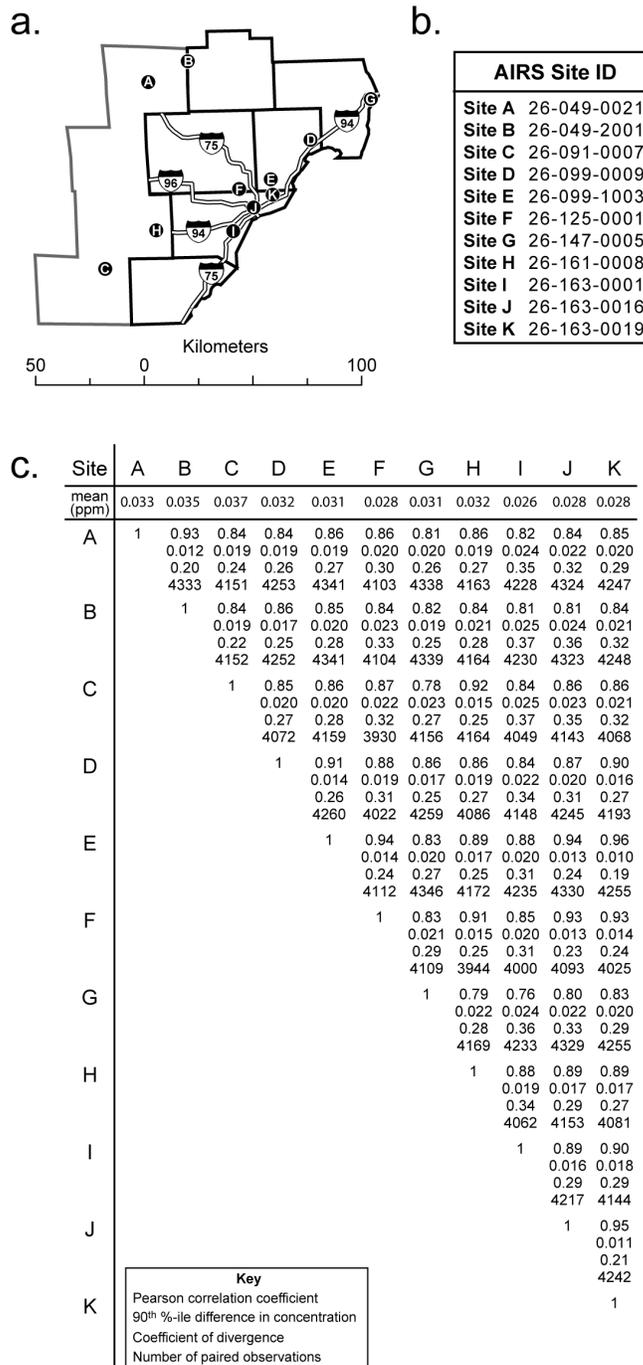


Figure AX3-30. Locations of O₃ sampling sites (a) by AQS ID# (b) and intersite correlation statistics (c) for the Detroit-Ann Arbor-Flint, MI CMSA. The mean hourly measured O₃ concentration at each site is given above its letter code. For each data pair, the Pearson correlation coefficient, 90th percentile difference in absolute concentrations, the coefficient of divergence, and number of observations are given.

St. Louis, MO - IL CMSA

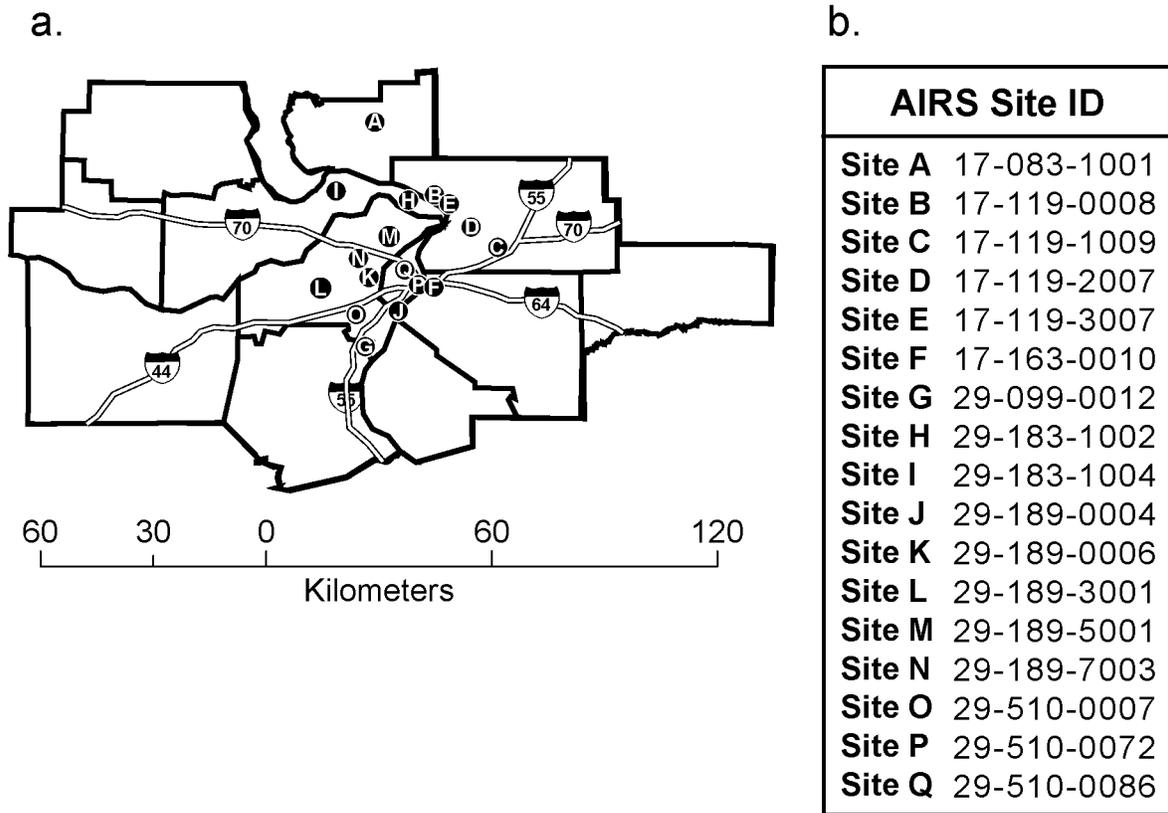


Figure AX3-31. Locations of O₃ sampling sites (a) by AQS ID# (b) and intersite correlation statistics (c) for the St. Louis, MO-IL MSA. The mean hourly measured O₃ concentration at each site is given above its letter code. For each data pair, the Pearson correlation coefficient, 90th percentile difference in absolute concentrations, the coefficient of divergence, and number of observations are given.

St. Louis, MO - IL CMSA

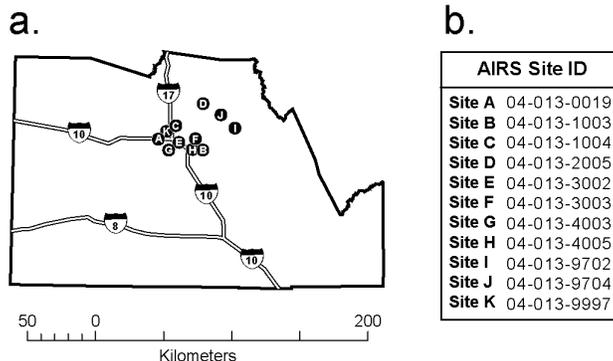
C.

Site	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
mean (ppm)	0.037	0.035	0.031	0.029	0.031	0.028	0.035	0.034	0.035	0.032	0.031	0.025	0.030	0.030	0.028	0.024	0.030
A	1	0.88 0.015 0.19 5055	0.84 0.020 0.26 4935	0.84 0.022 0.29 5032	0.85 0.021 0.29 5021	0.83 0.025 0.38 5045	0.81 0.021 0.28 5049	0.89 0.016 0.21 5052	0.91 0.014 0.20 4735	0.82 0.022 0.28 5077	0.84 0.021 0.29 5073	0.80 0.029 0.37 5075	0.86 0.022 0.31 5077	0.85 0.021 0.32 5071	0.80 0.026 0.36 5035	0.82 0.027 0.40 5034	0.85 0.022 0.34 5065
B		1	0.87 0.017 0.26 4963	0.90 0.016 0.26 5061	0.93 0.013 0.23 5048	0.86 0.021 0.34 5077	0.82 0.019 0.28 5078	0.93 0.012 0.18 5082	0.90 0.014 0.19 4766	0.83 0.020 0.27 5106	0.85 0.018 0.27 5102	0.84 0.024 0.34 5105	0.87 0.015 0.26 5106	0.84 0.020 0.30 5101	0.84 0.022 0.33 5064	0.87 0.022 0.35 5064	0.88 0.018 0.27 5094
C			1	0.92 0.012 0.24 4941	0.88 0.015 0.26 4933	0.92 0.014 0.29 4952	0.87 0.018 0.26 4958	0.90 0.015 0.23 4963	0.88 0.016 0.24 4680	0.88 0.016 0.25 4985	0.87 0.016 0.26 4981	0.85 0.020 0.32 4983	0.90 0.015 0.26 4985	0.88 0.016 0.27 4979	0.86 0.018 0.30 4943	0.88 0.017 0.32 4942	0.91 0.014 0.27 4973
D				1	0.93 0.012 0.22 5024	0.90 0.014 0.29 5050	0.85 0.019 0.26 5055	0.91 0.016 0.23 5058	0.88 0.017 0.25 4742	0.86 0.018 0.27 5083	0.84 0.018 0.27 5079	0.84 0.020 0.30 5081	0.87 0.016 0.27 5085	0.85 0.017 0.28 5077	0.86 0.017 0.28 5042	0.88 0.016 0.29 5040	0.90 0.015 0.27 5073
E					1	0.90 0.015 0.29 5039	0.84 0.019 0.22 5045	0.93 0.013 0.23 5046	0.90 0.015 0.27 4728	0.85 0.018 0.29 5069	0.84 0.018 0.29 5065	0.88 0.018 0.32 5067	0.88 0.016 0.29 5069	0.86 0.017 0.29 5065	0.88 0.016 0.29 5027	0.89 0.017 0.30 5027	0.90 0.015 0.28 5057
F						1	0.90 0.018 0.28 5067	0.90 0.018 0.32 5070	0.89 0.016 0.32 4754	0.91 0.017 0.29 5095	0.88 0.017 0.30 5091	0.90 0.016 0.32 5093	0.92 0.014 0.27 5095	0.91 0.015 0.27 5091	0.92 0.013 0.26 5053	0.92 0.015 0.28 5053	0.94 0.012 0.23 5083
G							1	0.87 0.017 0.23 5075	0.86 0.017 0.24 4756	0.95 0.012 0.22 5100	0.91 0.015 0.33 5096	0.88 0.022 0.27 5098	0.88 0.018 0.26 5100	0.88 0.017 0.26 5094	0.89 0.020 0.29 5058	0.86 0.023 0.35 5057	0.91 0.016 0.26 5088
H								1	0.94 0.011 0.15 4759	0.87 0.017 0.24 5103	0.88 0.016 0.32 5099	0.87 0.022 0.26 5101	0.92 0.015 0.27 5103	0.90 0.015 0.27 5097	0.86 0.020 0.31 5062	0.87 0.022 0.35 5060	0.91 0.015 0.29 5091
I									1	0.86 0.017 0.28 4784	0.90 0.015 0.25 4782	0.88 0.022 0.27 4782	0.91 0.016 0.28 4784	0.90 0.016 0.28 4778	0.85 0.021 0.32 4742	0.86 0.022 0.35 4743	0.90 0.017 0.30 4773
J										1	0.92 0.013 0.26 5124	0.91 0.018 0.30 5126	0.91 0.015 0.24 5128	0.91 0.014 0.23 5122	0.90 0.016 0.25 5086	0.88 0.019 0.30 5085	0.93 0.013 0.22 5116
K											1	0.87 0.019 0.29 5122	0.90 0.015 0.23 5124	0.91 0.014 0.23 5118	0.86 0.018 0.28 5082	0.87 0.020 0.30 5081	0.90 0.015 0.25 5112
L												1	0.88 0.018 0.28 5126	0.90 0.017 0.28 5120	0.90 0.015 0.27 5084	0.88 0.016 0.27 5083	0.92 0.016 0.26 5114
M													1	0.96 0.009 0.18 5122	0.87 0.018 0.26 5086	0.87 0.019 0.29 5085	0.95 0.011 0.21 5116
N														1	0.87 0.017 0.26 5080	0.86 0.019 0.31 5079	0.94 0.011 0.20 5110
O															1	0.92 0.014 0.26 5045	0.92 0.014 0.25 5074
P																1	0.92 0.016 0.28 5074
Q																	1

Key	
Pearson correlation coefficient	
90 th %-ile difference in concentration	
Coefficient of divergence	
Number of paired observations	

Figure AX3-31 (cont'd).

Phoenix - Mesa, AZ MSA



c.

Site	A	B	C	D	E	F	G	H	I	J	K
mean (ppm)	0.021	0.025	0.028	0.046	0.021	0.024	0.024	0.028	0.038	0.041	0.024
A	1	0.87 0.017 0.38 7580	0.91 0.018 0.35 8031	0.59 0.046 0.59 7991	0.93 0.012 0.31 7925	0.89 0.016 0.35 7593	0.91 0.014 0.32 7901	0.90 0.017 0.34 6651	0.78 0.034 0.54 8020	0.78 0.037 0.55 8081	0.95 0.011 0.27 7920
B		1	0.90 0.018 0.25 7962	0.69 0.038 0.46 7912	0.89 0.016 0.41 7872	0.92 0.013 0.33 7502	0.89 0.015 0.30 7826	0.93 0.014 0.22 6768	0.83 0.027 0.38 7895	0.85 0.029 0.41 8011	0.90 0.016 0.32 7858
C			1	0.62 0.040 0.47 8377	0.92 0.019 0.34 8326	0.92 0.016 0.28 7965	0.91 0.017 0.28 8273	0.92 0.016 0.24 7022	0.82 0.027 0.39 8367	0.82 0.030 0.41 8468	0.95 0.013 0.28 8319
D				1	0.58 0.047 0.61 8286	0.63 0.043 0.56 7925	0.58 0.042 0.51 8231	0.61 0.043 0.49 6992	0.67 0.025 0.23 8332	0.79 0.018 0.16 8429	0.58 0.045 0.56 8281
E					1	0.92 0.014 0.35 7894	0.94 0.012 0.35 8180	0.93 0.015 0.37 6938	0.82 0.033 0.57 8279	0.80 0.037 0.58 8369	0.95 0.012 0.31 8238
F						1	0.90 0.015 0.35 7863	0.94 0.012 0.30 6599	0.82 0.030 0.50 7913	0.84 0.033 0.52 8009	0.93 0.013 0.31 7846
G							1	0.93 0.014 0.25 6882	0.81 0.029 0.44 8225	0.80 0.033 0.46 8322	0.93 0.013 0.29 8166
H								1	0.82 0.029 0.41 6963	0.83 0.032 0.43 7078	0.93 0.013 0.25 6912
I									1	0.86 0.016 0.17 8411	0.81 0.031 0.50 8265
J										1	0.80 0.035 0.51 8367
K											1

Key

Pearson correlation coefficient

90th %-ile difference in concentration

Coefficient of divergence

Number of paired observations

Figure AX3-32. Locations of O₃ sampling sites (a) by AQS ID# (b) and intersite correlation statistics (c) for the Phoenix-Mesa, AZ MSA. The mean hourly measured O₃ concentration at each site is given above its letter code. For each data pair, the Pearson correlation coefficient, 90th percentile difference in absolute concentrations, the coefficient of divergence, and number of observations are given.

Fresno, CA MSA

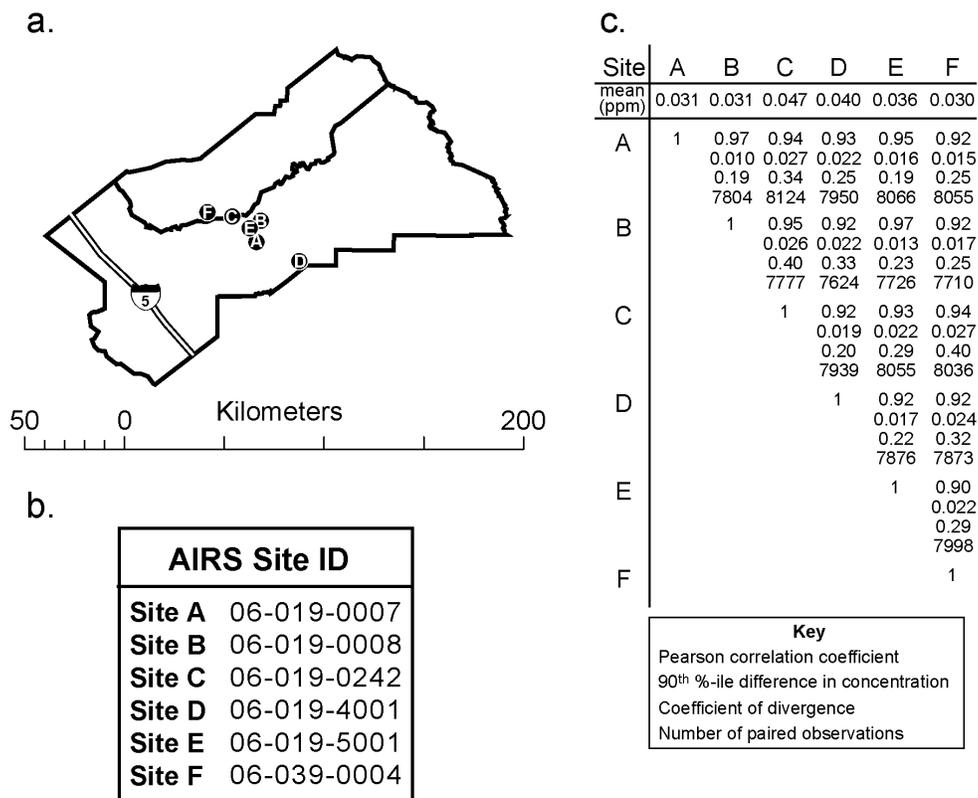


Figure AX3-33. Locations of O₃ sampling sites (a) by AQS ID# (b) and intersite correlation statistics (c) for the Fresno, CA MSA. The mean hourly measured O₃ concentration at each site is given above its letter code. For each data pair, the Pearson correlation coefficient, 90th percentile difference in absolute concentrations, the coefficient of divergence, and number of observations are given.

In general, the variability in O₃ concentrations is larger than for PM_{2.5} concentrations and comparable to that obtained for PM_{10-2.5}. Intersite correlation coefficients in some areas (e.g., Philadelphia, PA; Atlanta, GA; Portland, OR) can be very similar for both PM_{2.5} and for O₃. However, there is much greater variability in the concentration fields of O₃ as evidenced by the much higher COD values. Indeed, COD values are higher for O₃ than for PM_{2.5} in each of the urban areas examined. In all of the urban areas examined for O₃ some site pairs are always very highly correlated with each other (i.e., $r > 0.9$) as seen for PM_{2.5}. These sites also show less

Bakersfield, CA MSA

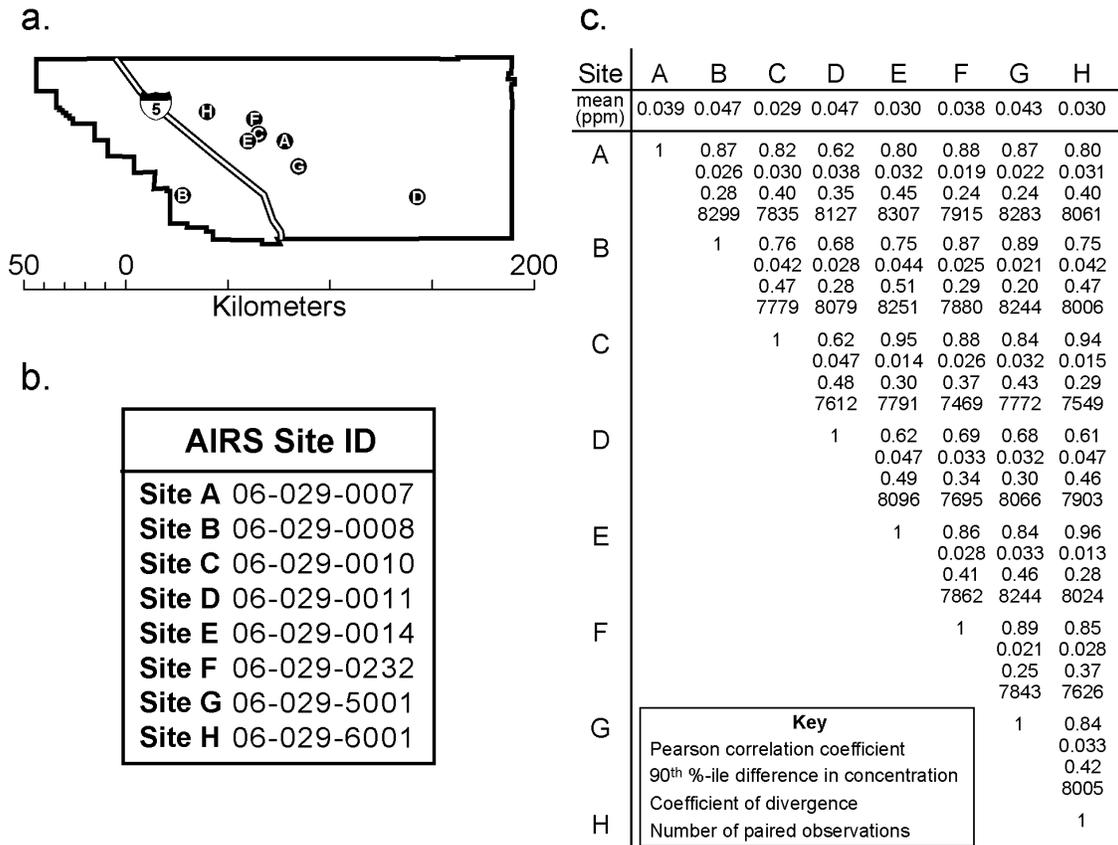


Figure AX3-34. Locations of O₃ sampling sites (a) by AQS ID# (b) and intersite correlation statistics (c) for the Bakersfield, CA MSA. The mean hourly measured O₃ concentration at each site is given above its letter code. For each data pair, the Pearson correlation coefficient, 90th percentile difference in absolute concentrations, the coefficient of divergence, and number of observations are given.

variability in concentration and are probably influenced most strongly by regional production mechanisms.

Los Angeles - Orange County, CA CMSA

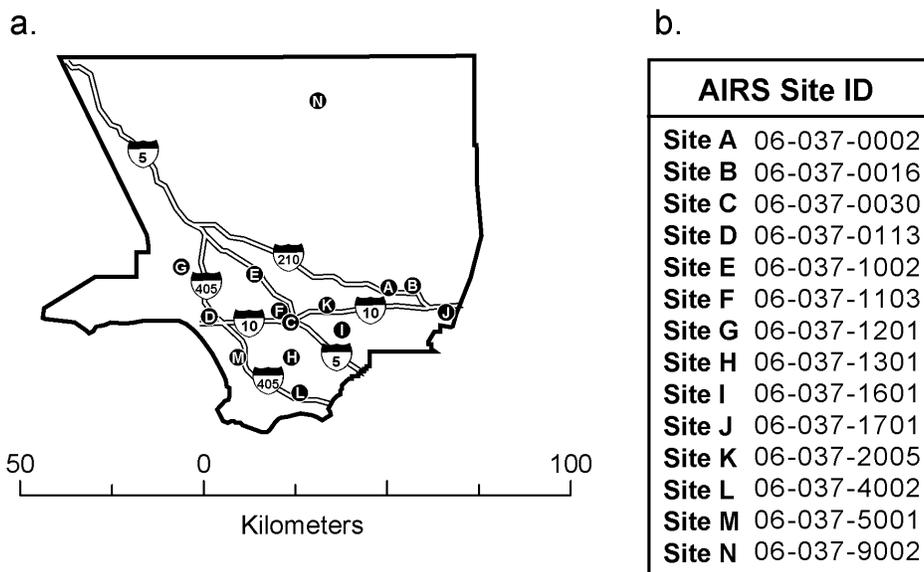


Figure AX3-35. Locations of O₃ sampling sites (a) by AQS ID# (b) and intersite correlation statistics (c) for the Los Angeles-Orange County, CA CMSA. The mean hourly measured O₃ concentration at each site is given above its letter code. For each data pair, the Pearson correlation coefficient, 90th percentile difference in absolute concentrations, the coefficient of divergence, and number of observations are given.

Los Angeles - Orange County, CA CMSA

C.

Site	A	B	C	D	E	F	G	H	I	J	K	L	M	N
mean (ppm)	0.021	0.029	0.021	0.020	0.018	0.019	0.021	0.013	0.016	0.013	0.021	0.022	0.027	0.042
A	1	0.95 0.017 0.32 8378	0.87 0.020 0.41 6723	0.64 0.028 0.38 8387	0.88 0.018 0.36 8202	0.85 0.020 0.37 8292	0.82 0.021 0.44 8364	0.72 0.029 0.41 8362	0.89 0.019 0.46 8381	0.91 0.022 0.33 8386	0.91 0.015 0.44 8384	0.61 0.029 0.45 8379	0.55 0.035 0.46 8341	0.58 0.048 0.47 6321
B		1	0.82 0.029 0.36 6722	0.60 0.034 0.44 8386	0.86 0.028 0.45 8201	0.80 0.029 0.42 8291	0.80 0.027 0.53 8363	0.67 0.038 0.52 8361	0.84 0.030 0.59 8380	0.88 0.032 0.39 8385	0.87 0.024 0.31 8383	0.57 0.033 0.47 8378	0.53 0.034 0.37 8340	0.56 0.042 0.45 6321
C			1	0.75 0.021 0.32 6731	0.88 0.018 0.22 6546	0.95 0.010 0.29 6636	0.84 0.019 0.37 6708	0.83 0.020 0.37 6729	0.91 0.013 0.49 6725	0.85 0.020 0.24 6730	0.90 0.017 0.24 6728	0.72 0.022 0.31 6723	0.68 0.030 0.37 6686	0.61 0.048 0.45 4998
D				1	0.76 0.023 0.31 8210	0.82 0.018 0.31 8300	0.73 0.023 0.36 8372	0.77 0.022 0.43 8370	0.77 0.027 0.35 8389	0.69 0.024 0.34 8394	0.73 0.021 0.34 8392	0.75 0.021 0.30 8387	0.81 0.025 0.30 8349	0.62 0.046 0.40 6321
E					1	0.90 0.014 0.29 8184	0.86 0.019 0.35 8187	0.79 0.023 0.33 8185	0.90 0.015 0.38 8204	0.87 0.019 0.28 8210	0.91 0.014 0.37 8207	0.67 0.027 0.37 8202	0.66 0.034 0.37 8164	0.59 0.050 0.45 6322
F						1	0.85 0.018 0.31 8277	0.85 0.019 0.36 8275	0.93 0.012 0.42 8294	0.86 0.019 0.26 8300	0.91 0.015 0.26 8297	0.76 0.021 0.35 8292	0.74 0.029 0.40 8254	0.66 0.047 0.50 6325
G							1	0.74 0.026 0.36 8347	0.86 0.020 0.35 8366	0.84 0.023 0.45 8371	0.86 0.017 0.31 8369	0.67 0.026 0.36 8364	0.68 0.028 0.36 8349	0.70 0.042 0.43 6326
H								1	0.86 0.017 0.26 8364	0.74 0.018 0.37 8369	0.80 0.025 0.38 8367	0.84 0.021 0.35 8362	0.73 0.033 0.43 8324	0.61 0.053 0.51 6299
I									1	0.89 0.016 0.31 8388	0.93 0.015 0.30 8386	0.77 0.022 0.34 8381	0.71 0.032 0.39 8343	0.66 0.048 0.48 6321
J										1	0.90 0.021 0.43 8391	0.67 0.028 0.46 8386	0.62 0.037 0.50 8348	0.63 0.053 0.56 6323
K											1	0.71 0.025 0.37 8384	0.65 0.031 0.40 8346	0.65 0.045 0.46 6321
L												1	0.74 0.025 0.33 8341	0.62 0.043 0.42 6321
M													1	0.63 0.038 0.36 6299
N														1

Key	
Pearson correlation coefficient	
90 th %-ile difference in concentration	
Coefficient of divergence	
Number of paired observations	

Figure AX3-35 (cont'd).

Riverside - Orange County, CS CMSA

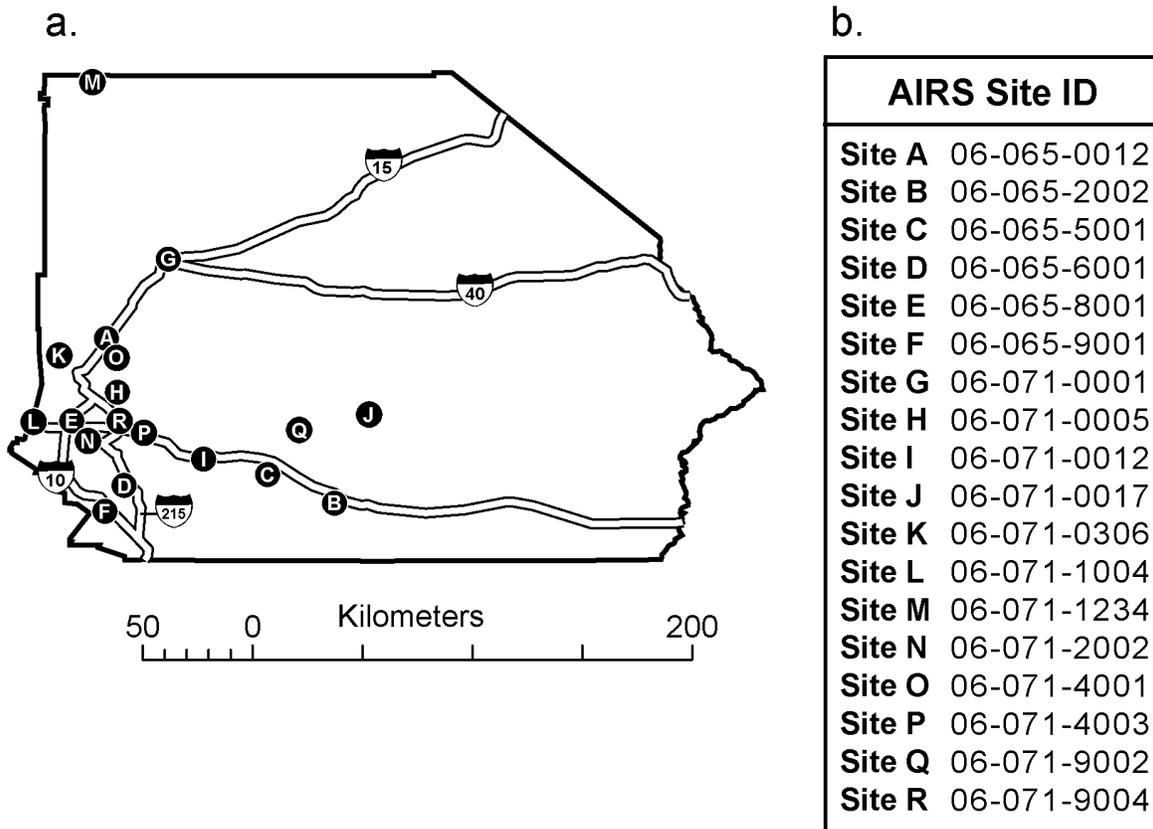


Figure AX3-36. Locations of O₃ sampling sites (a) by AQS ID# (b) and intersite correlation statistics (c) for the Riverside-Orange County, CA CMSA. The mean hourly measured O₃ concentration at each site is given above its letter code. For each data pair, the Pearson correlation coefficient, 90th percentile difference in absolute concentrations, the coefficient of divergence, and number of observations are given.

Riverside - Orange County, CS CMSA

C.

Site	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	
mean (ppm)	0.037	0.035	0.042	0.033	0.026	0.036	0.030	0.047	0.048	0.044	0.032	0.022	0.038	0.020	0.037	0.032	0.040	0.026	
A	1	0.71	0.77	0.84	0.79	0.81	0.76	0.70	0.69	0.69	0.75	0.76	0.55	0.75	0.76	0.81	0.53	0.80	
		0.032	0.030	0.026	0.034	0.027	0.031	0.038	0.037	0.034	0.031	0.037	0.036	0.040	0.029	0.028	0.037	0.033	
		0.33	0.35	0.34	0.42	0.33	0.38	0.38	0.39	0.37	0.36	0.47	0.38	0.54	0.35	0.35	0.38	0.41	
		8397	8392	8394	8386	8035	7741	8393	8051	7844	7498	8385	7815	8394	7997	8391	7887	8364	
B		1	0.85	0.69	0.64	0.66	0.75	0.62	0.64	0.81	0.72	0.60	0.65	0.56	0.71	0.61	0.52	0.61	
			0.023	0.035	0.039	0.036	0.031	0.041	0.038	0.029	0.031	0.043	0.031	0.046	0.031	0.038	0.035	0.040	
			0.25	0.34	0.42	0.33	0.33	0.33	0.34	0.30	0.34	0.46	0.31	0.51	0.31	0.37	0.33	0.42	
			8394	8395	8388	8040	7919	8393	8233	8017	7678	8389	7990	8395	8179	8392	8059	8369	
C			1	0.73	0.66	0.69	0.74	0.67	0.72	0.81	0.73	0.61	0.67	0.59	0.75	0.65	0.65	0.65	
				0.037	0.044	0.036	0.035	0.036	0.030	0.025	0.034	0.049	0.030	0.052	0.030	0.039	0.031	0.045	
				0.38	0.47	0.35	0.39	0.32	0.32	0.28	0.38	0.52	0.30	0.56	0.32	0.40	0.33	0.46	
				8393	8385	8034	7752	8391	8059	7852	7506	8384	7823	8393	8005	8390	7896	8362	
D				1	0.90	0.91	0.79	0.70	0.68	0.67	0.77	0.87	0.57	0.84	0.75	0.87	0.47	0.89	
					0.023	0.019	0.029	0.041	0.041	0.039	0.031	0.028	0.039	0.032	0.033	0.023	0.040	0.024	
					0.33	0.25	0.34	0.41	0.45	0.42	0.37	0.42	0.41	0.51	0.38	0.33	0.44	0.35	
					8387	8036	7742	8393	8049	7842	7496	8386	7813	8395	7995	8392	7885	8364	
E					1	0.88	0.76	0.66	0.63	0.60	0.74	0.92	0.50	0.93	0.69	0.87	0.42	0.94	
						0.026	0.031	0.048	0.046	0.045	0.032	0.017	0.042	0.018	0.037	0.025	0.042	0.015	
						0.36	0.38	0.51	0.54	0.51	0.42	0.34	0.50	0.43	0.46	0.39	0.52	0.36	
						8028	7735	8385	8042	7835	7490	8378	7806	8387	7988	8384	7878	8356	
F						1	0.76	0.64	0.62	0.63	0.74	0.83	0.54	0.81	0.70	0.82	0.44	0.85	
							0.031	0.042	0.039	0.037	0.031	0.032	0.037	0.034	0.032	0.026	0.039	0.028	
							0.33	0.37	0.39	0.36	0.37	0.43	0.36	0.53	0.35	0.31	0.38	0.35	
							7402	8034	7709	7487	7171	8027	7610	8036	7640	8033	7545	8010	
G							1	0.68	0.68	0.75	0.85	0.72	0.68	0.68	0.78	0.72	0.46	0.73	
								0.042	0.041	0.035	0.022	0.035	0.033	0.038	0.029	0.032	0.038	0.033	
								0.40	0.43	0.40	0.33	0.41	0.39	0.49	0.36	0.37	0.41	0.40	
								7740	8067	7758	7684	7740	7669	7744	7861	7739	7592	7720	
H								1	0.72	0.65	0.74	0.66	0.59	0.65	0.80	0.71	0.55	0.70	
									0.030	0.033	0.038	0.051	0.037	0.054	0.030	0.041	0.036	0.047	
									0.26	0.26	0.40	0.56	0.27	0.59	0.31	0.39	0.28	0.46	
									8047	7840	7494	8384	7811	8393	7993	8390	7883	8363	
I									1	0.73	0.70	0.63	0.64	0.60	0.78	0.68	0.63	0.65	
										0.022	0.039	0.049	0.027	0.052	0.030	0.040	0.024	0.046	
										0.19	0.43	0.59	0.24	0.61	0.34	0.42	0.16	0.48	
										7983	7836	8047	7940	8051	8059	8046	7899	8027	
J										1	0.72	0.57	0.73	0.54	0.74	0.60	0.57	0.58	
											0.035	0.048	0.024	0.051	0.028	0.041	0.025	0.046	
											0.41	0.56	0.21	0.59	0.32	0.39	0.21	0.45	
											7576	7840	7677	7844	7826	7839	7689	7820	
K											1	0.70	0.64	0.67	0.84	0.70	0.49	0.72	
												0.036	0.032	0.039	0.024	0.033	0.037	0.034	
												0.44	0.40	0.51	0.34	0.41	0.42	0.42	
												7494	7430	7498	7626	7493	7352	7477	
L												1	0.46	0.95	0.68	0.88	0.38	0.92	
													0.044	0.013	0.041	0.027	0.045	0.018	
													0.54	0.40	0.50	0.43	0.55	0.40	
													7814	8386	7993	8383	7885	8357	
M													1	0.42	0.65	0.49	0.50	0.49	
														0.048	0.028	0.039	0.023	0.042	
														0.57	0.31	0.40	0.22	0.45	
														7815	7817	7811	7665	7796	
N														1	0.64	0.87	0.38	0.93	
															0.043	0.029	0.047	0.019	
															0.54	0.50	0.58	0.45	
															7996	8392	7887	8364	
O															1	0.72	0.58	0.70	
																0.033	0.030	0.037	
																0.37	0.33	0.43	
																7992	7842	7973	
P																1	0.46	0.92	
																	0.039	0.020	
																	0.41	0.33	
																	7882	8361	
Q																	1	0.45	
																		0.041	
																		0.46	
																		7866	
R																			1

Key	
Pearson correlation coefficient	
90 th %-ile difference in concentration	
Coefficient of divergence	
Number of paired observations	

Figure AX3-36 (cont'd).

AX3.3.2 Small-scale Horizontal and Spatial Variability in Ozone Concentrations

Ozone concentrations near roadways

Apart from the larger scale variability in surface O₃ concentrations, there is also significant variability on the micro-scale (< a few hundred meters), especially near roadways and other sources of emissions that react with O₃. These sources are not confined to urban areas. Sources of emissions that react with O₃ such as highways and power plants are also found in rural areas. Johnson (1995) described the results of studies examining O₃ upwind and downwind of roadways in Cincinnati, OH. In these studies, O₃ upwind of the roadway was about 50 ppb and values as high as this were not found again until distances of about 100 m downwind. The O₃ profile varied inversely with that of NO, as might be expected. For peak NO concentrations of 30 ppb, the O₃ mixing ratio was about 36 ppb, or about 70% of the upwind value. The magnitude of the downwind depletion of O₃ depends on the emissions of NO, the rate of mixing of NO from the roadway and ambient temperatures. So depletions of O₃ downwind of roadways are expected, but with variable magnitude, although scavenging of O₃ by NO near roadways was more pronounced before the implementation of stringent NO_x emissions controls.

Guidance for the placement of O₃ monitors (U.S. Environmental Protection Agency, 1998) states a separation distance that depends on traffic counts. For example, a minimum separation distance of 100 m from a road with 70,000 vehicles per day is recommended for siting an O₃ monitor to avoid interference that would mean a site is no longer representative of the surrounding area. An average rate of about 3,000 vehicles per hour passing by a monitoring site implies a road with rather heavy traffic. As noted earlier in Section AX3.3.1 for the Lakewood, CA monitoring, O₃ levels are lower at sites located near traffic than those located some distance away and the scavenging of O₃ by emissions of NO from roadways is a major source of spatial variability in O₃ concentrations.

Vertical Variations in Ozone Concentrations

In addition to horizontal variability in O₃ concentrations, consideration must also be given to variations in the vertical profile of O₃ in the lowest layers of the atmosphere. The planetary boundary layer consists of an outer and an inner portion. The inner part extends from the surface to about one-tenth the height of the planetary boundary layer. Winds and transported pollutants,

such as O_3 , are especially susceptible to interactions with obstacles, such as buildings and trees in the inner boundary layer (atmospheric surface layer) (e.g., Garratt, 1992). Inlets to ambient monitors (typically at heights of 3 to 5 meters) are located in, and human and vegetation exposures occur in this part of the boundary layer.

Photochemical production and destruction of O_3 occurs throughout the planetary boundary layer. However, O_3 is also destroyed on the surfaces of buildings, vegetation, etc. On most surfaces, O_3 is destroyed with every collision. In addition, O_3 is scavenged by NO emitted by motor vehicles and soils. These losses imply that the vertical gradient of O_3 should always be directed downward. The magnitude of the gradient is determined by the intensity of turbulent mixing in the surface layer.

Most work characterizing the vertical profile of O_3 near the surface has been performed in nonurban areas with the aim of calculating fluxes of O_3 and other pollutants through forest canopies and to crops and short vegetation etc. Corresponding data are sparse for urban areas. However, monitoring sites are often set up in open areas such as parks and playgrounds where surface characteristics may resemble those in rural areas more than those in the surrounding urban area. The vertical profile of O_3 measured over low vegetation is shown in Figure AX3-37. These measurements were obtained as part of a field campaign to measure the fluxes of several gas and aerosol phase pollutants using the gradient-flux technique in a remote area in Hortobagy National Park in Hungary during late spring of 1994 (Horvath et al., 1995). The labels stable and unstable in the figure refer to atmospheric stability conditions and average represents the overall average. Ozone concentrations were normalized relative to their values at a height of 4 m. As can be seen from the figure, there was a decrease of about 20% in going from a height of 4 m down to 0.5 m above the surface during stable conditions, but O_3 decreased by only about 7% during unstable conditions. The average decrease was about 10% for all measurements. As might be expected, O_3 concentrations at all heights were very highly correlated with one another. Of course, these values represent averages and there is scatter about them, particularly under strongly stable conditions. However, these conditions tend to occur mainly during night and the stability regime during the day in urban areas tends more towards instability because of the urban heat island effect. Figure AX3-38 shows the vertical profile of O_3 obtained in a spruce forest in northwestern Hungary in late summer 1991 (Horvath et al., 2003). The fall off in O_3 for

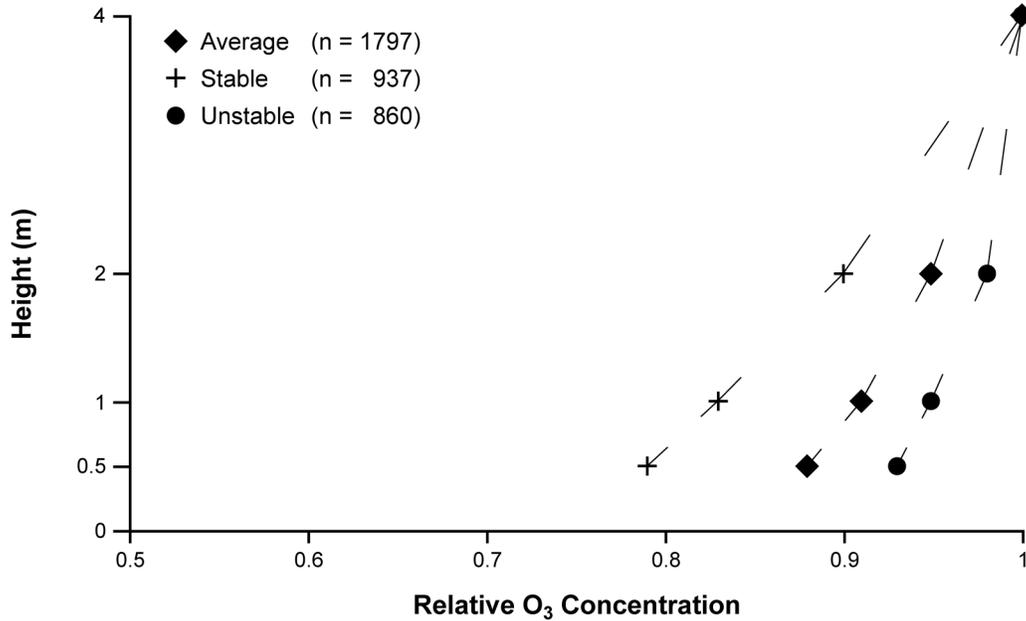


Figure AX3-37. Vertical profile of O₃ obtained over low vegetation. Values shown are relative to concentrations at 4 m above the surface. Ozone concentrations for stable and unstable conditions were 41.3 and 24.1 ppb, and average O₃ concentration weighted by stability class was 33.1 ppb at 4 m.

Source. Horvath et al. (1995).

this case is due to uptake by trees, reaction with ambient NO and with NO emitted by the soil in the forest in addition to deposition on the surface.

AX3.3.3 Ozone Concentrations at High Elevations

The distributions of hourly average concentrations experienced at high-elevation cities are similar to those experienced in low-elevation cities. For example, the distribution of hourly average concentrations for several O₃ sites located in Denver were similar to distributions observed at many low-elevation sites elsewhere in the United States. However, the use of absolute concentrations (e.g., in units of micrograms per cubic meter) in assessing the possible impacts of O₃ on vegetation at high-elevation sites instead of mixing ratios (e.g., parts per million) may be an important consideration (see Chapter 9, for further considerations about exposure and effective dose considerations for vegetation assessments).

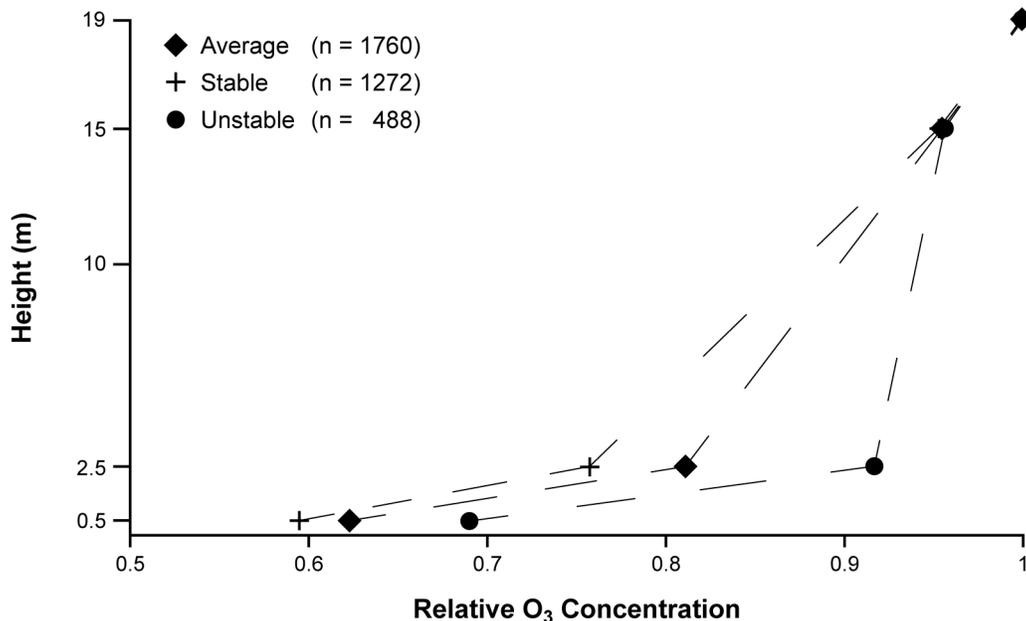


Figure AX3-38. Vertical profile of O₃ obtained in a spruce forest. Values shown are relative to concentrations at 19 m above the surface. Mean tree height is 14.5 m. Ozone concentrations for stable and unstable conditions were 36.7 and 33.8 ppb, and the average O₃ concentration weighted by stability class was 34.6 ppb at 19 m.

Source: Horvath et al. (2003).

Concentrations of O₃ vary with altitude and latitude. Although a number of reports contain data on O₃ concentrations at high altitudes (e.g., Coffey et al., 1977; Reiter, 1977; Singh et al., 1977; Evans et al., 1985; Lefohn and Jones, 1986), fewer reports present data for different elevations in the same locality. Monitoring data collected by the Mountain Cloud Chemistry Project (MCCP) provide useful information about O₃ exposure differences at different elevations. When applying different exposure indices to the MCCP data, there appears to be no consistency in the relationship between O₃ exposure and elevation.

Lefohn et al. (1990a) summarized the characterization of gaseous exposures at rural sites in 1986 and 1987 at several MCCP high-elevation sites (see Table AX3-6). Aneja and Li (1992) have summarized the O₃ concentrations for 1986 to 1988 (see Table AX3-7). Table AX3-7 summarizes the concentrations and exposures that occurred at several of the sites for the period 1987 to 1988.

Table AX3-6. Description of Mountain Cloud Chemistry Program Sites

Site	Elevation (m)	Latitude			Longitude		
Howland Forest (HF1), ME	65	458°	11'		68°	46'	
Mt. Moosilauke (MS1), NH	1000	438°	59'	18"	71°	48'	28"
Whiteface Mountain (WF1), NY	1483	448°	23'	26"	73°	51'	34"
Shenandoah NP (SH1), VA	1015	38°	37'	12"	78°	20'	48"
Shenandoah NP (SH2), VA	716	38°	37'	30"	78°	21'	13"
Shenandoah NP (SH3), VA	524	38°	37'	45"	78°	21'	28"
Whitetop Mountain (WT1), VA	1689	36°	38'	20"	81°	36'	21"
Mt. Mitchell (MM1), NC	2006	35°	44'	15"	82°	17'	15"
Mt. Mitchell (MM2), NC	1760	35°	45'		82°	15'	

Table AX3-7. Seasonal (April-October) Percentiles, SUM06, SUM08, and W126 Values for the MCCP Sites

Site	Year	Min.	10	30	50	70 (ppm)	90	95	99	Max.	No. Obs.	SUM06	SUM08 (ppm-h)	W126
Howland Forest, ME (HF1)	1987	0.000	0.013	0.021	0.028	0.035	0.046	0.052	0.065	0.076	4766	5.9	0.0	7.7
	1988	0.000	0.012	0.021	0.028	0.036	0.047	0.054	0.076	0.106	4786	10.9	2.9	11.6
Mt. Moosilauke, NH (MS1)	1987	0.006	0.027	0.036	0.045	0.053	0.065	0.074	0.086	0.102	4077	45.0	9.5	40.1
	1988	0.010	0.026	0.033	0.043	0.055	0.076	0.087	0.113	0.127	2835	51.9	21.2	43.4
Whiteface Mountain, NY (WF1) (36-031-0002)	1987	0.011	0.029	0.037	0.046	0.053	0.067	0.074	0.087	0.104	4703	63.5	12.2	50.5
	1988	0.014	0.025	0.033	0.043	0.056	0.078	0.089	0.110	0.135	4675	94.4	40.8	78.3
Whiteface Mountain, NY (WF3)	1987	0.010	0.025	0.033	0.039	0.047	0.064	0.075	0.091	0.117	4755	45.4	14.4	40.3
Whiteface Mountain, NY (WF4)	1987	0.000	0.011	0.023	0.031	0.041	0.056	0.065	0.081	0.117	4463	23.8	5.1	21.3
Mt. Mitchell, NC (MM1)	1987	0.008	0.034	0.044	0.051	0.058	0.067	0.074	0.085	0.105	3539	59.4	7.8	46.5
	1988	0.011	0.038	0.054	0.065	0.075	0.095	0.106	0.126	0.145	2989	145.1	69.7	116.6
	1989	0.010	0.038	0.047	0.054	0.059	0.068	0.072	0.081	0.147	2788	54.8	3.5	40.7
	1992	0.005	0.036	0.043	0.048	0.053	0.063	0.069	0.081	0.096	3971	37.8	4.4	36.7
Mt. Mitchell, NC (MM2)	1987	0.017	0.032	0.042	0.049	0.056	0.067	0.073	0.083	0.096	3118	47.0	5.1	37.4
	1988	0.009	0.029	0.041	0.050	0.060	0.080	0.092	0.110	0.162	2992	68.7	28.1	57.7
Shenandoah Park, VA (SH1)	1987	0.000	0.023	0.036	0.044	0.054	0.069	0.076	0.085	0.135	3636	54.2	8.5	42.0
	1988	0.006	0.024	0.036	0.047	0.058	0.077	0.087	0.103	0.140	3959	80.9	29.6	67.2
Shenandoah Park, VA (SH2)	1987*	0.003	0.027	0.040	0.049	0.059	0.071	0.077	0.086	0.145	2908	55.7	7.8	41.8
	1988	0.006	0.029	0.042	0.054	0.064	0.083	0.095	0.108	0.145	4661	133.8	55.8	109.4

AX3-61

Table AX3-7 (cont'd). Seasonal (April-October) Percentiles, SUM06, SUM08, and W126 Values for the MCCP Sites

Site	Year	Min.	10	30	50	70 (ppm)	90	95	99	Max.	No. Obs.	SUM06	SUM08 (ppm-h)	W126
Shenandoah Park, VA (SH3)	1987	0.000	0.018	0.029	0.037	0.047	0.061	0.068	0.080	0.108	3030	23.1	2.6	19.2
	1988	0.000	0.020	0.031	0.040	0.051	0.067	0.076	0.097	0.135	4278	52.3	15.6	44.2
Whitetop Mountain, VA (WT1)	1987	0.01	0.038	0.051	0.059	0.066	0.078	0.085	0.096	0.111	4326	147.7	32.4	105.7
	1988	0.000	0.030	0.046	0.058	0.068	0.084	0.094	0.119	0.163	3788	133.8	51.0	102.8

*Calculations based on a May-September season.

In 1987, the 7- and 12-h seasonal means were similar at the Whiteface Mountain WF1 and WF3 sites (Figure AX3-39a). The 7-h mean values were 0.0449 and 0.0444 ppm, respectively, and the 12-h mean values were 0.0454 and 0.0444 ppm, respectively. Note that, in some cases, the 12-h mean was slightly higher than the 7-h mean value. In fact, at higher elevations, the 24-h level was larger still (Table AX3-8). This resulted when the 7-h mean period (0900 to 1559 hours) did not capture the period of the day when the highest hourly mean O₃ concentrations were measured. A similar observation was made, using the 1987 data, for the MCCP Shenandoah National Park sites. The 7-h and 12-h seasonal means were similar for the SH1 and SH2 sites (Figure AX3-39b). Based on cumulative indices, the Whiteface Mountain summit (1483-m) site (WF1) experienced a higher exposure than the WF3 (1026-m) site (Figure AX3-39c). The site at the base of Whiteface Mountain (WF4) experienced the lowest exposure of the three O₃ sites. Among the MCCP Shenandoah National Park sites, marginally higher O₃ exposures were found at the SH2 site, based on the index that sums all of the hourly average concentrations (referred to as “total dose” in Figure AX3-39c) and sigmoidal values, than the SH1 high-elevation site (Figure AX3-39d). The reverse was true for concentrations ≥ 0.07 ppm (SUM07) and the number of hourly concentrations ≥ 0.07 ppm the sums of the concentrations ≥ 0.07 ppm and the number of hourly concentrations ≥ 0.07 ppm. When the Big Meadows, Dickey Ridge, Sawmill Run, and Shenandoah National Park data for 1983 to 1987 were compared, it again was found that the 7-h and 12-h seasonal means were insensitive to the different O₃ exposure patterns. Cumulative exposures at three sites in Shenandoah National Park are shown in Figure AX3-40. There was no evidence that the highest elevation site, Big Meadows, consistently had experienced higher O₃ exposures than the other sites. In 2 of the 5 years, the Big Meadows site experienced lower exposures than the Dickey Ridge and Sawmill Run sites, based on the sum of all concentration or sigmoidal indices. For 4 of the 5 years, the SUM07 index yielded the same result.

Taylor et al. (1992) indicated that the forests they monitored experienced differences in O₃ exposure. The principal spatial factors underlying this variation were elevation, proximity to anthropogenic sources of oxidant precursors, regional-scale meteorological conditions, and airshed dynamics between the lower free troposphere and the surface boundary layer. Table AX3-8 summarizes the exposure values for the 10 EPRI Integrated Forest Study sites located in North America.

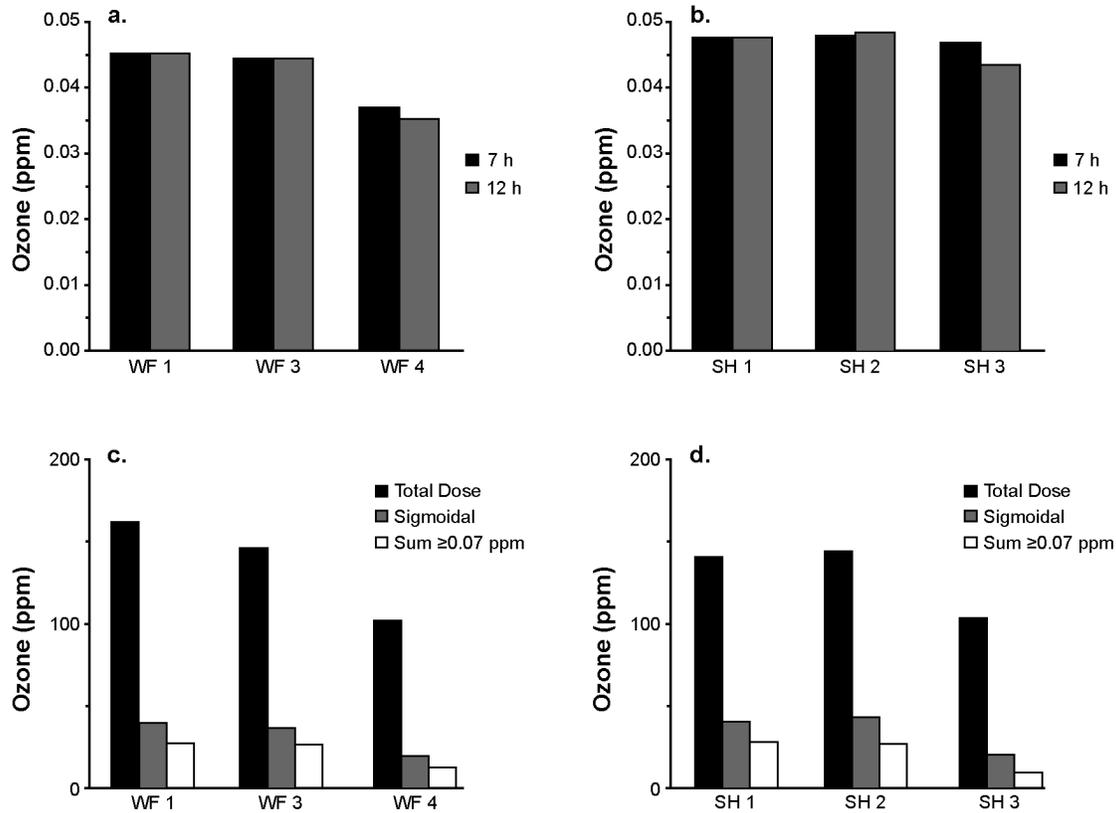


Figure AX3-39a-d. Seven- and 12-h seasonal means at (a) Whiteface Mountain and (b) Shenandoah National Park for May to September 1987, and integrated exposures at (c) Whiteface Mountain and (d) Shenandoah National Park for May to September 1987.

Source: Lefohn et al. (1990a).

An important issue for assessing possible impacts of O₃ at high-elevation sites requiring further attention is the use of mixing ratios (e.g., parts per million) instead of absolute concentration (e.g., in units of micrograms per cubic meter) to describe O₃ concentration. In most cases, mixing ratios or mole fractions are used to describe O₃ concentrations. Lefohn et al. (1990b) pointed out that the manner in which concentration is reported may be important when assessing the potential impacts of air pollution on high-elevation forests. Even when parts-per-million values at high- and low-elevation sites are equal, the absolute concentrations (i.e., micrograms per cubic meter) at the two elevations will be different, because both O₃ and ambient air are gases, and changes in pressure directly affect their volume. According to Boyle's law, if

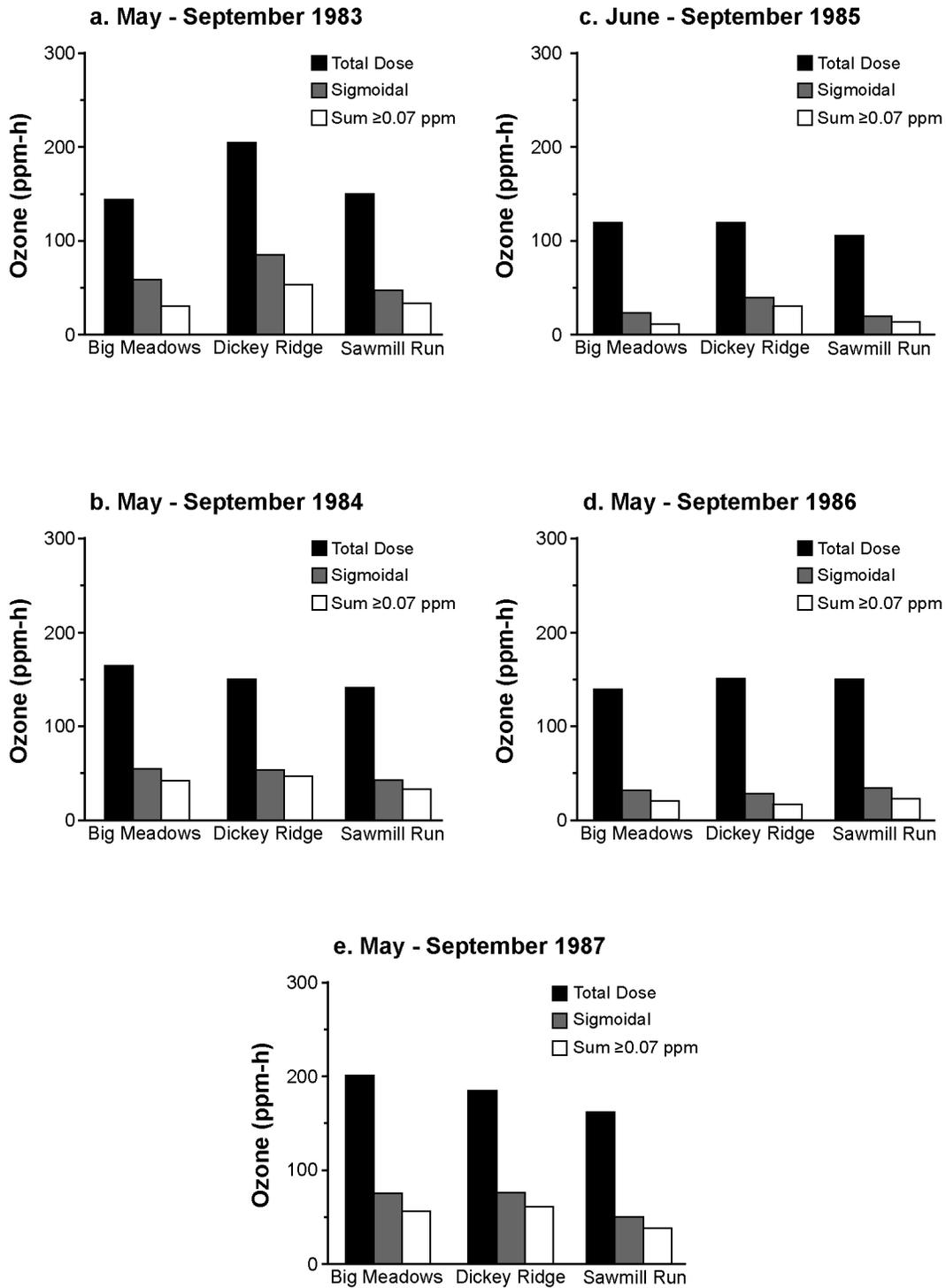


Figure AX3-40a-e. Cumulative exposures for three non-Mountain Cloud Chemistry Program Shenandoah National Park sites, 1983 to 1987.

Source: Lefohn et al. (1990b).

Table AX3-8. Summary Statistics for 11 Integrated Forest Study Sites^a

Site	Year	Quarter	24-h	12-h	7-h	1-h Max.	SUM06 10 ³ ppb-h	SUM08 10 ³ ppb-h
HIGH ELEVATION SITES								
Whiteface Mtn, NY	1987	2	42	43	42	104	13.2	2.5
	1987	3	45	44	43	114	30.1	11.8
	1988	2	49	50	49	131	33.5	13.9
	1988	3	44	43	43	119	22.6	10.4
Great Smoky Mtns NP	1987	2	54	52	49	99	57.1	10.9
	1987	3	53	51	49	95	34.3	8.8
	1988	2	71	70	68	119	126.3	61.2
	1988	3	59	57	55	120	74.7	22.2
Coweeta Hydrologic Lab, NC	1987	2	50	48	47	85	32.4	2.6
	1987	3	47	44	42	95	24.1	2.4
	1988	2	61	59	59	104	81.6	18.5
	1988	3	57	54	51	100	63.6	19.8
LOW ELEVATION SITES								
Huntington Forest, NY	1987	2	36	42	42	88	9.8	0.9
	1987	3	24	32	33	76	5.4	0.2
	1988	2	40	46	46	106	19.2	6.1
	1988	3	37	46	48	91	18.6	2.7
Howland, ME	1987	2	34	39	39	69	1.9	0.0
	1987	3	26	32	31	76	3.8	0.0
	1988	2	36	41	41	90	8.1	2.9
	1988	3	24	30	30	71	1.7	0.0
Oak Ridge, TN	1987	2	42	53	50	112	39.5	13.5
	1987	3	29	44	41	105	24.3	9.0
	1988	2	40	57	58	104	26.4	9.8
	1988	3	32	47	51	122	19.7	7.7
Thompson Forest, WA	1987	2	36	43	41	103	10.7	3.6
	1987	3	30	36	34	94	10.3	2.1
	1988	2	32	39	37	103	8.1	2.3
	1988	3	32	39	36	140	13.5	6.7

Table AX3-8 (cont'd). Summary Statistics for 11 Integrated Forest Study Sites^a

Site	Year	Quarter	24-h	12-h	7-h	1-h Max.	SUM06 10 ³ ppb-h	SUM08 10 ³ ppb-h
LOW ELEVATION SITES (cont'd)								
B.F. Grant Forest, GA	1987	2	32	46	48	99	26.1	5.1
	1987	3	33	52	54	102	31.3	10.3
	1988	2	47	63	64	127	53.1	21.9
	1988	3	32	47	48	116	24.1	7.4
Gainesville, FL	1987	2	42	53	50	b	b	b
	1987	3	29	44	41	b	b	b
	1988	2	35	48	51	84	23.4	0.5
	1988	3	20	29	30	70	1.9	0.1
Duke Forest, NC	1987	2	38	48	52	100	29.2	7.8
	1987	3	52	59	50	124	b	b
	1988	2	54	69	75	115	b	b
	1988	3	38	51	54	141	52.9	23.4
Nordmoen, Norway	1987	2	32	40	41	75	2.4	0.0
	1987	3	14	18	20	32	0.0	0.0
	1988	2	22	28	29	53	0.0	0.0
	1988	3	11	15	16	30	0.0	0.0

^aConcentration in ppb.

^bData were insufficient to calculate statistic.

Source: Taylor et al. (1992).

the temperature of a gas is held constant, the volume occupied by the gas varies inversely with the pressure (i.e., as pressure decreases, volume increases). This pressure effect must be considered when measuring absolute pollutant concentrations. At any given sampling location, normal atmospheric pressure variations have very little effect on air pollutant measurements. However, when mass/volume units of concentration are used and pollutant concentrations measured at significantly different altitudes are compared, pressure (and, hence, volume) adjustments are necessary. In practice, the summit site at Whiteface Mountain had a slightly

higher O₃ exposure than the two low-elevation sites (Lefohn et al., 1991). However, at Shenandoah National Park sites, the higher elevation site experienced lower exposures than lower elevation sites in some years.

These exposure considerations are relatively unimportant at low-elevation sites. However, the differences between exposure-effects at high- and low-elevation sites, may be significant (Lefohn et al., 1990b). In particular, assuming the sensitivity of the biological target to be identical at low- and high-elevations, some adjustment will be necessary when attempting to link experimental data obtained at low-elevation sites with air quality data monitored at the high-elevation stations. This topic is further discussed in Annex AX9 when considering effective dose considerations for predicting vegetation effects associated with O₃.

AX3.4 DIURNAL PATTERNS IN OZONE CONCENTRATION

AX3.4.1 Introduction

Diurnal variations in O₃ at a given location are controlled by a number of factors such as the relative importance of transport versus local photochemical production and loss rates, the timing for entrainment of air from the nocturnal residual boundary layer and the diurnal variability in mixing layer height.

The form of an average diurnal pattern provides some information on sources, transport, and chemical formation and destruction effects at various sites (Lefohn, 1992). Atmospheric conditions leading to limited transportation from source regions will produce early afternoon peaks. However, long-range transport processes will influence the actual timing of a peak, from afternoon to evening or early morning hours. Ozone is rapidly depleted near the surface below the nocturnal inversion layer (Berry, 1964). Mountainous sites, which are above the nocturnal inversion layer, do not necessarily experience this depletion (Stasiuk and Coffey, 1974). Taylor and Hanson (1992) reported similar findings, using data from the Integrated Forest Study. The authors reported that intraday variability was most significant for the low-elevation sites due to the pronounced daily amplitude in O₃ concentration between the predawn minimum and mid-afternoon-to-early evening maximum. The authors reported that interday variation was more significant in the high-elevation sites. Ozone trapped below the inversion layer is depleted by dry deposition and chemical reactions if other reactants are present in sufficient quantities

(Kelly et al., 1984). Above the nocturnal inversion layer, dry deposition does not generally occur, and the concentration of O₃ scavengers is generally lower, so O₃ concentrations remain fairly constant (Wolff et al., 1987). A flat diurnal pattern is usually interpreted as indicating a lack of efficient scavenging of O₃ or a lack of photochemical precursors, whereas a strongly varying diurnal pattern is taken to indicate the opposite.

An analysis that identified when the highest hourly average concentrations were observed at rural agricultural and forested sites was described in 1996 O₃ AQCD. A review of the hourly average data collected at all rural agricultural and forested sites in Environmental Protection Agency's AQS database for 1990 to 1992 was undertaken to evaluate the percentage of time hourly average concentrations ≥ 0.1 ppm occurred during the period of 0900 to 1559 hours in comparison with the 24-h period. It was found that 70% of the rural-agricultural and forested sites used in the analysis experienced at least 50% of the occurrences ≥ 0.1 ppm during the period of 0900 to 1559 hours when compared to the 24-h period. When O₃ monitoring sites in California were eliminated, approximately 73% of the remaining sites experienced at least 50% of the occurrences ≥ 0.10 ppm during the daylight 7-h period when compared with the 24-h period.

Diurnal Variations in the Nationwide Data Set

Composite urban, diurnal variations in hourly averaged O₃ for April through October 2000 to 2004 are shown in Figure AX3-41. As can be seen from Figure AX3-41, daily 1-h O₃ maxima tend to occur in mid-afternoon and daily 1-h O₃ minima tend to occur during the early morning. However, there is also considerable spread in these times. Therefore, some caution must be exercised in extrapolating results from one city to another and when attempting to judge the time of day when the daily 1-h maximum occurs.

Corresponding data for 8 hour average O₃ data are shown in Figure AX3-42. As can be seen from Figure AX3-42, daily maximum eight hour O₃ concentrations tend to occur from about 10 a.m. to about 6 p.m. As can be seen from Figure AX3-42, they can also occur at slightly different times and the variation in the 8-h averages is smoother than for the 1-h averages. The minima in the 8 h averages tend to occur starting at about midnight.

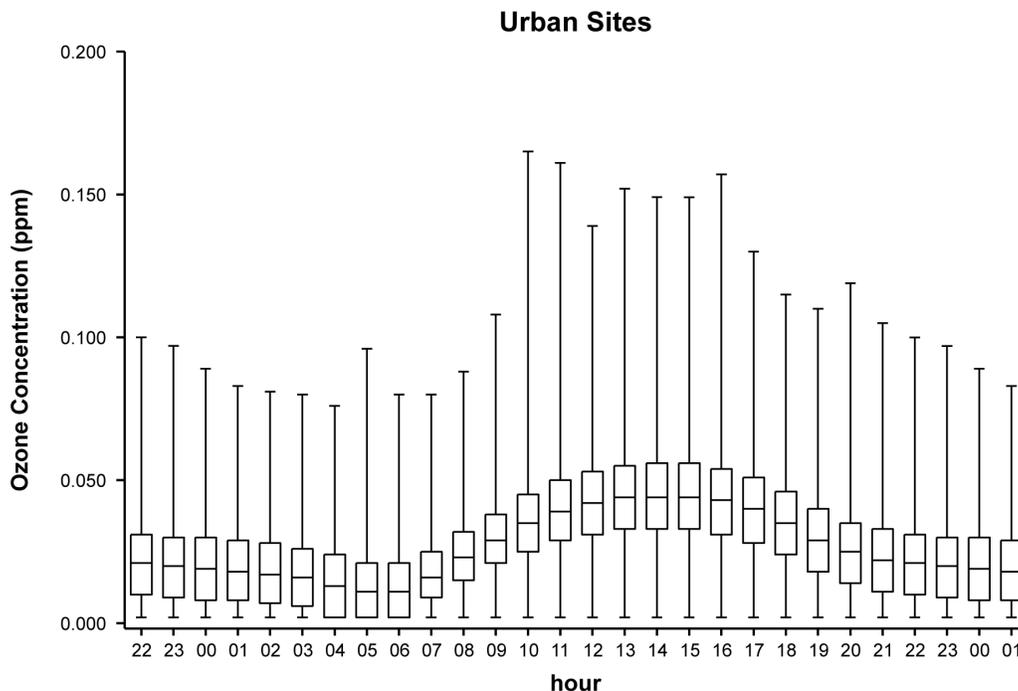


Figure AX3-41. Composite, nationwide diurnal variability in hourly averaged O₃ in urban areas. Values shown are averages from April to October 2000 to 2004. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

AX3.4.2 Diurnal Patterns in Urban Areas

Diurnal Variations in EPA's 12 Cities

The diurnal variability of hourly averaged O₃ in the twelve urban areas considered for inclusion in EPA's human health exposure assessment-risk assessment for the current review is illustrated in Figure AX3-43a-l for April to October. Daily maximum 1-h concentrations tend to occur in mid-afternoon. However, as can be seen from the figures, the diurnal patterns vary from city to city, with high values (≥ 0.100 ppm) occurring either late in the evening as in Boston, past midnight as in Los Angeles and Sacramento, or mid-morning as in Houston. Typically, high values such as these are found during the daylight hours in mid to late afternoon. The reasons for the behavior of O₃ during the night at the above mentioned locations are not clear. Measurement issues may be involved or there may be physical causes such as transport

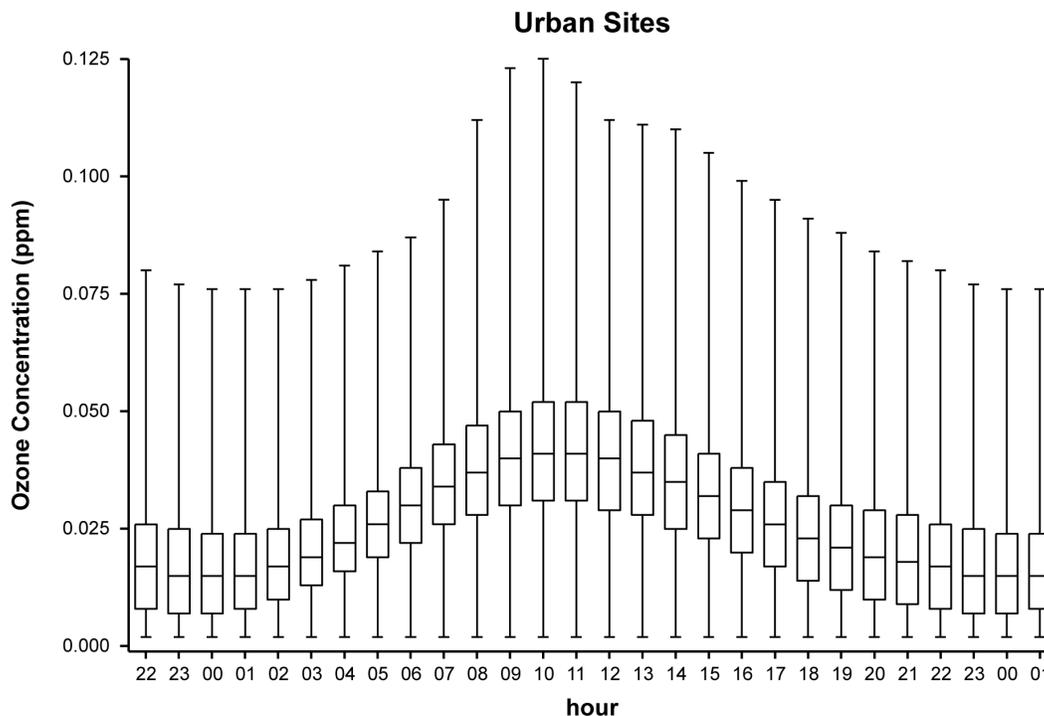


Figure AX3-42. Composite, nationwide diurnal variability in 8 hour average O₃ in urban areas. Values shown are averages from April to October 2000 to 2004. Boxes define the interquartile range and the whiskers, the minima and maxima. The hour refers to the start of the 8-h averaging period.

Source: Fitz-Simons et al. (2005).

phenomena, as discussed in Chapter 2. As discussed in Chapter 2, and in greater detail in Section AX2.3.3, nocturnal low level jets are capable of producing secondary O₃ maxima at night.

The diurnal variability of O₃ averaged over 8 hours in the same twelve urban areas is shown in Figures AX3-44a-l. The diurnal patterns of 1-h O₃ averages are broadly similar to 8-h averages. Typically, although the 8-h daily maximum occurs between 10 a.m to 6 p.m., actual starting and ending times can differ from these characteristic times, depending on location. For example, as shown in Figures AX3-44a for Boston and AX3-44k for Sacramento, the highest 8-h daily maximum values can start in mid-afternoon and extend into late evening. These results suggest that transport processes are playing the dominant role in determining the timing of the highest daily maxima in these areas.

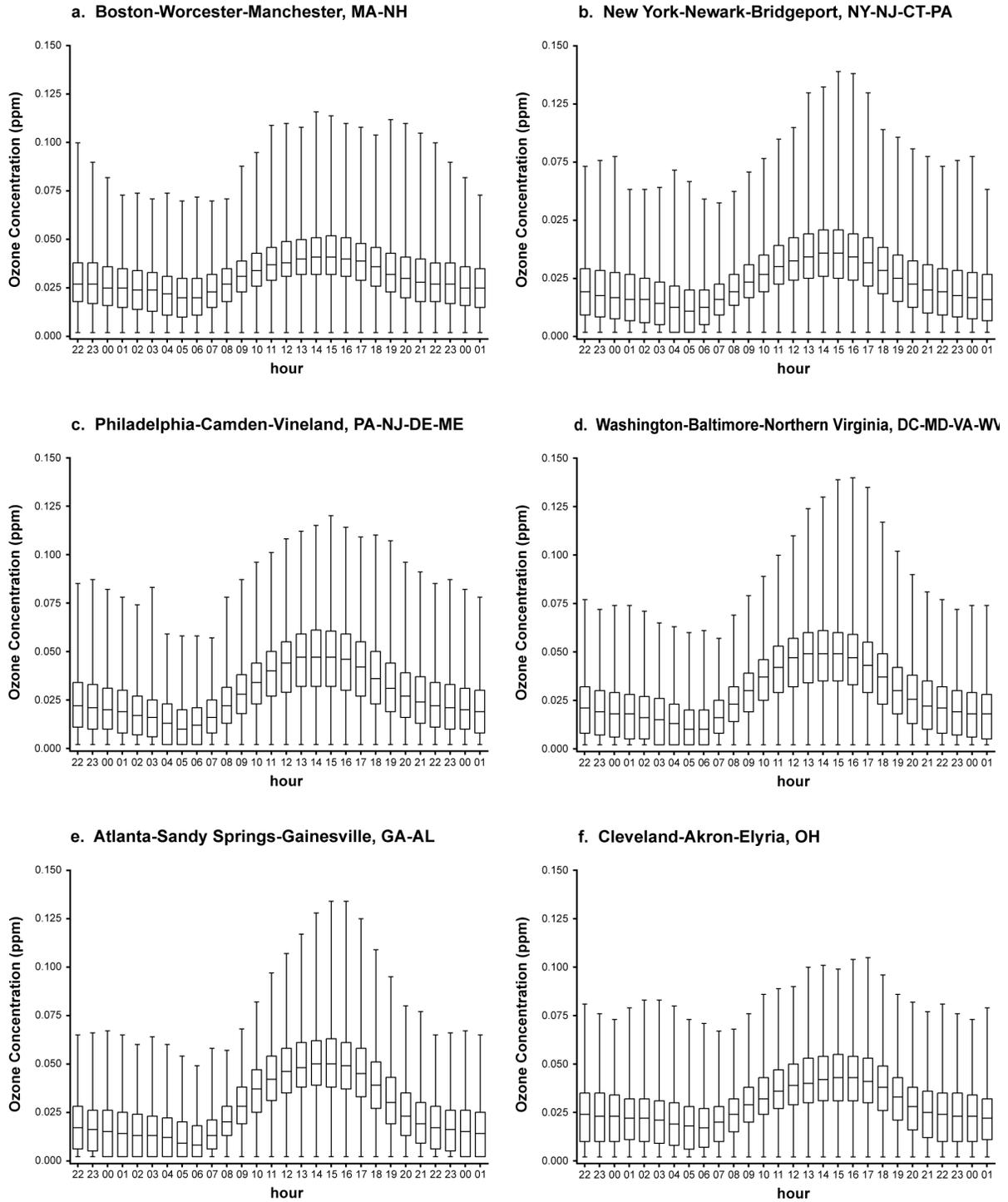


Figure AX3-43a-f. Diurnal variability in hourly averaged O₃ in selected urban areas. Values shown are averages from April to October 2000 to 2004. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

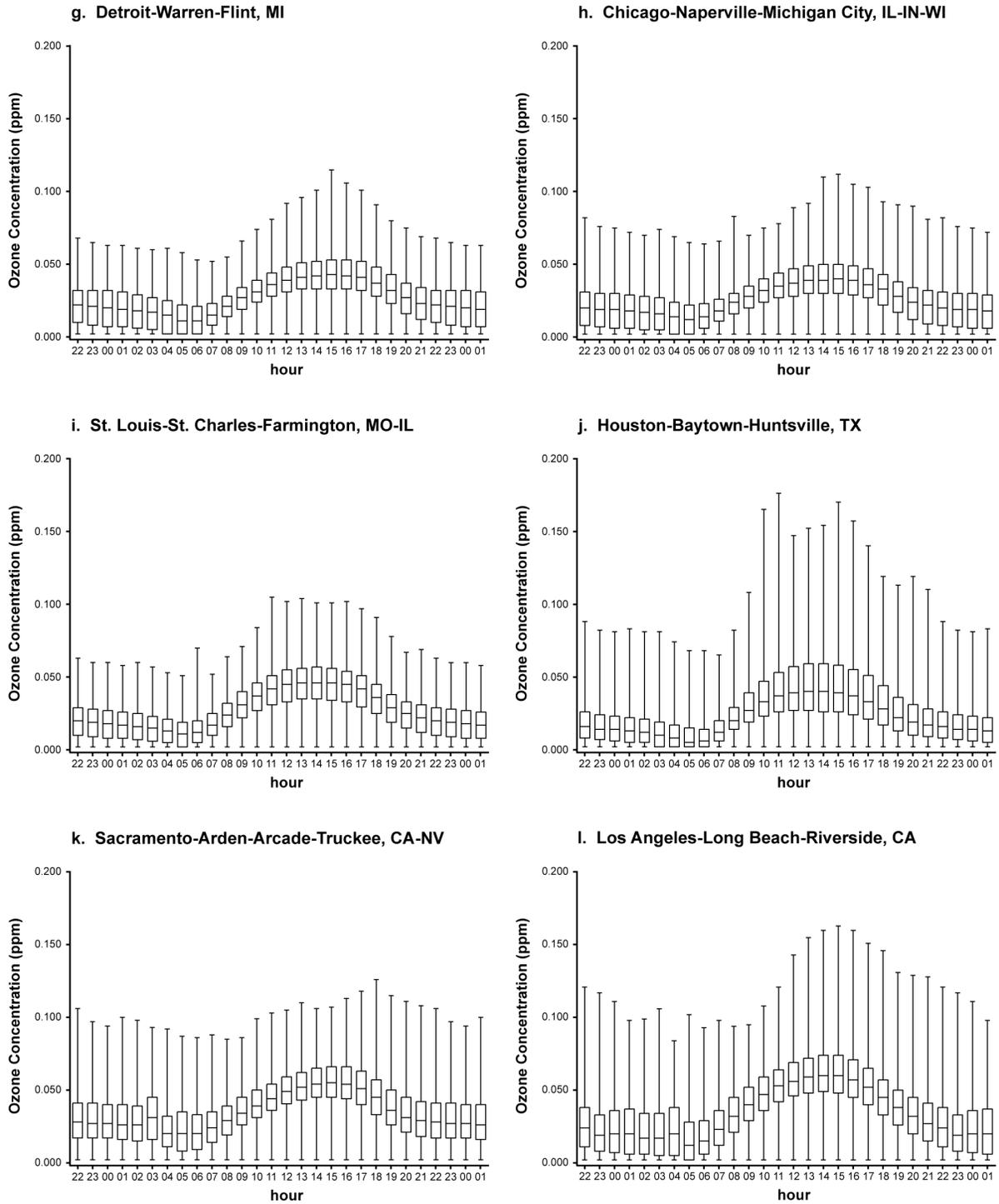


Figure AX3-43g-l. Diurnal variability in hourly averaged O_3 in selected urban areas. Values shown are averages from April to October 2000 to 2004. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

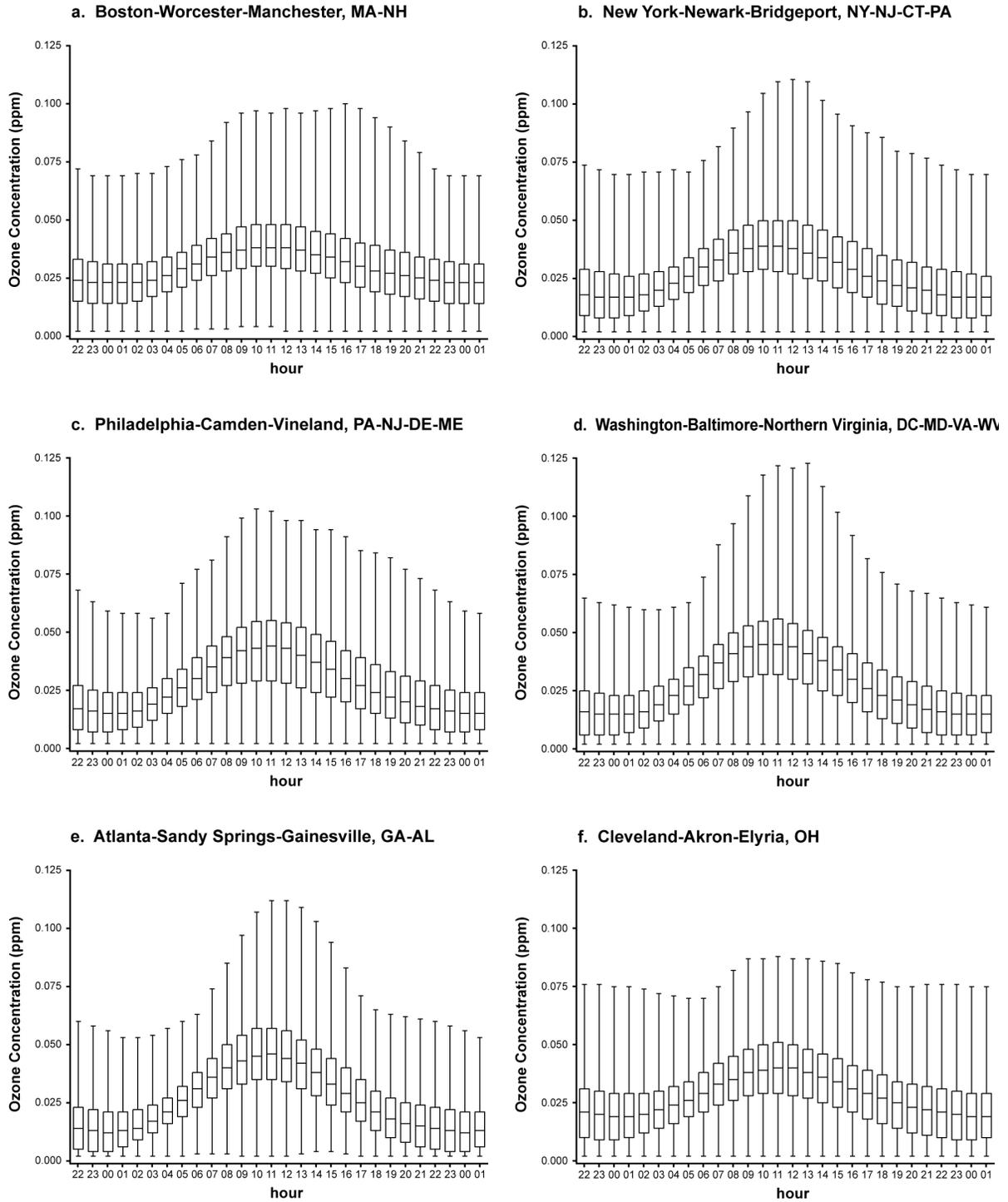


Figure AX3-44a-f. Diurnal variability in 8 hour averaged O_3 in selected urban areas. Values shown are averages from April to October 2000 to 2004. Boxes define the interquartile range and the whiskers, the minima and maxima. The hour refers to the start of the 8-h averaging period.

Source: Fitz-Simons et al. (2005).

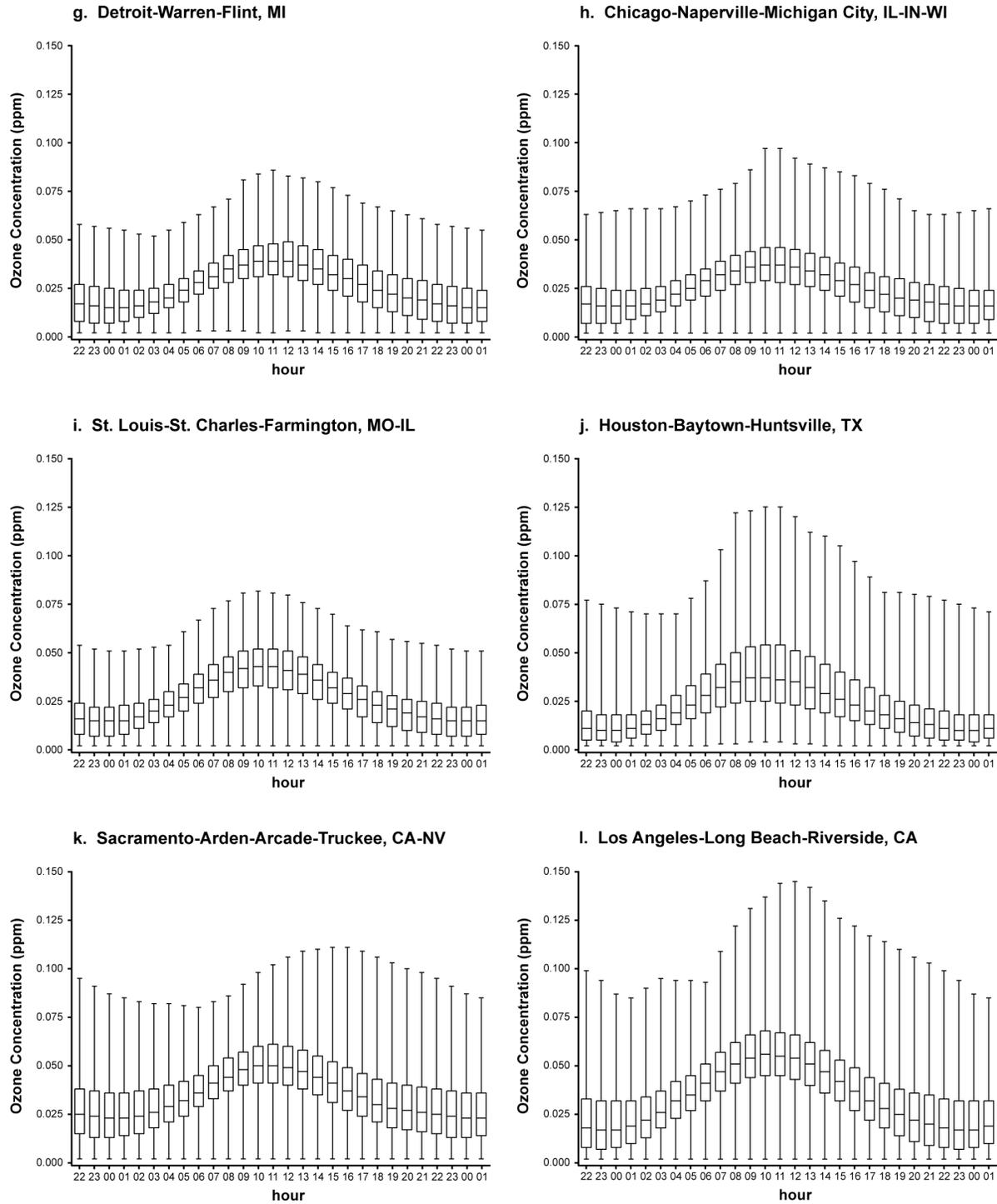


Figure AX3-44g-l. Diurnal variability in 8 hour averaged O_3 in selected urban areas. Values shown are averages from April to October 2000 to 2004. Boxes define the interquartile range and the whiskers, the minima and maxima. The hour refers to the start of the 8-h averaging period.

Source: Fitz-Simons et al. (2005).

On days with high 1-h daily maximum concentrations (e.g., ≥ 0.12 ppm) the maxima tend to occur in a smaller time window centered in the middle of the afternoon, compared to days in which the maximum is lower. For example, on the high O₃ days the 1-h maximum occurs from about 11 a.m. to about 6 p.m. However, on days in which the 1-h daily maximum is ≤ 0.080 ppm, the daily maximum can occur at any time during the day or night, with only a 50% probability that it occurs between 1 and 3 p.m., in each of the 12 cities. Photochemical reactions in combination with diurnal emissions patterns are expected to produce mid-afternoon peaks in urban areas. These results suggest that transport from outside the urban airshed plays a major role in determining the timing of the daily maxima for low peak O₃ levels. This pattern is more typical for the Los Angeles-Long Beach-Riverside, CA area even for high O₃ days.

The same general timing patterns are found for 1-h daily maximum O₃ concentrations as for the daily maximum 8-h average O₃ concentration. As mentioned above, the daily maximum 8-h O₃ concentrations are generally found between the hours of 10 a.m and 6 p.m. However, there are a significant number of days when this is not the case for high values, as in Houston, TX and Los Angeles, CA, or in general for low values at any of the cities examined. Although the 8-h average O₃ concentration is highly correlated with the daily maximum 1-h average O₃ concentration, there are situations where the daily maximum 8-h average O₃ concentration may be driven by very high values in the daily maximum 1-h average O₃ concentration as illustrated in Figure AX3-43j. In cases such as these, the predicted 8-h average might overestimate the short-term O₃ concentration later in the day.

As an aid to better understanding the nature of the diurnal patterns shown in the figures for EPA's 12 cities, Figures AX3-45a-d show the hours in which the 1-h daily maximum O₃ concentration occurs in four of the cities. As can be seen from Figures AX3-45a-c for the Philadelphia, Atlanta, and Houston areas, the maximum tends to occur from about 2 p.m. to 4 p.m. about half of the time, and most values occur between about 12 p.m to 6 p.m at higher values of the daily maximum 1-h O₃ concentration. Although values at Houston can occur earlier, these are most likely due to episodic releases from the petrochemical industries. For small values of the 1-h daily maximum, most of the daily maxima still occur in the afternoon, but maxima can also occur at any time of the day or night. In the Los Angeles area, as shown in Figure AX3-45d high values of daily 1-h O₃ maxima can occur at any time during the day or night but with most values occurring during the afternoon.

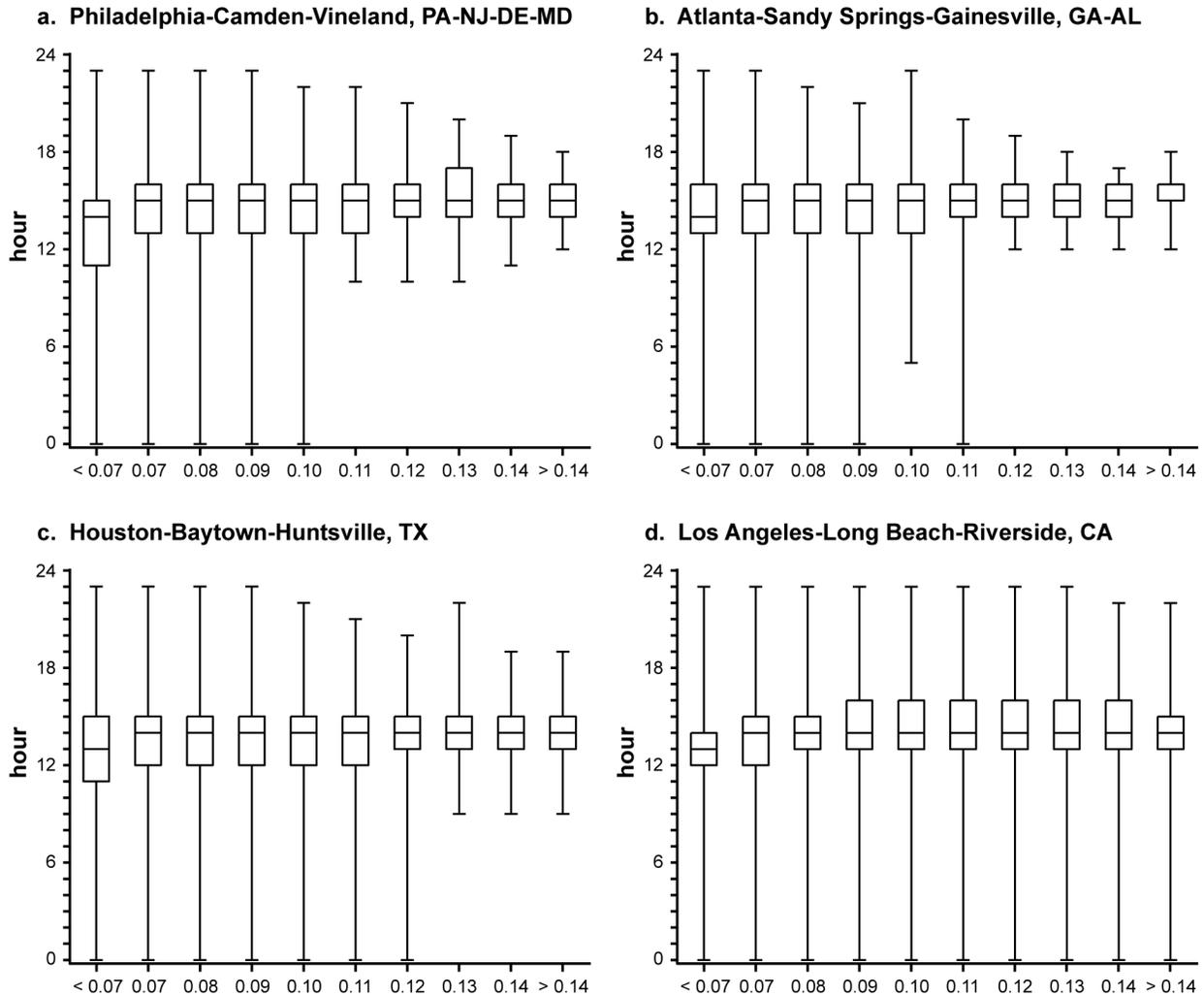


Figure AX3-45a-d. Time of occurrence of daily maximum 1-h O₃ concentration in four cities, averaged from April to October, 2000 to 2004.

Source: Fitz-Simons et al. (2005).

Figures AX3-46a-d show the hours in which the 8-h daily maximum O₃ concentration begins. The mean time is about 10 a.m. at these four cities indicating that the 8-h daily maximum tends to occur on average from about 10 a.m. to 6 p.m. However, there can be deviations from these times. The same general pattern in which the maxima tend to occur within a narrower time frame at high values than at low values is found in the four cities shown.

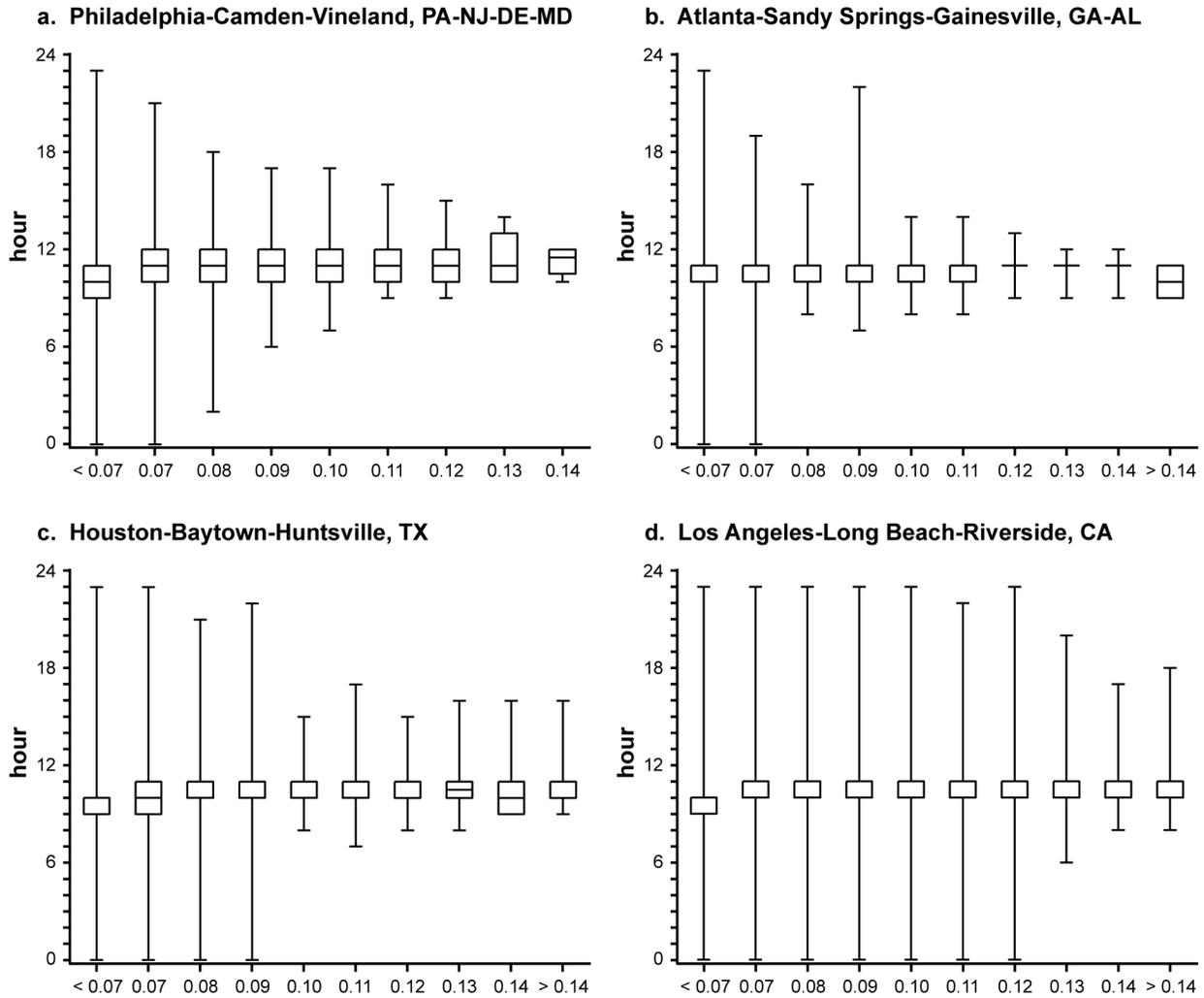


Figure AX3-46a-d. Time of occurrence of daily maximum 8-h average O₃ concentration in four cities, averaged from April to October, 2000 to 2004. The hour refers to the start of the 8-h averaging period.

Source: Fitz-Simons et al. (2005).

The patterns of diurnal variability for both 1-h and 8-h averages have remained quite stable over the 15 year period from 1990 to 2004, with times of occurrence of the daily maxima varying by no more than an hour from year to year in each of the 12 cities.

Weekday/Weekend Differences

In addition to varying diurnally, O₃ concentrations differ from weekdays to weekends. Heuss et al. (2003) described the results of a nationwide analysis of weekday/weekend differences that demonstrated significant variation in these differences across the United States. Weekend 1-h or 8-h maximum O₃ concentrations varied from 15% lower to 30% higher than weekday levels across the U.S. The weekend O₃ increases were primarily found in and around large coastal cities in California and large cities in the Midwest and Northeast Corridor. Many sites that experienced elevated weekday O₃ concentrations also had higher O₃ on weekends even though the traffic and O₃ precursor levels were substantially reduced on weekends. The authors reported that detailed studies of this phenomenon indicated that the primary cause of the higher O₃ on weekends was the reduction in oxides of nitrogen emissions on weekends in a volatile organic compound (VOC)-limited (NO_x-saturated) chemical regime (cf., Chapter 2). Heuss et al. (2003) hypothesized that the lower O₃ on weekends in other locations may result from NO_x reductions in a NO_x-limited regime (cf., Chapter 2).

Pun et al. (2003) described the day-of-week behavior for O₃ in Chicago, Philadelphia, and Atlanta. In Chicago and Philadelphia, maximum 1-h average O₃ increases on weekends. In Atlanta, O₃ builds up from Mondays to Fridays and declines during the weekends. Fujita et al. (2003) pointed out that since the mid-1970s, O₃ levels in portions of California's South Coast Air Basin on weekends have been as high as or higher than levels on weekdays, even though emissions of O₃ precursors are lower on weekends. Blanchard and Tanebaum (2003) noted that despite significantly lower O₃ precursor levels on weekends, 20 of 28 South Coast Air Basin sites showed statistically significant higher mean O₃ levels on Sundays than on weekdays. Chinkin et al. (2003) noted that ambient O₃ levels in California's South Coast Air Basin can be as much as 55% higher on weekends than on weekdays under comparable meteorological conditions.

Figures AX3-47a-h show the contrast in the patterns of hourly averaged O₃ in the greater Philadelphia, Atlanta, Houston and Los Angeles areas from weekdays to weekends from May to September 2004. Daily maximum concentrations occur basically at the same time on either weekdays or weekends. Mean O₃ concentrations at midday are about the same on weekdays and weekends in Atlanta, Philadelphia, and Houston, but are higher on weekends in the Los Angeles area. Figures AX3-48a-h show the weekday/weekend differences for the 8-h averages. As can

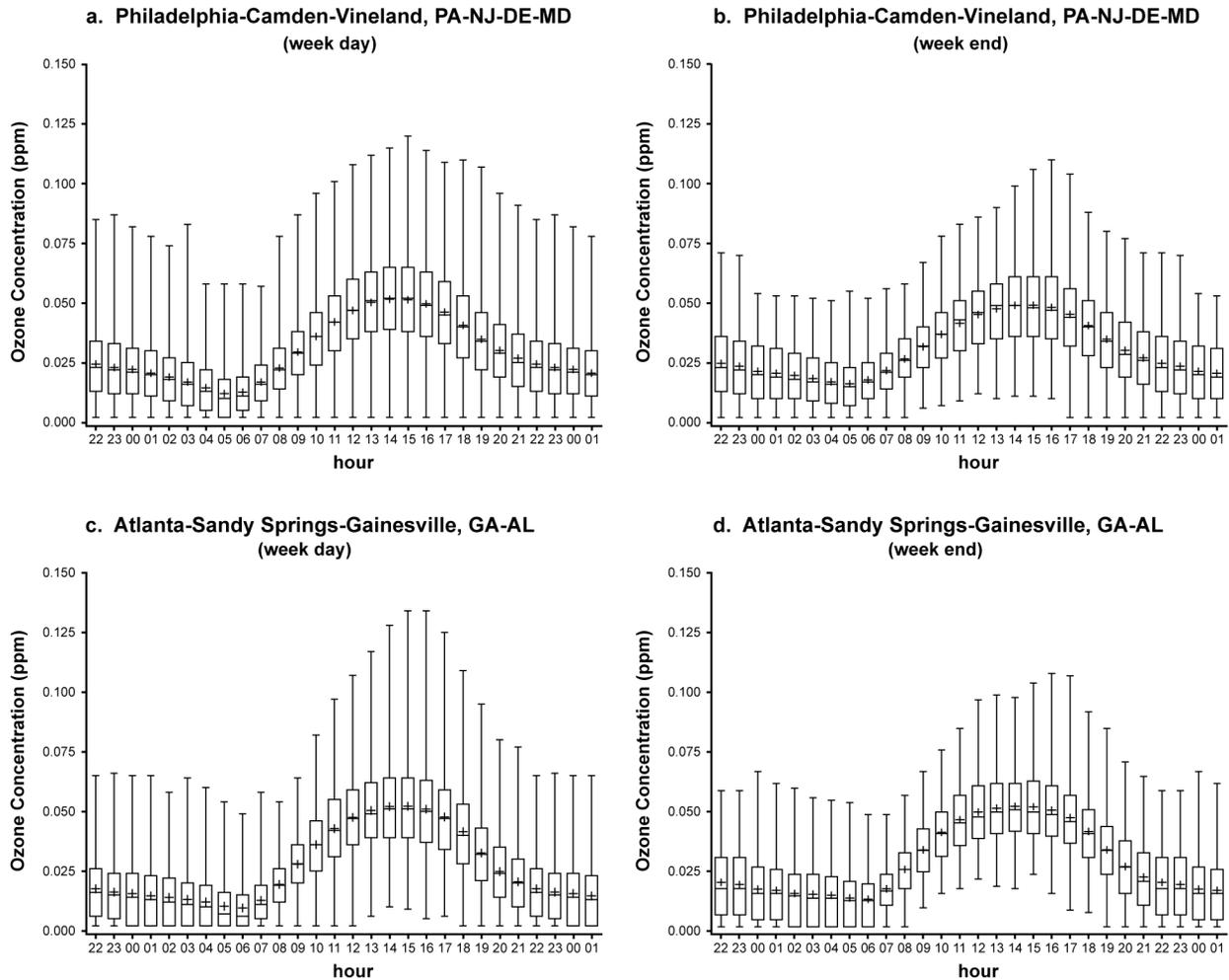


Figure AX3-47a-d. Diurnal variations in hourly averaged O₃ on weekdays and weekends in four cities. Values shown represent averages from May to September of 2004. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

be seen from the figures, the lowest O₃ concentration observed during weekend afternoons tend to be higher than on weekday afternoons. On weekends, traffic volumes are lower and there are fewer diesel vehicles on the road, resulting in a lower rate of scavenging by NO. The spike in values for Houston in mid-morning shown in Figure AX3-47, resulted from the release of highly reactive hydrocarbons from the petrochemical industry (which could occur on any day of the

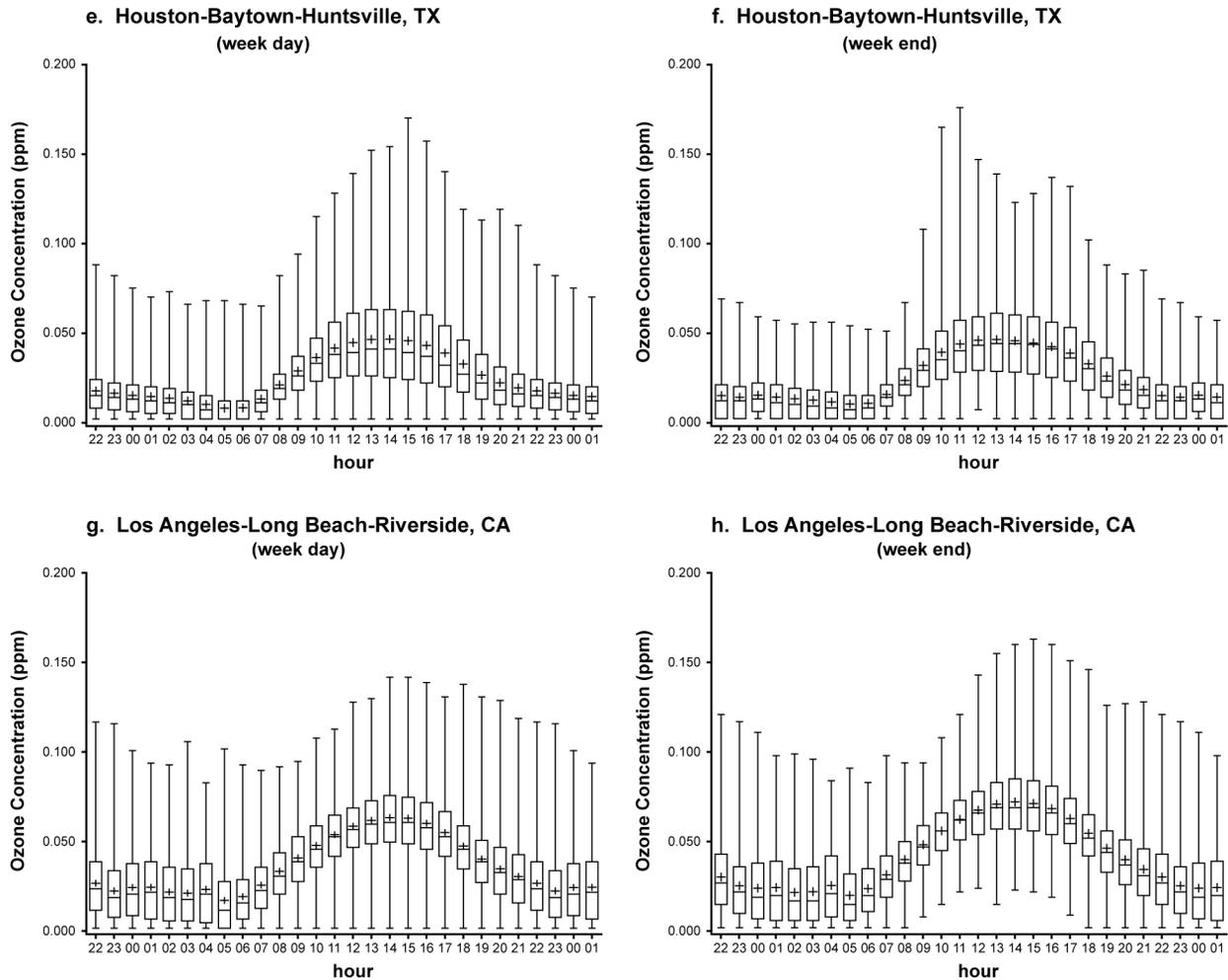


Figure AX3-47e-h. Diurnal variations in hourly averaged O_3 on weekdays and weekends in four cities. Values shown represent averages from May to September of 2004. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

week). Otherwise, the maximum O_3 concentrations could be seen to occur during the week as they do in Philadelphia and Atlanta, in contrast to Los Angeles.

Spatial Variability in Diurnal Patterns

Daily maxima in either the 1-h or 8-h averages do not necessarily occur at the same time of day at each site in the 12 cities, and the diurnal pattern observed at individual sites can vary from

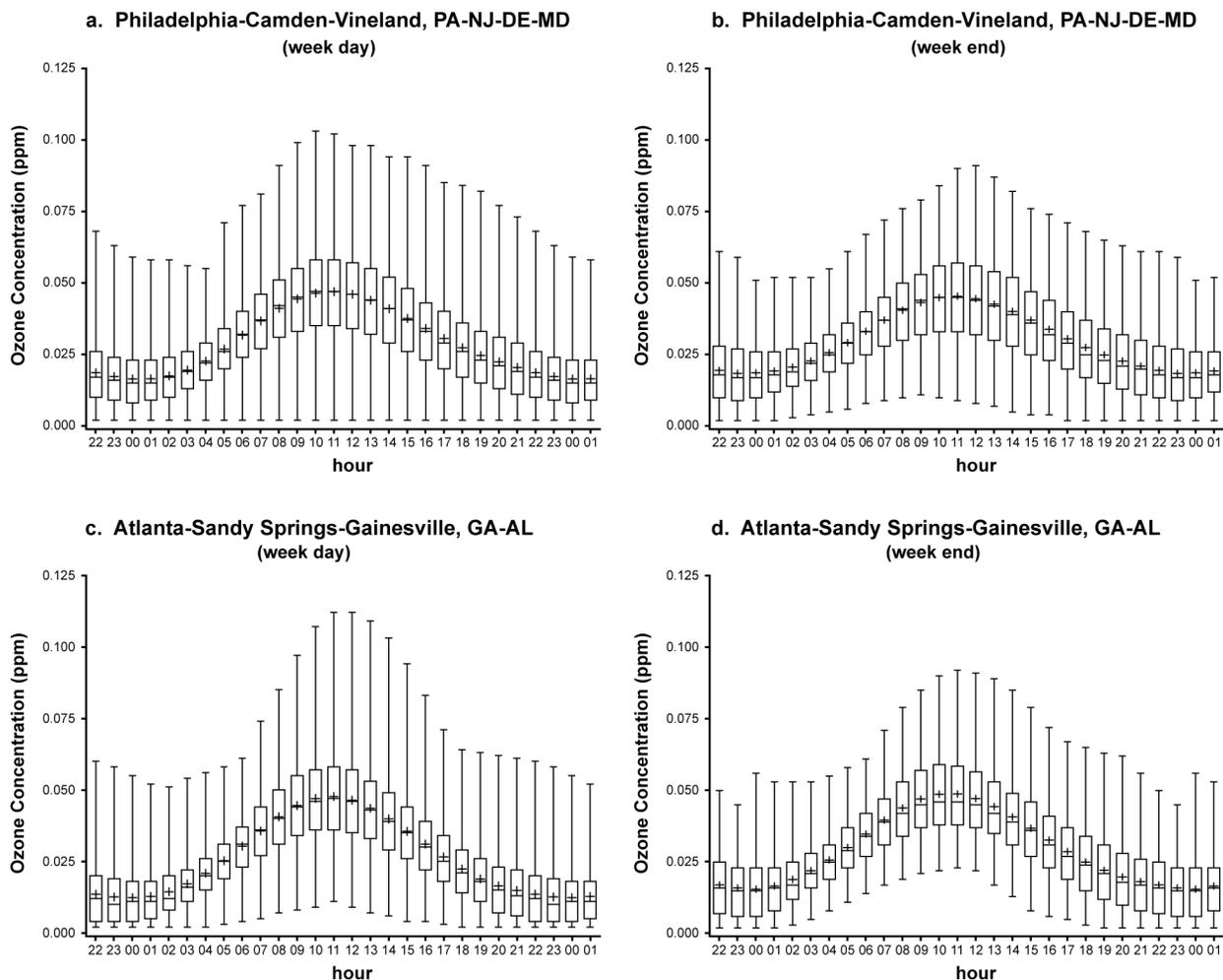


Figure AX3-48a-d. Diurnal variations in 8-h averaged O_3 on weekdays and weekends in four cities. Values shown represent averages from May to September of 2004. The hour refers to the start of the 8-h averaging period. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

the composites shown in Figures AX3-41 and 42. Differences in diurnal patterns between sites are related to differences in transport times from sources of precursors and chemical reactions, in particular, titration of O_3 by NO from local sources. Figure AX3-49a shows the diurnal pattern of 1-h average O_3 at a site in downtown Detroit, MI (cf., Site J in Figure AX3-30). This site is affected by nearby traffic emissions. Figure AX3-49b shows the diurnal pattern at a site well

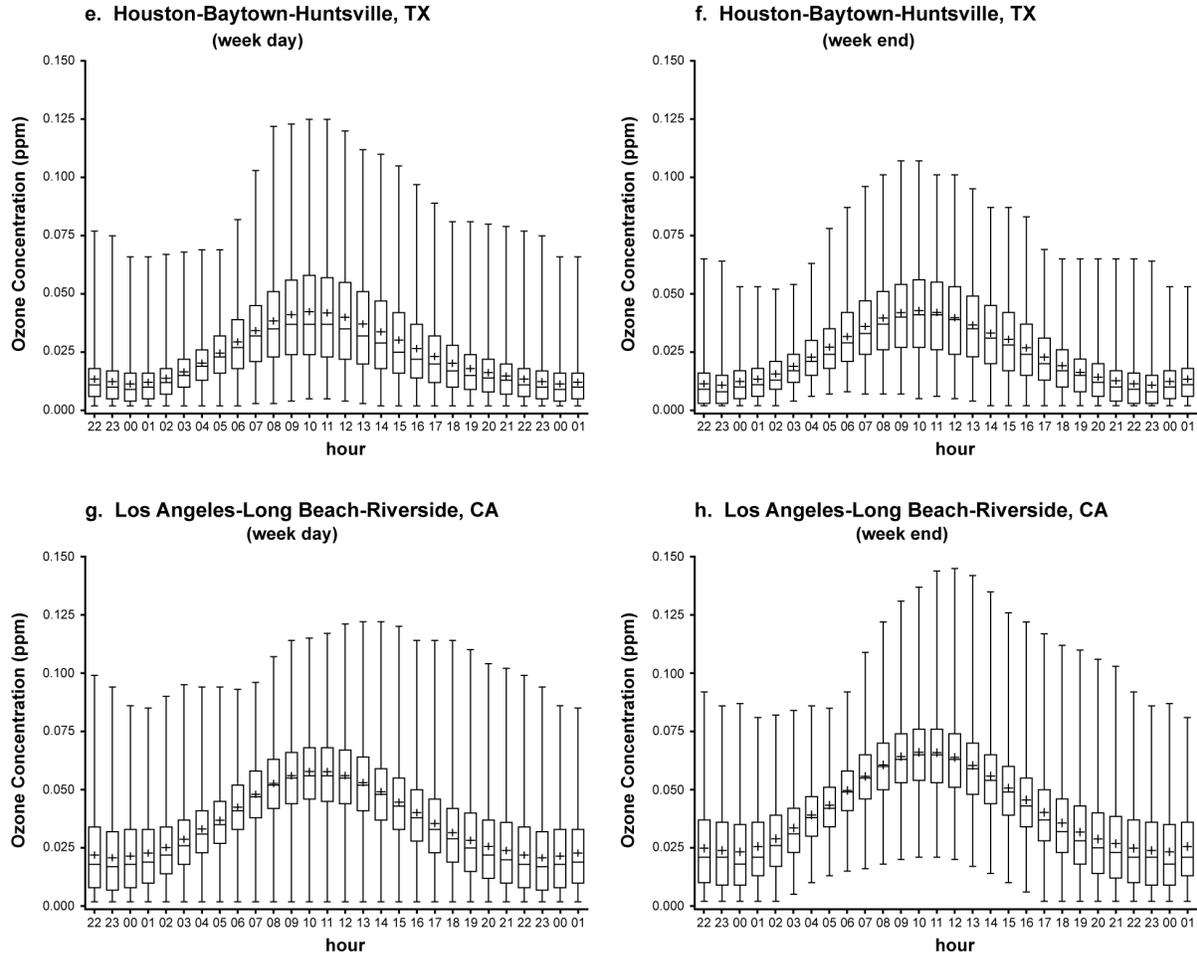


Figure AX3-48e-h. Diurnal variations in 8-h averaged O_3 on weekdays and weekends in four cities. Values shown represent averages from May to September of 2004. The hour refers to the start of the 8-h averaging period. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

downwind (cf., Site D in Figure AX3-30). The peak 1-h average O_3 concentrations tend to be higher at the downwind site than at the site in the urban core. Figure AX3-50a shows the diurnal patterns at a site in downtown St. Louis (cf., Site P in Figure AX3-31) and Figure AX3-50b shows the diurnal pattern at a site downwind (Site A in Figure AX3-31). The same general relations are observed at the two sites in the St. Louis urban area as in the Detroit urban area. Figure AX3-51a shows the diurnal pattern observed at a site in San Bernardino, CA. This site is

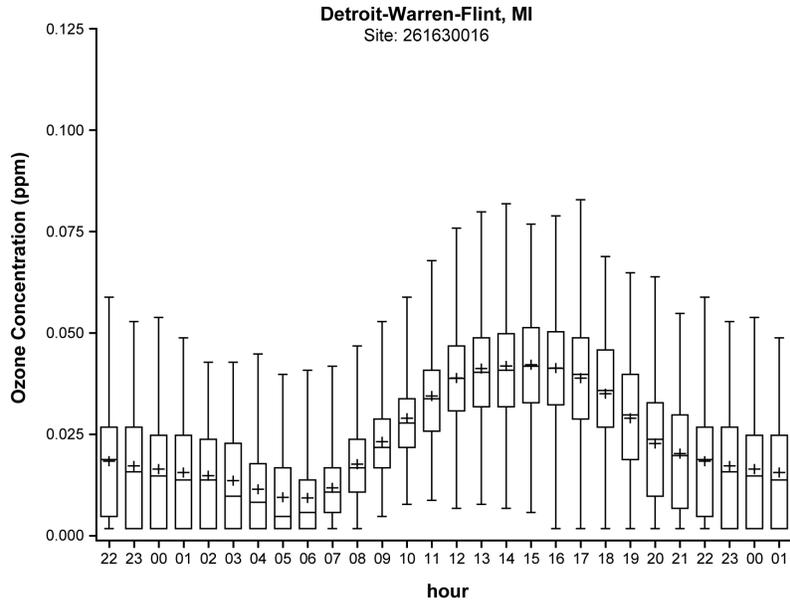


Figure AX3-49a. Diurnal variations in hourly averaged O₃ at a site in downtown Detroit, MI. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

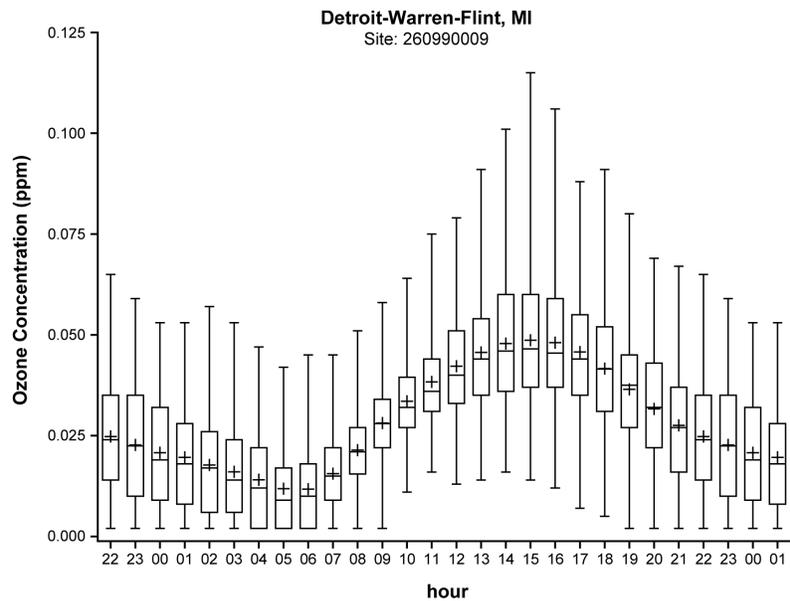


Figure AX3-49b. Diurnal variations in hourly averaged O₃ at a site downwind of downtown Detroit. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

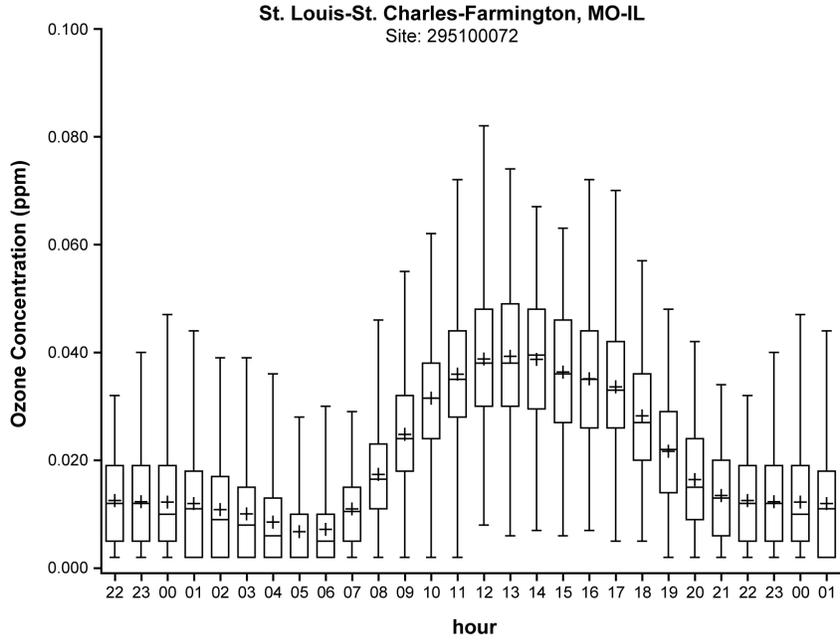


Figure AX3-50a. Diurnal variations in hourly averaged O₃ at a site in downtown St. Louis, MO. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

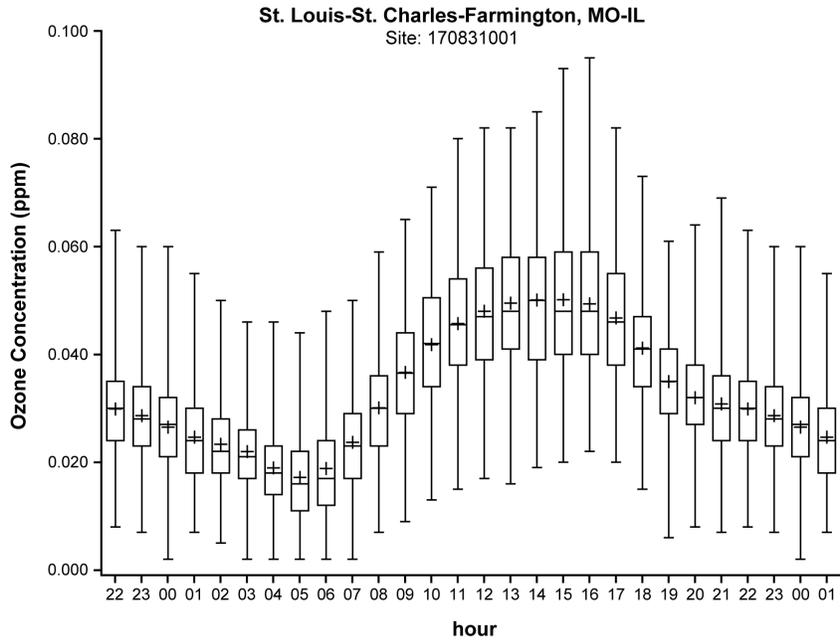


Figure AX3-50b. Diurnal variations in hourly averaged O₃ at a site downwind of downtown St. Louis. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

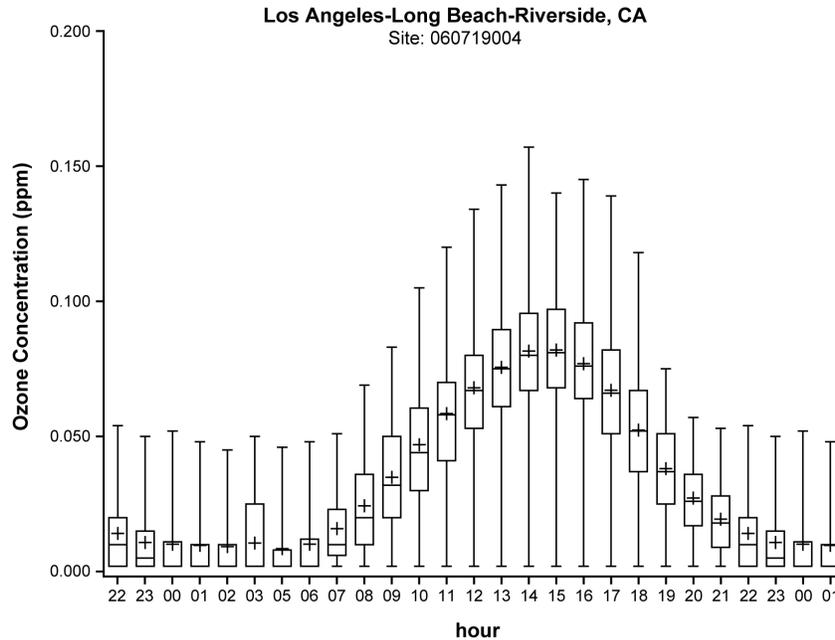


Figure AX3-51a. Diurnal variations in hourly averaged O₃ at a site in San Bernadino, CA. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

affected by transport of precursors from Los Angeles County, production from local precursors and by nearby NO sources, driving O₃ to very low levels at night as shown. A relatively high peak 1-h O₃ concentrations is reached at 2 to 3 p.m. Figure AX3-51b shows the diurnal pattern of O₃ at a site about 80 km to the east of the site mentioned above (cf., Site Q in Figure AX3-36) in a relatively unpopulated area. The diurnal pattern of hourly averaged O₃ is much flatter and the 1-h peak concentration is reached about 5 or 6 p.m., on average. The cause of the rise in concentrations at 2 a.m. is not clear.

The diurnal variation in the 8-h averages observed at the two contrasting sites in these three areas are shown in Figures AX3-52a,b, 53a,b, and 54a,b. As might be expected the patterns are somewhat flatter than for the 1-h averages. This implies that the difference in 8-h averages can be substantial (i.e., over a factor of two) during early morning, afternoon, and evening.

The general pattern that emerges from the site to site variability within the urban areas examined is that peaks in 1-h average concentrations are higher and tend to occur later at

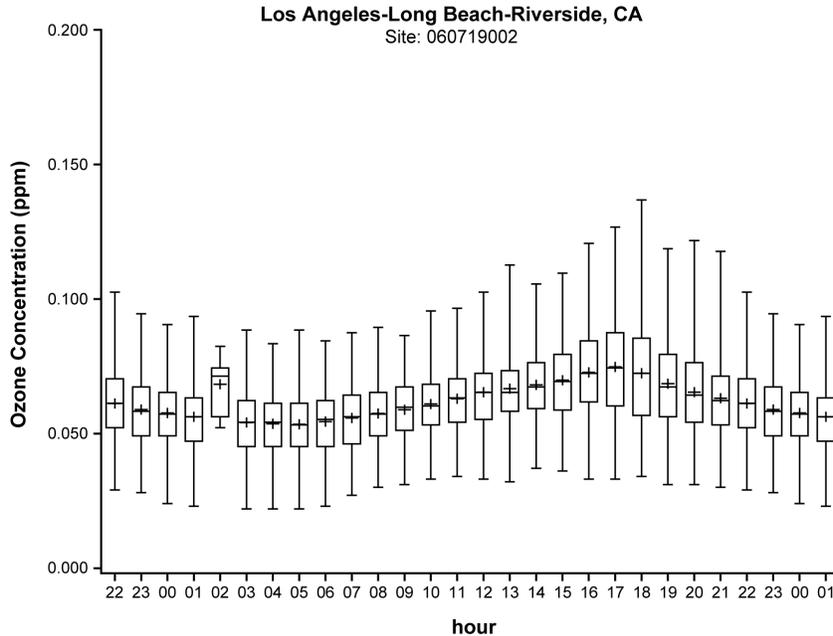


Figure AX3-51b. Diurnal variations in hourly averaged O₃ at a site in Riverside County well downwind of sources. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

downwind sites than in the urban cores. To the extent that monitoring site are either near to or remote from sources of precursors in urban/suburban areas, the behavior of O₃ will follow these basic patterns. Similar relations are found for the 8-h average O₃ concentrations.

AX3.4.3 Diurnal Patterns in Nonurban Areas

Composite diurnal patterns of O₃ are shown in Figure AX3-55 for hourly averaged O₃ and in Figure AX3-56 for 8 hour average O₃ at rural (CASTNET) sites. As can be seen from a comparison of Figures AX3-55 and AX3-56 with Figures AX3-42 and AX3-43, diurnal patterns of O₃ are smoother and shallower at the rural sites than at the urban sites. Maxima in hourly averaged O₃ concentrations also tend to occur in afternoon. However, highest concentrations observed during any particular hour at night at the CASTNET sites (~0.130 ppm) are substantially higher than observed in urban areas (<0.100 ppm) and daily 1-h maxima at CASTNET sites have exceeded 0.150 ppm. The diurnal variations in 8-h average O₃

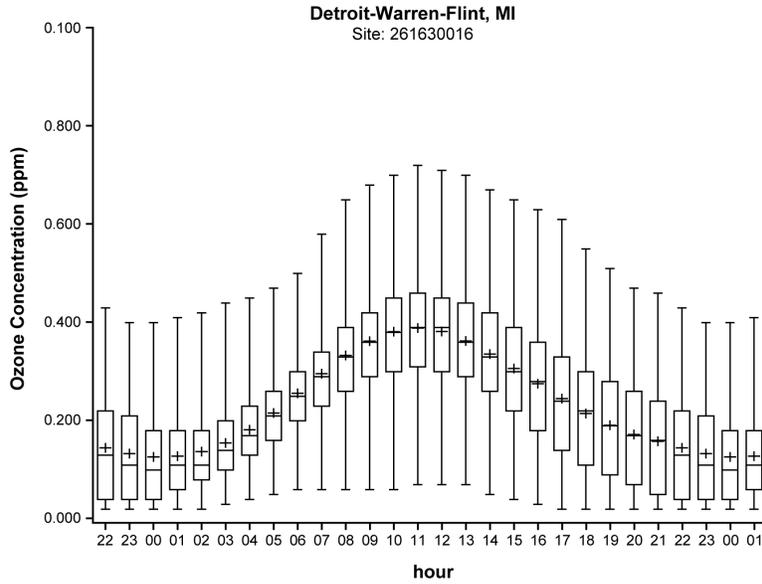


Figure AX3-52a. Diurnal variations in 8-h average O₃ at a site in downtown Detroit, MI. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

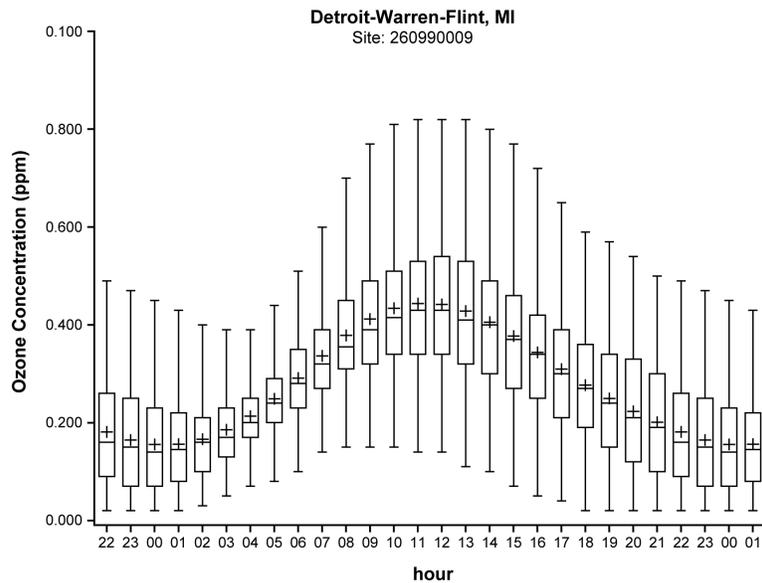


Figure AX3-52b. Diurnal variations in 8-h average O₃ at a site downwind of downtown Detroit, MI. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

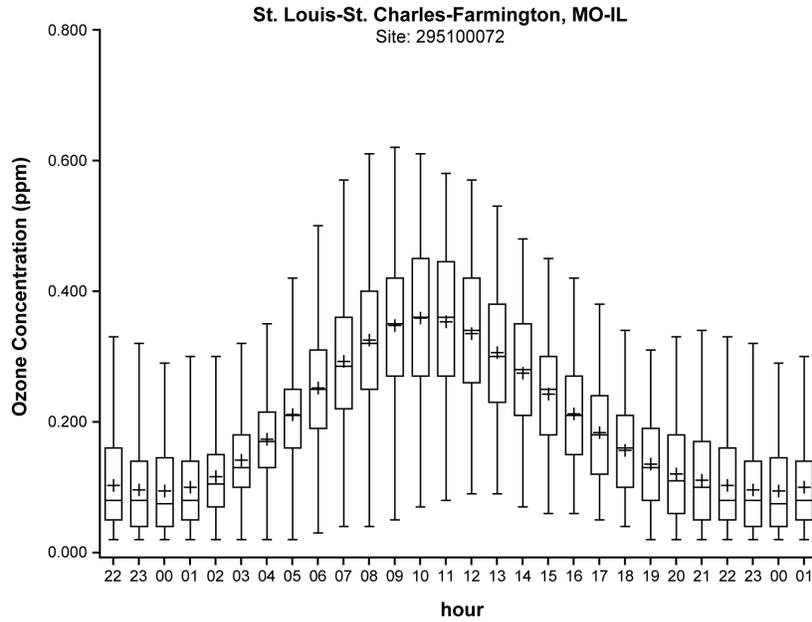


Figure AX3-53a. Diurnal variations in 8-h average ozone at a site in downtown St. Louis, MO. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

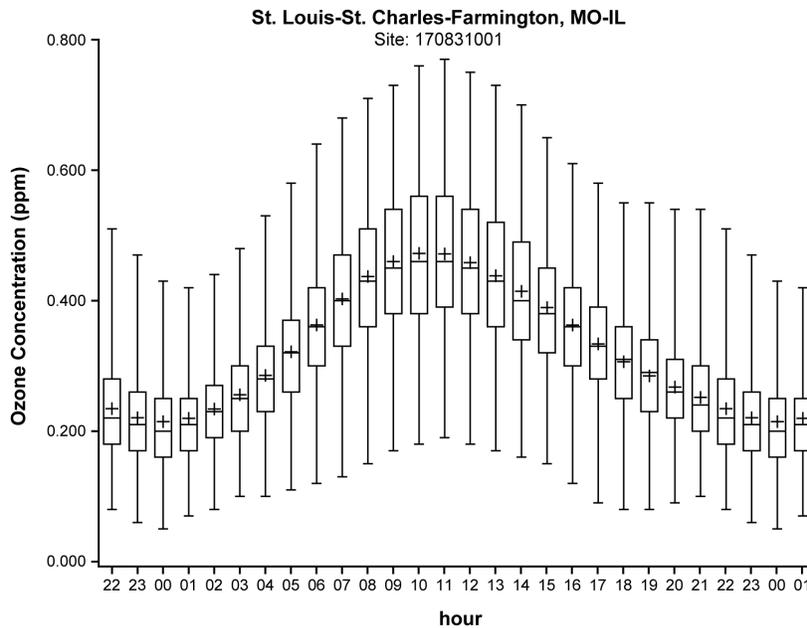


Figure AX3-53b. Diurnal variations in 8-h average O₃ at a site downwind of downtown St. Louis, MO. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

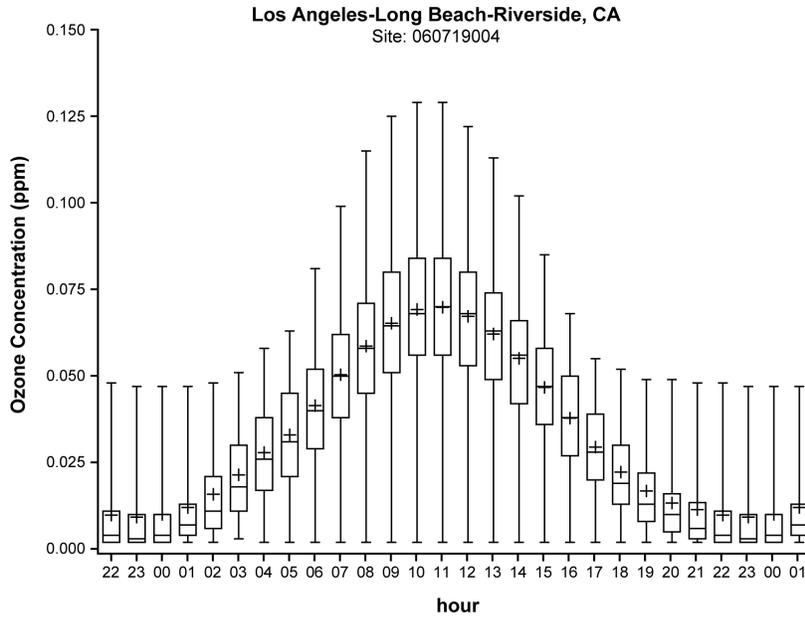


Figure AX3-54a. Diurnal variations in 8-h average O₃ at a site in San Bernadino, CA. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

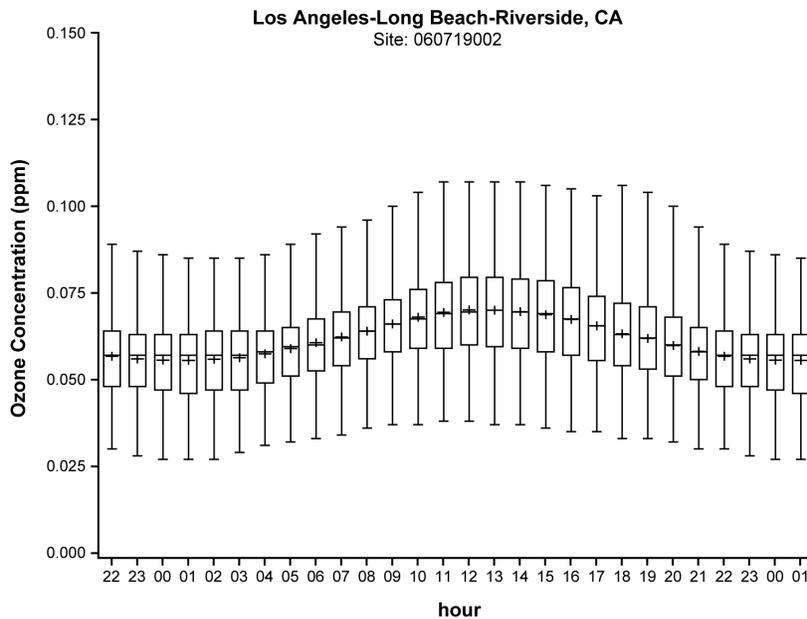


Figure AX3-54b. Diurnal variations in 8-h average O₃ at a site in Riverside County well downwind of sources. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

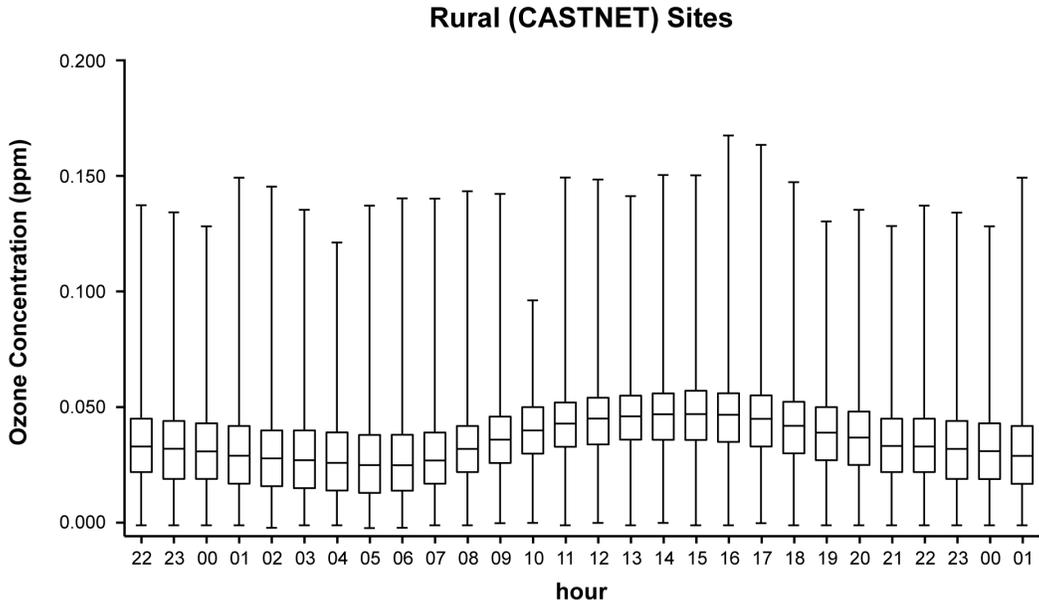


Figure AX3-55. Composite diurnal variability in hourly O₃ concentrations observed at CASTNET sites. Values shown are averages from April to October 2000 to 2004. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

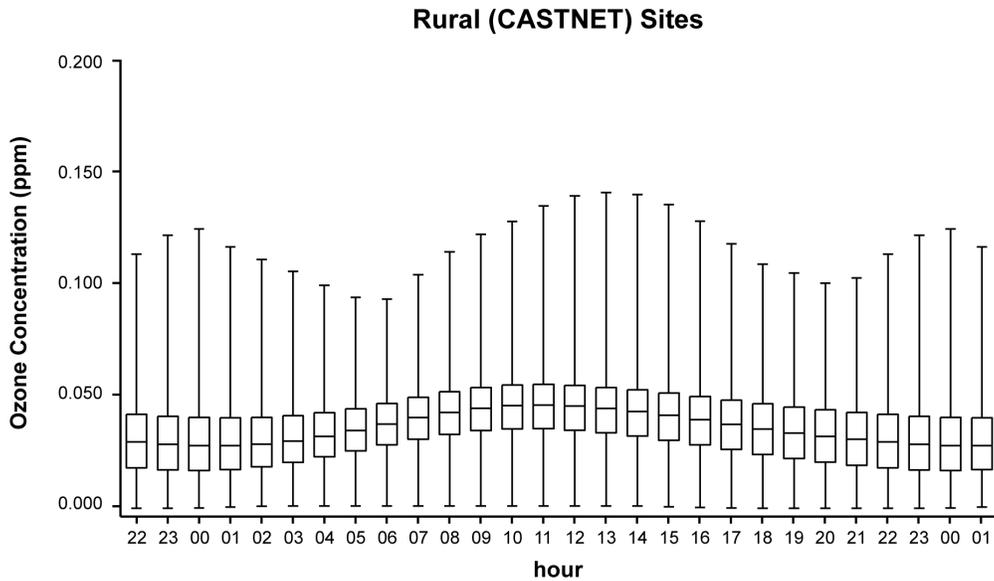


Figure AX3-56. Composite diurnal variability in 8-h average O₃ concentrations observed at CASTNET sites. Values shown are averages from April to October 2000 to 2004. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

concentrations are also much smaller at the CASTNET sites than at the urban sites. Note also that the maxima in 8-h average O₃ concentrations are higher at the CASTNET sites than at the urban sites.

The diurnal variability of O₃ in urban/suburban areas or in areas affected by local power plants and highways is usually much greater than in other more isolated areas. The diurnal variability of two sites that are characteristic of these two patterns is shown in Figure AX3-57. The Jefferson County, KY site is characterized as suburban-residential in the AQS database and is near Louisville, KY. High levels of O₃ and NO can be found there. The Oliver County, ND site is characterized as rural-agricultural in the AQS database. This site is fairly isolated from combustion sources of precursors and is not near any large urban area. As can be seen from Figure AX3-57, the diurnal variability of O₃ is much smaller at the North Dakota site than it is at the Kentucky site. The Kentucky site is influenced strongly by emissions of NO that scavenge O₃ during the night and by photochemical reactions that form O₃ during the day. These sources are lacking in the vicinity of the North Dakota site, and O₃ observed there arrives mainly from transport from distant source regions.

Logan (1989) described the diurnal variability of O₃ at several rural locations, shown in Figure AX3-58, and noted that on average, daily profiles show a broad maximum from about noon to about 6 p.m. at all the eastern sites, except for the peak of Mt. Washington. Further results that document the diurnal behavior of O₃ in the United States during the past few decades can be found in the previous AQCD for O₃. Figure AX3-59 shows diurnal patterns for several national forest sites in the EPA AQS database for 2002. Several of the sites analyzed exhibit fairly flat average diurnal patterns. Such a pattern is based on average concentrations calculated over an extended period and caution is urged in drawing conclusions concerning whether some monitoring sites illustrated in the figure experience higher cumulative O₃ exposures than other sites. Variation in O₃ concentration occurs from hour to hour on a daily basis, and, in some cases, elevated hourly average concentrations are experienced either during daytime or nighttime periods (Lefohn and Mohnen, 1986; Lefohn and Jones, 1986; Logan, 1989; Lefohn et al., 1990a; Taylor et al., 1992). Because the diurnal patterns represent averaged concentrations calculated over an extended period, the smoothing from the averaging tends to mask the elevated hourly average concentrations.

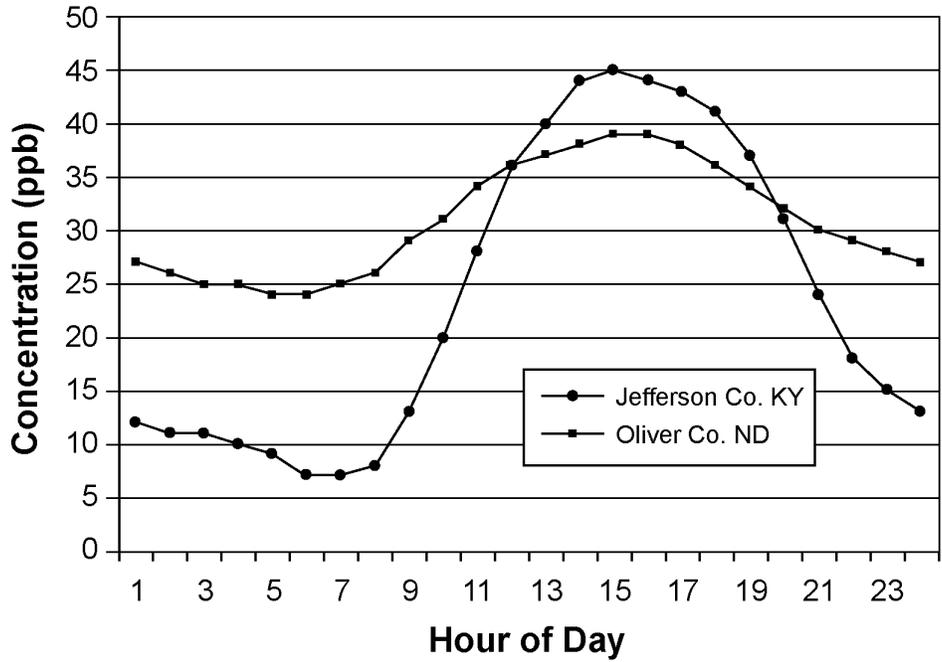


Figure AX3-57. The comparison of the seasonal diurnal patterns for urban-influenced (Jefferson County, KY) and a rural-influenced (Oliver County, ND) monitoring sites using 2002 hourly data for April-October.

Lefohn et al. (1990b) characterized O₃ concentrations at high-elevation monitoring sites. The authors reported that a fairly flat diurnal pattern for the Whiteface Mountain summit site (WF1) was observed (Figure AX3-60a), with the maximum hourly average concentrations occurring in the late evening or early morning hours. A similar pattern was observed for the mid-elevation site at Whiteface Mountain (WF3). In contrast, the site at the base of Whiteface Mountain (WF4) showed the typical diurnal pattern expected from sites that experience some degree of O₃ scavenging. More variation in the diurnal pattern for the highest Shenandoah National Park sites occurred than for the higher elevation Whiteface Mountain sites, with the typical variation for urban-influenced sites in the diurnal pattern at the lower elevation Shenandoah National Park site (Figure AX3-60b). Aneja and Li (1992), in their analysis of the five high-elevation Mountain Cloud Chemistry Program (MCCP) sites, noted the presence of the flat diurnal pattern typical of high-elevation sites that has been described previously in the literature. Aneja and Li (1992) noted that the peak of the diurnal patterns over the period of May to October (1986 to 1988) occurred between 1800 and 2400 hours for the five sites, whereas

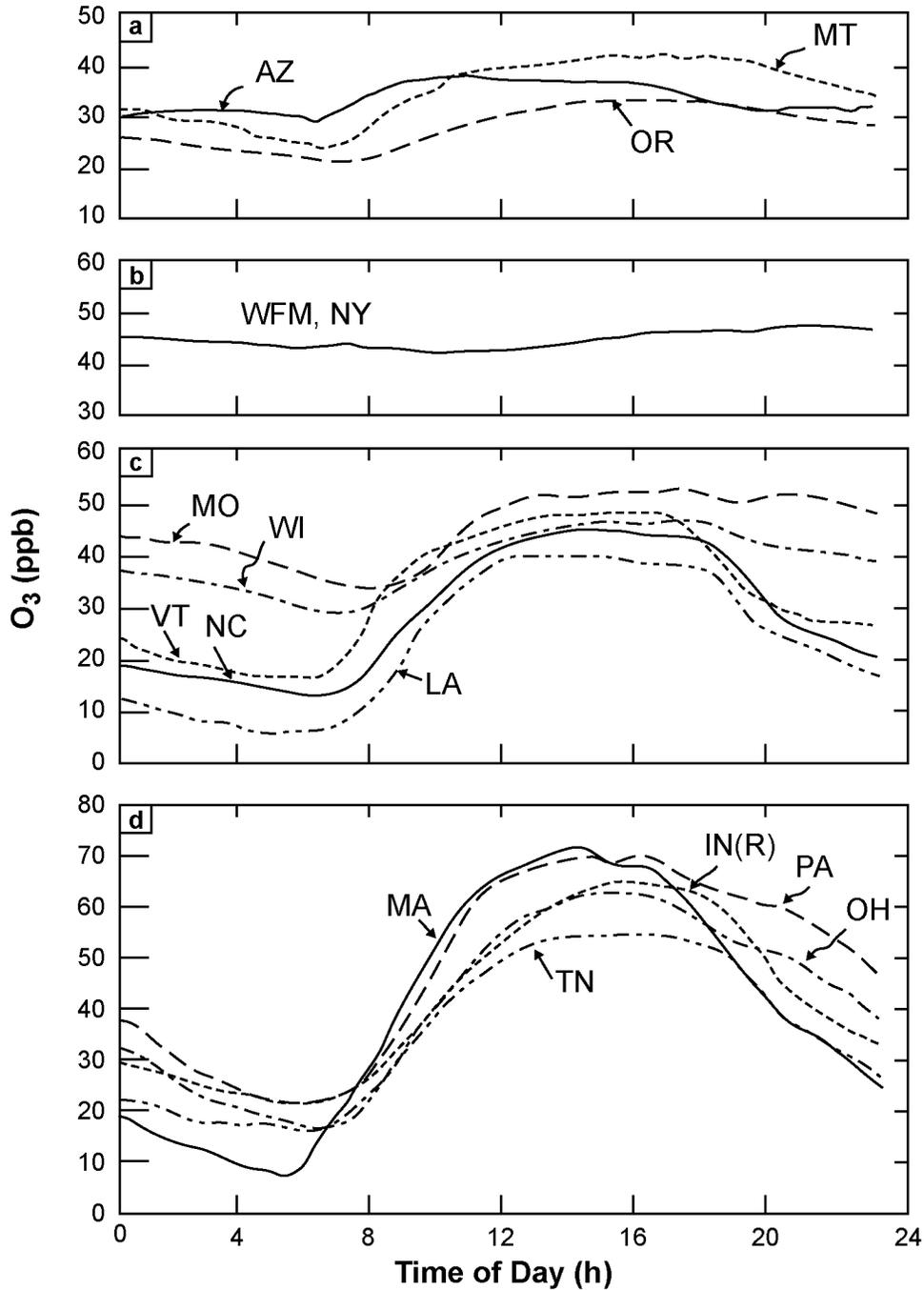


Figure AX3-58a-d. Diurnal behavior of O₃ at rural sites in the United States in July. Sites are identified by the state in which they are located. (a) Western National Air Pollution Background Network sites (NAPBN); (b) Whiteface Mountain (WFM) located at 1.5 km above sea level; (c) eastern NAPBN sites; and (d) sites selected from the Electric Power Research Institute's Sulfate Regional Air Quality Study. IN(R) refers to Rockport.

Source: Logan (1989).

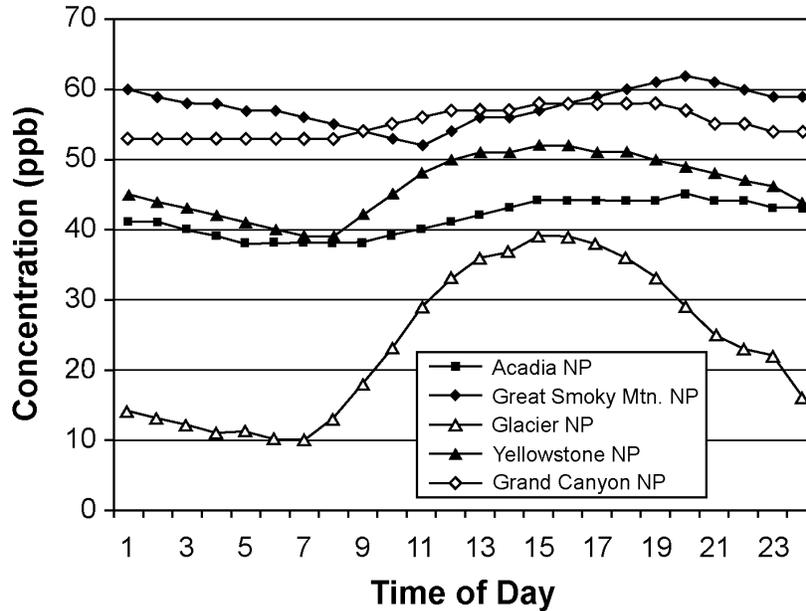


Figure AX3-59. Composite diurnal O₃ pattern at selected national forest sites in the United States using 2002 hourly average concentration data.

Source: U.S. Environmental Protection Agency (2003).

the minimum was observed between 0900 and 1200 hours. However, it is important to note that, as indicated by Lefohn et al. (1990b), the flat diurnal pattern was not observed for all high-elevation sites. As mentioned earlier, nonurban areas only marginally affected by nearby sources usually have a flatter diurnal profile than sites located in urban areas. Nonurban O₃ monitoring sites experience differing types of diurnal patterns, as shown in this section. The difference in diurnal patterns may influence the potential for O₃ exposures to affect vegetation.

AX3.5 SEASONAL VARIATIONS IN OZONE CONCENTRATIONS

AX3.5.1 Seasonal Variations in Urban Areas

Seasonal Variability

Figures AX3-61a-h show maximum 1-h O₃ concentrations by month for selected urban sites for 2002. As can be seen from the figure, maximum 1-h O₃ concentrations tend to occur mainly in July and August, but may also occur in other months. For example, they occurred in

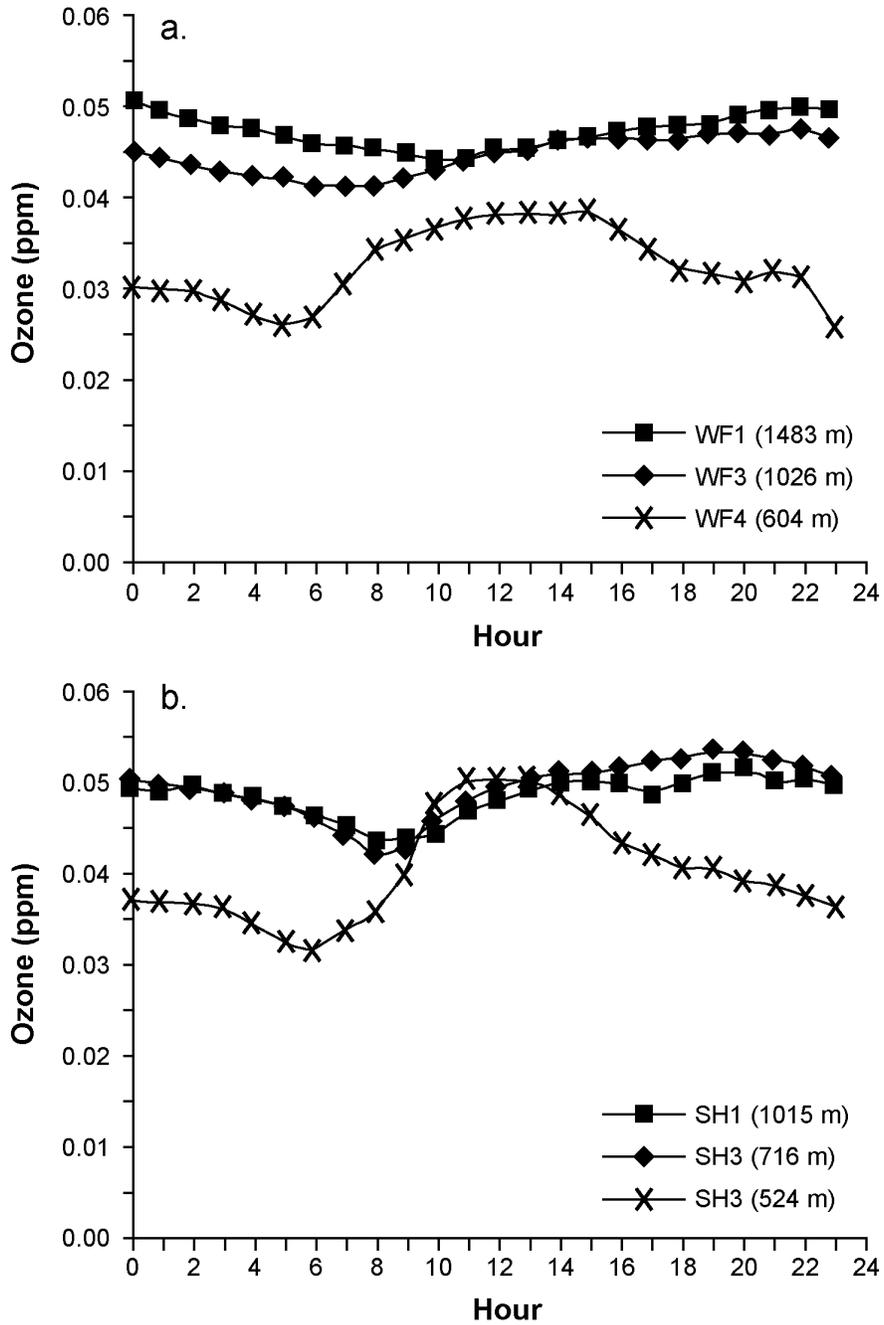


Figure AX3-60a,b. Composite diurnal pattern at (a) Whiteface Mountain, NY and (b) the Mountain Cloud Chemistry Program Shenandoah National Park site for May to September 1987.

Source: Lefohn et al. (1990a).

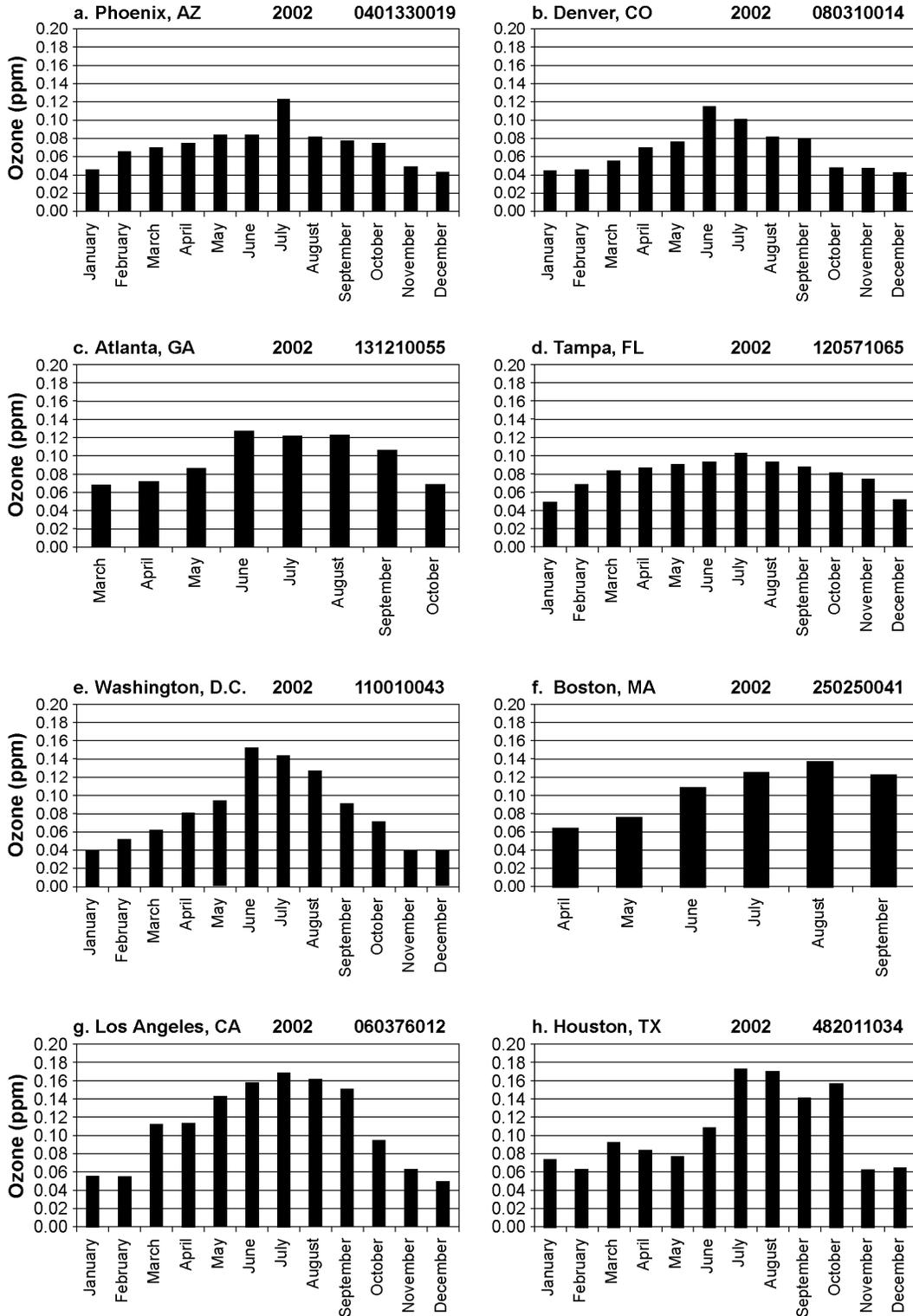


Figure AX3-61a-h. Seasonal variations in O₃ concentrations as indicated by the 1-h maximum in each month at selected sites, 2002.

Source: U.S. Environmental Protection Agency (2003).

June in Washington, DC and Denver, CO. The number of months for which data are shown depends on local preference for the length of monitoring during the year. Due to a number of factors, the absolute magnitude and the timing of the maximum hourly average concentrations varies from year to year.

It should not be assumed that highest O₃ levels are confined to the summer. Highest average O₃ concentrations generally occur at RRMS during the second quarter (i.e., during April or May) versus the third quarter of the year as for urban sites or for nonurban sites heavily affected by regional pollution sources.

The seasonal behavior of O₃ varies across the 12 cities and high O₃ values are also found at some of the 12 cities outside of summer (e.g., Houston and Los Angeles). Figures AX3-62a-1 show the diurnal variability of hourly average O₃ averaged over November through March for EPA's 12 cities. Daily maxima tend to occur between about 1 and 2 p.m. standard time is used across the U.S. accounting for the one hour shift from the warm season. As expected, maximum values tend to be lower than during the warmer months. The diurnal patterns are not as clear as in the warmer season as there is a greater tendency for highest values to occur throughout the day and not only during early afternoon. In most northern cities, the extreme values of the daily maximum 8-h average O₃ concentration are a little more than half of those during the warm season and the ratio of the medians are more similar as can be judged by comparison of Figures AX3-41a-1 with Figures AX3-62a-1. Differences are even smaller for the southern cities. Indeed, some of the highest values are found in the Houston CSA outside of summer.

Figures AX3-63a-1 show the diurnal variability of 8-h average O₃ averaged over November through March for EPA's 12 cities.

AX3.5.2 Seasonal Variations in Nonurban Areas

In assessing the effects of O₃ on vegetation, it is important to characterize the seasons in which the highest O₃ concentrations would be expected to occur in nonurban areas. It should not be assumed that highest O₃ concentrations occur at all locations during the summer. For example, places where highest average O₃ concentrations are observed during the spring (i.e., the months of April or May) versus the summer (Evans et al., 1983; Singh et al., 1978; Lefohn et al., 2001) are found at many national parks in the West. Figure AX3-23 shows the hourly average concentrations for Yellowstone National Park (WY) for the period of January to December 2001.

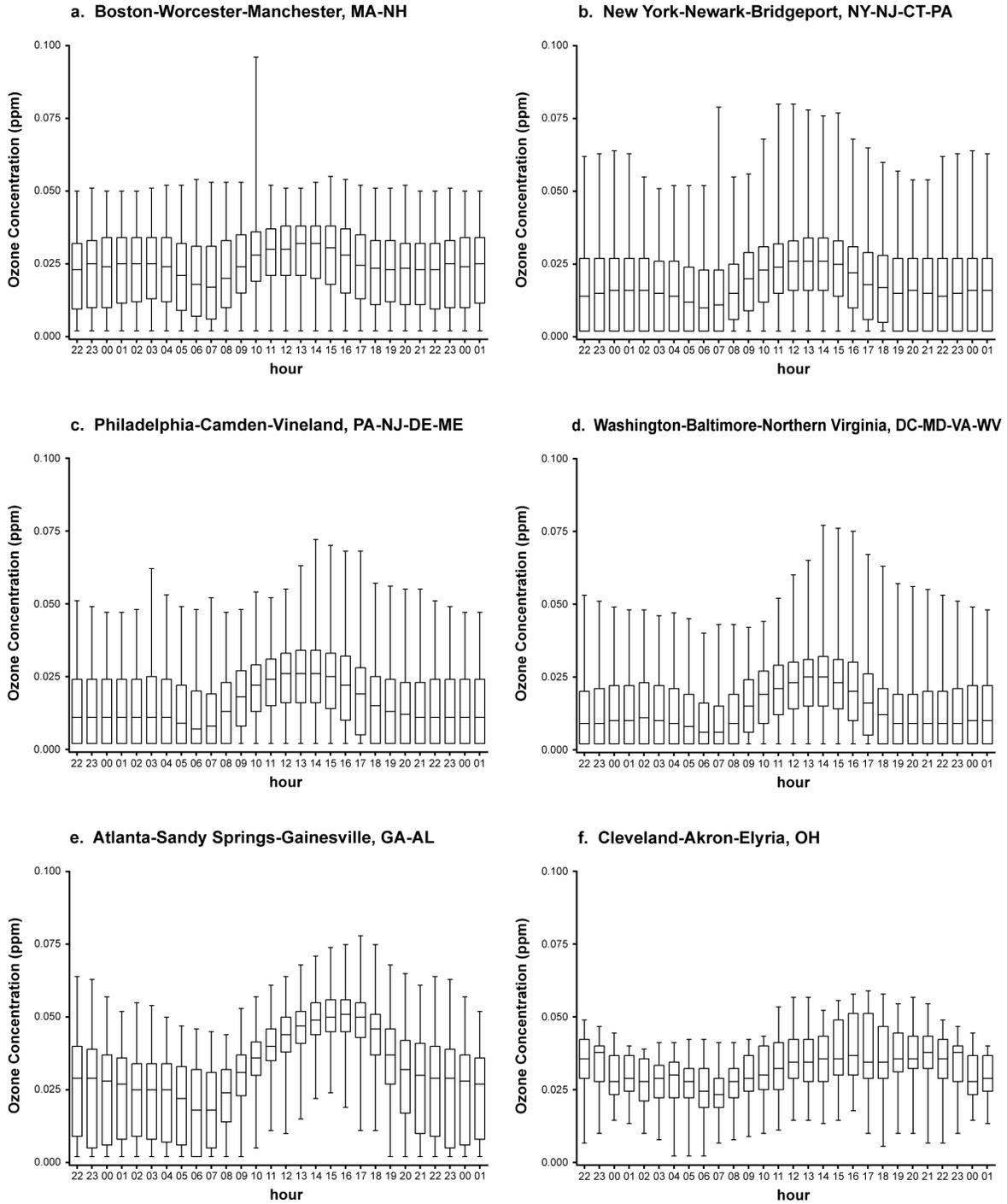


Figure AX3-62a-f. Diurnal variability in 1-h average O₃ concentrations in EPA's 12 cities. Values shown represent averages from November through March, 2000 to 2004. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al., (2005)

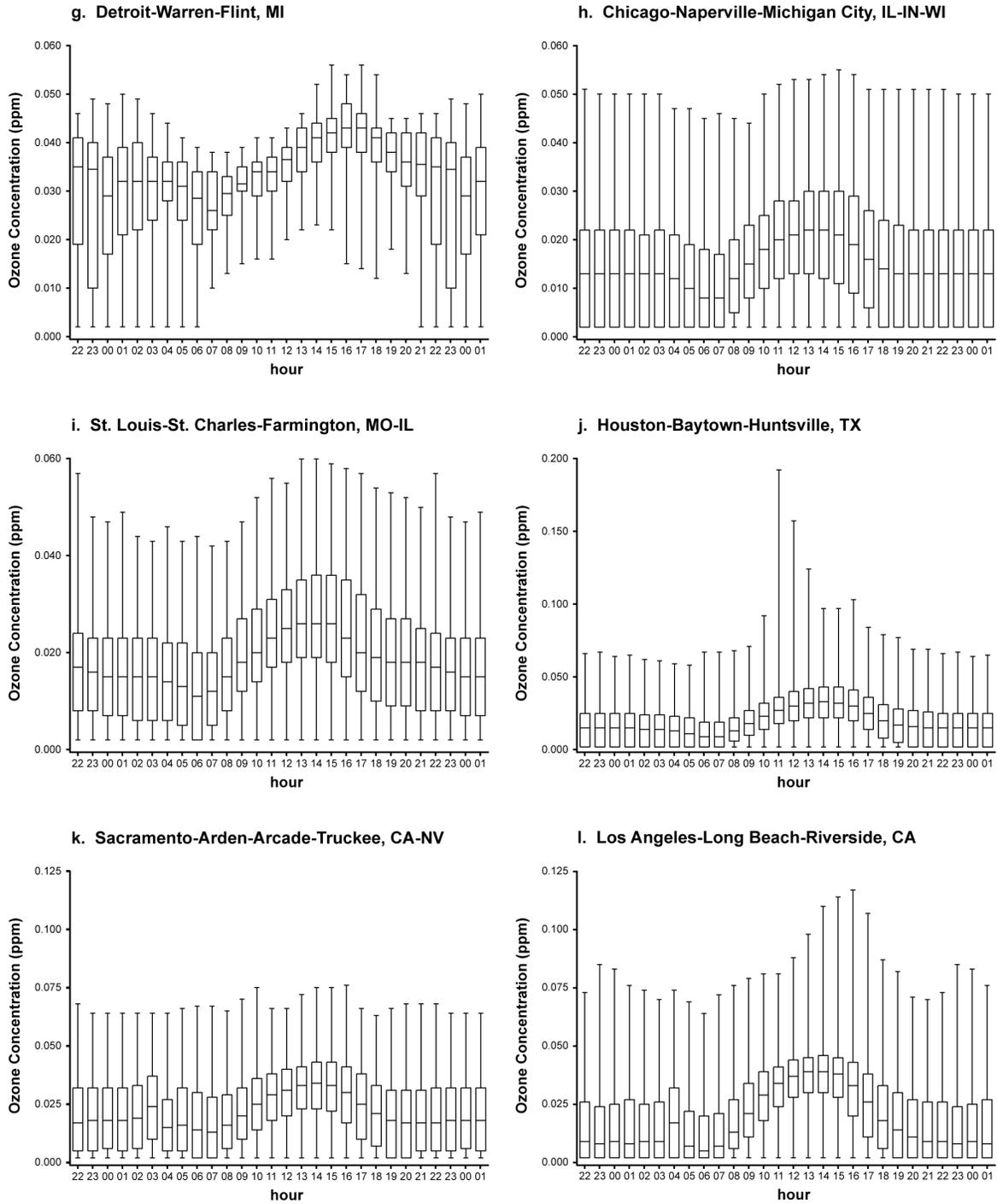


Figure AX3-62g-l. Diurnal variability in 1-h average O₃ concentrations in EPA's 12 cities. Values shown represent averages from November through March, 2000 to 2004. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al., (2005)

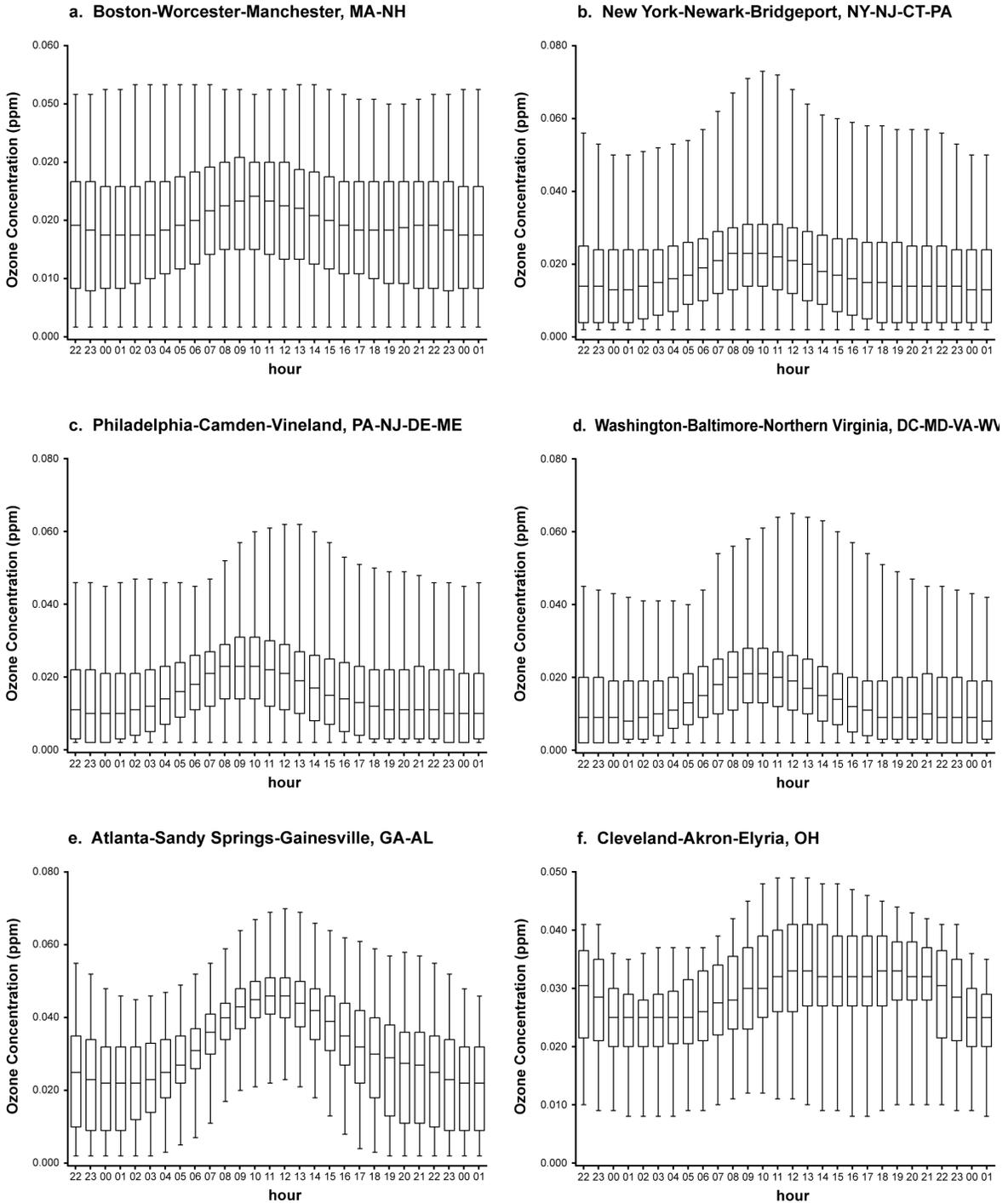


Figure AX3-63a-f. Diurnal variability in 8-h average O₃ concentrations in EPA's 12 cities. Values shown represent averages from November through March, 2000 to 2004. Boxes define the interquartile range and the whiskers, the minima and maxima. The hour refers to the start of the 8-h averaging period.

Source: Fitz-Simons et al. (2005).

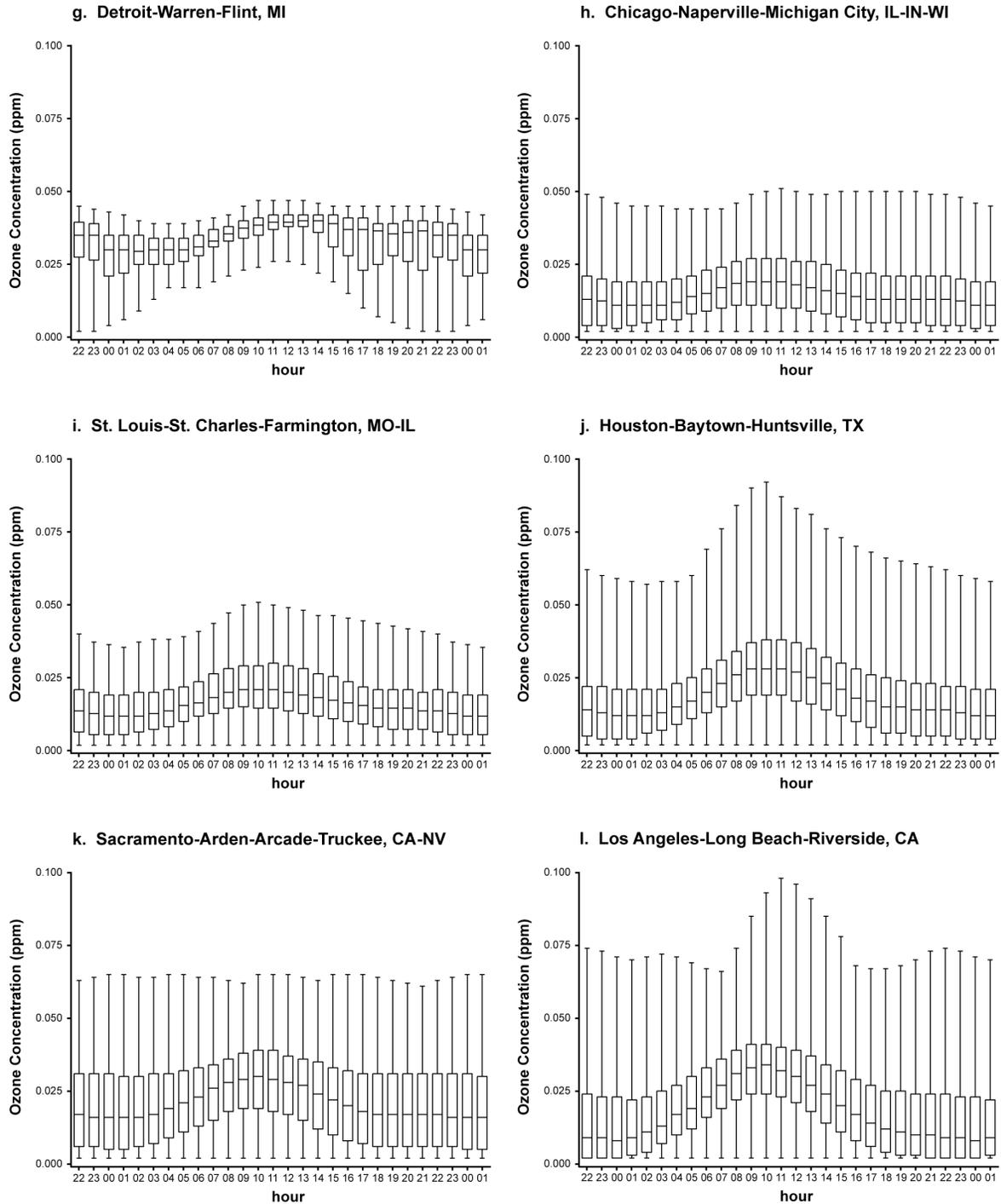


Figure AX3-63g-l. Diurnal variability in 8-h average O₃ concentrations in EPA's 12 cities. Values shown represent averages from November through March, 2000 to 2004. Boxes define the interquartile range and the whiskers, the minima and maxima. The hour refers to the start of the 8-h averaging period.

Source: Fitz-Simons et al. (2005).

Note that, at the Yellowstone National Park site, the highest hourly average concentrations tend to occur during April and May. Lefohn et al. (2001) and Monks (2000) noted that this was also observed for other RRMS in North America and northern Europe.

During spring and summer, O₃ concentrations in rural areas of the eastern United States are affected differently by anthropogenic and natural emissions of NO_x and hydrocarbons. These differences can affect the timing of occurrence of local peak O₃ concentrations (Logan, 1989). O₃ episodes occur when the weather is particularly conducive to photochemical formation of O₃. Taylor et al. (1992) reported that the temporal patterns of O₃ during quarterly or annual periods did not exhibit definitive patterns at 10 forest sites in North America. Based on the exposure index selected, different patterns were reported. Meagher et al. (1987) reported that for rural O₃ sites in the southeastern United States, the daily maximum 1-h average concentration was found to peak during the summer months. Taylor and Norby (1985) reported that at Shenandoah National Park, both the highest frequency of episodes and the highest mean duration of exposure events are found during the month of July.

Aneja and Li (1992) reported that the maximum monthly O₃ levels at several rural sites occurred in either the spring or the summer (May to August), and the minimum occurred in the fall (September and October). The timing of the maximum monthly values differed across sites and years. However, in 1988, an exceptionally high O₃ concentration year occurred, and the highest monthly average concentration occurred in June for almost all of the five sites investigated. June 1988 was also the month in which the greatest number of O₃ episodes occurred in the eastern United States.

Lefohn et al. (1990a) characterized the O₃ concentrations for several sites in the United States exhibiting low maximum hourly average concentrations. Of the three western national forest sites evaluated by Lefohn et al. (1990a), Apache National Forest (AZ), Custer National Forest (MT), and Ochoco National Forest (OR), only at Apache National Forest (AZ) did maximum monthly mean concentrations occur in the spring. The Apache National Forest site was above mean nocturnal inversion height, and no decrease of concentrations occurred during the evening hours. Highest hourly maximum concentration, as well as the highest W126 O₃ exposures were also found at this site. Most of the maximum monthly mean concentrations occurred in the summer at the other two sites. Maximum monthly mean O₃

concentrations were found at the White River Oil Shale site in Colorado during the spring and summer months.

The W126 sigmoidal weighting exposure index was also used to identify the month of highest exposure of vegetation to O₃. A somewhat more variable pattern was observed than when the maximum monthly average concentration was used. In some cases, the highest W126 exposures occurred earlier in the year than was indicated by the maximum monthly concentration. For example, in 1979, the Custer National Forest site experienced its highest W126 exposure in April, although the maximum monthly mean occurred in August. In 1980, the reverse occurred.

There was no consistent pattern for those sites located in the continental United States. Maximum exposures to O₃ during the spring and summer at the Theodore Roosevelt NP, Ochoco, and Custer National Forest sites and the White River Oil Shale site. Likewise, the sites at which highest exposures to O₃ occurred during the period from fall to spring did not always have the lowest exposures to O₃.

AX3.6 TRENDS IN OZONE CONCENTRATIONS

Evidence for Trends in Ozone Concentrations at Rural Sites in the United States

Year-to-year variability in the nationwide May to September, mean daily maximum 8-h O₃ concentrations are shown in Figure AX3-64. Data flagged because of quality control issues was removed with concurrence of the local monitoring agency. Only days for which there was 75% data capture (i.e., 18 of 24 hours) were kept, and a minimum of 115 of 153 days (i.e., 75% data capture) were required in each year. Data for missing years at individual sites were filled in using simple linear interpolation, as done in EPA Trends reports. Year-to-year variability in the corresponding 95th percentile values of the daily maximum 8-h O₃ concentrations are shown in Figure AX3-65. Sites considered in this analysis are shown in the map in Figure AX3-3. Mean O₃ concentrations were slightly lower in 2003 and 2004 than in earlier years, and as was shown in Figures AX3-1 and AX3-2, most sites are located in the East. The summer of 2003 was slightly cooler than normal in the East (Levinson and Waple, 2004) and the summer of 2004 was much cooler than normal in the East (Levinson, 2005) accounting in part for the dip in O₃ during these 2 years. Trends in compliance metrics such as the fourth

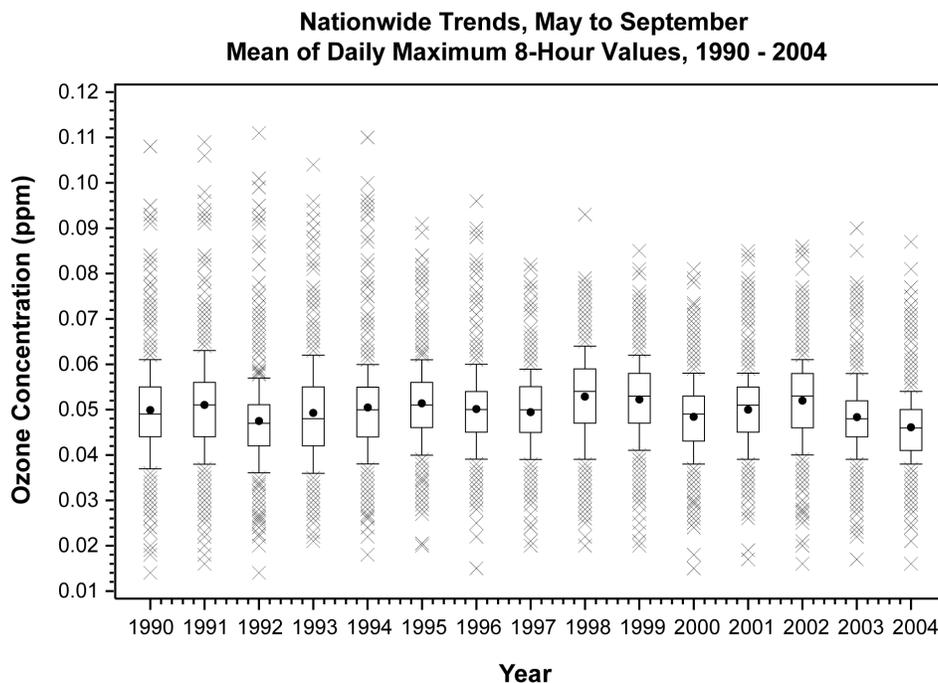


Figure AX3-64. Year-to-year variability in nationwide mean daily maximum 8-h O₃ concentrations. The whiskers on the box plot represent the 10th and 90th percentile concentrations. The “X”s above and below the whiskers are the values that fall below and above the 10th and 90th percentile concentrations. The dots inside the box represent the mean, for the statistic, at all sites.

Source: Fitz-Simons et al. (2005).

highest daily maximum 8-h average O₃ concentration can be found in the EPA Trends reports and so are not repeated here.

Figures AX3-66a-h show year-to-year variability in mean daily 8-h O₃ concentrations observed at selected national park sites across the United States. Figures AX3-67a-h show year-to-year variability in the 95th percentile value of daily maximum 8-h O₃ concentrations at the same sites shown in Figures AX3-66a-h. The same criteria used for calculating values in Figures AX3-64 and AX3-65 were used for calculating the May to September seasonal averages for the national parks shown in Figures AX3-66a-h and 67a-h. Trends at these national parks are shown in Table AX3-9. However, several monitoring sites were moved during the period from 1990 to 2004. Sites were moved at Acadia NP in 1996, Joshua Tree NP in 1993, Mammoth

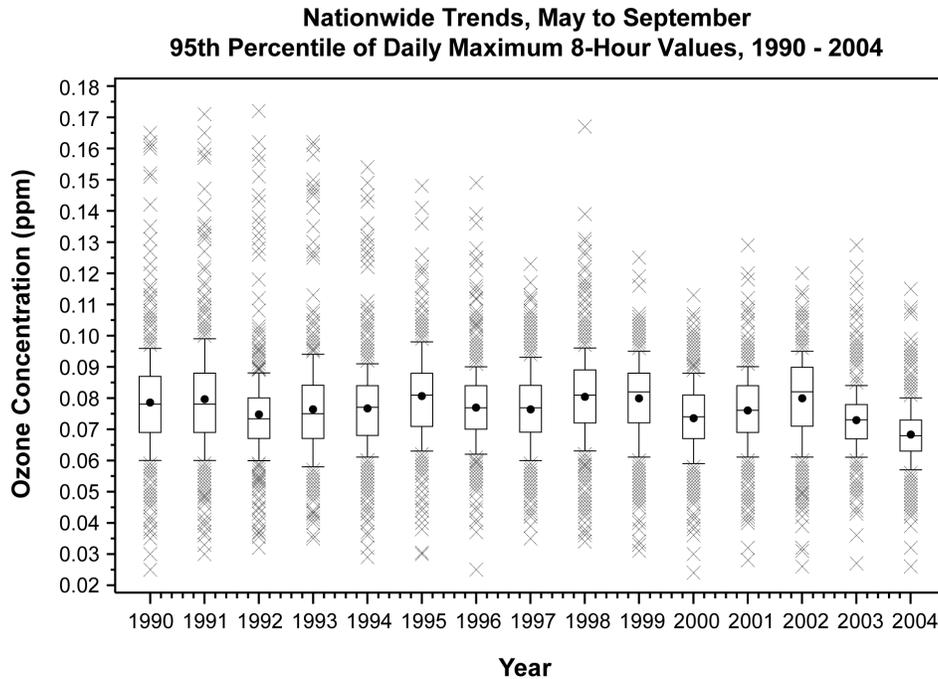


Figure AX3-65. Year-to-year variability in nationwide 95th percentile value of the daily maximum 8-h O₃ concentrations. The whiskers on the box plot represent the 10th and 90th percentile values for the statistic. The “X”s above and below the whiskers are the values that fall below and above the 10th and 90th percentile values. The dots inside the box represent the mean, for the statistic, at all sites.

Source: Fitz-Simons et al. (2005).

Cave NP in 1996, Voyageurs NP in 1996, and Yellowstone NP in 1996 and offsets in O₃ concentrations have resulted. As a result, trends are not shown for these sites.

As noted in The Ozone Report—Measuring Progress through 2003 (U.S. Environmental Protection Agency, 2004b), O₃ trends in national parks in the South and the East are similar to nearby urban areas and reflect the regional nature of O₃ pollution. For example, O₃ trends in Charleston, SC and Charlotte, NC track those in nearby Cowpens NP and Cape Romaine NP in South Carolina; O₃ in Knoxville and Nashville, TN tracks O₃ in Great Smoky NP; O₃ in Philadelphia, PA and Baltimore, MD tracks Brigantine NP in New Jersey; and New York, NY and Hartford, CT track O₃ in Cape Cod NS. The situation is not as clear in the West, where national parks are affected differently by pollution sources that are located at varying distances away (e.g., Lassen Volcanic National Park and Yosemite National Park, CA). However, data

May to September Mean of Daily Maximum 8-Hour Values, 1990 - 2004

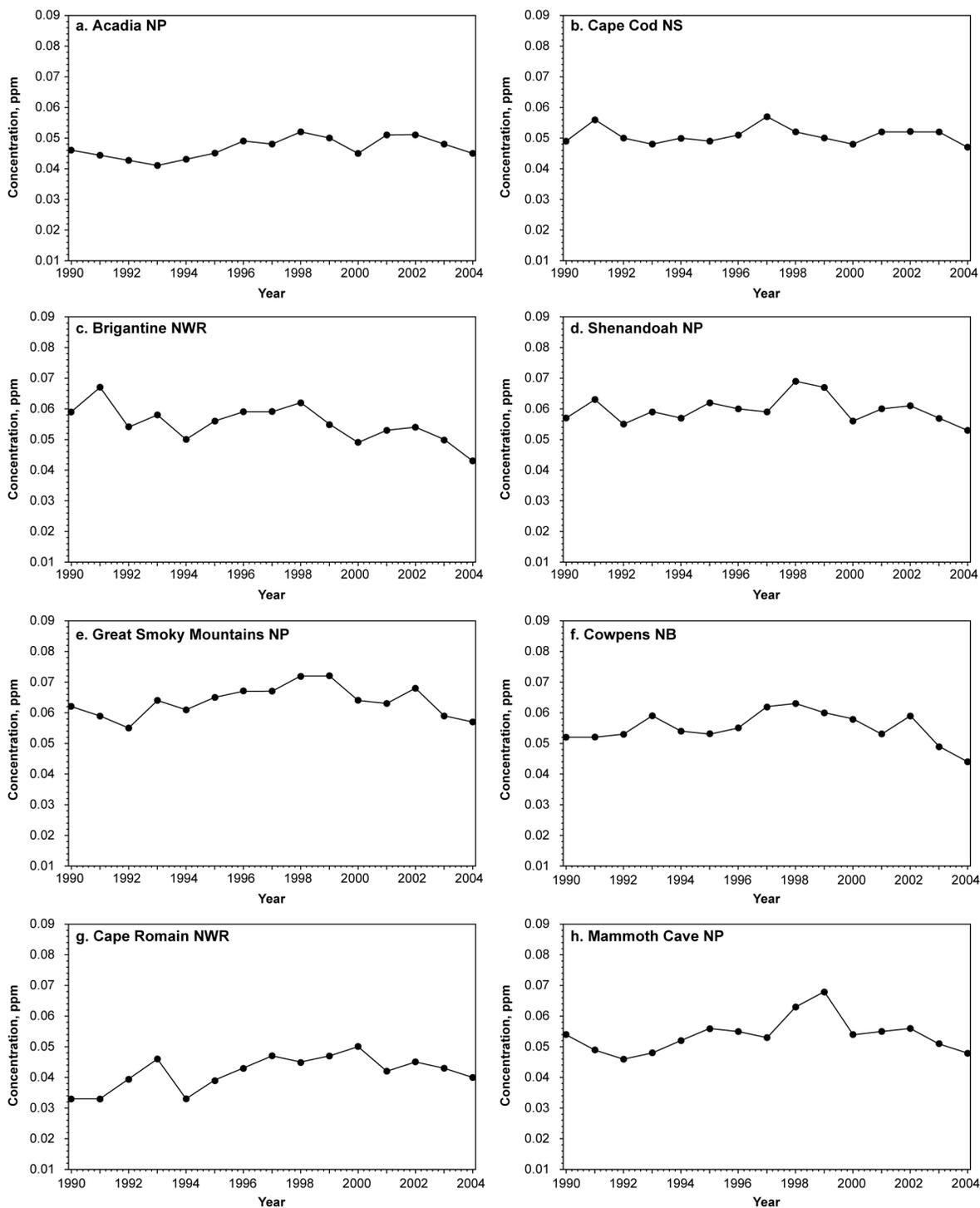


Figure AX3-66a-h. Year-to-year variability in mean daily maximum 8-h O₃ concentrations at selected national park (NP), national wildlife refuge (NWR), and national monument (NM) sites.

Source: Fitz-Simons et al. (2005).

May to September Mean of Daily Maximum 8-Hour Values, 1990 - 2004

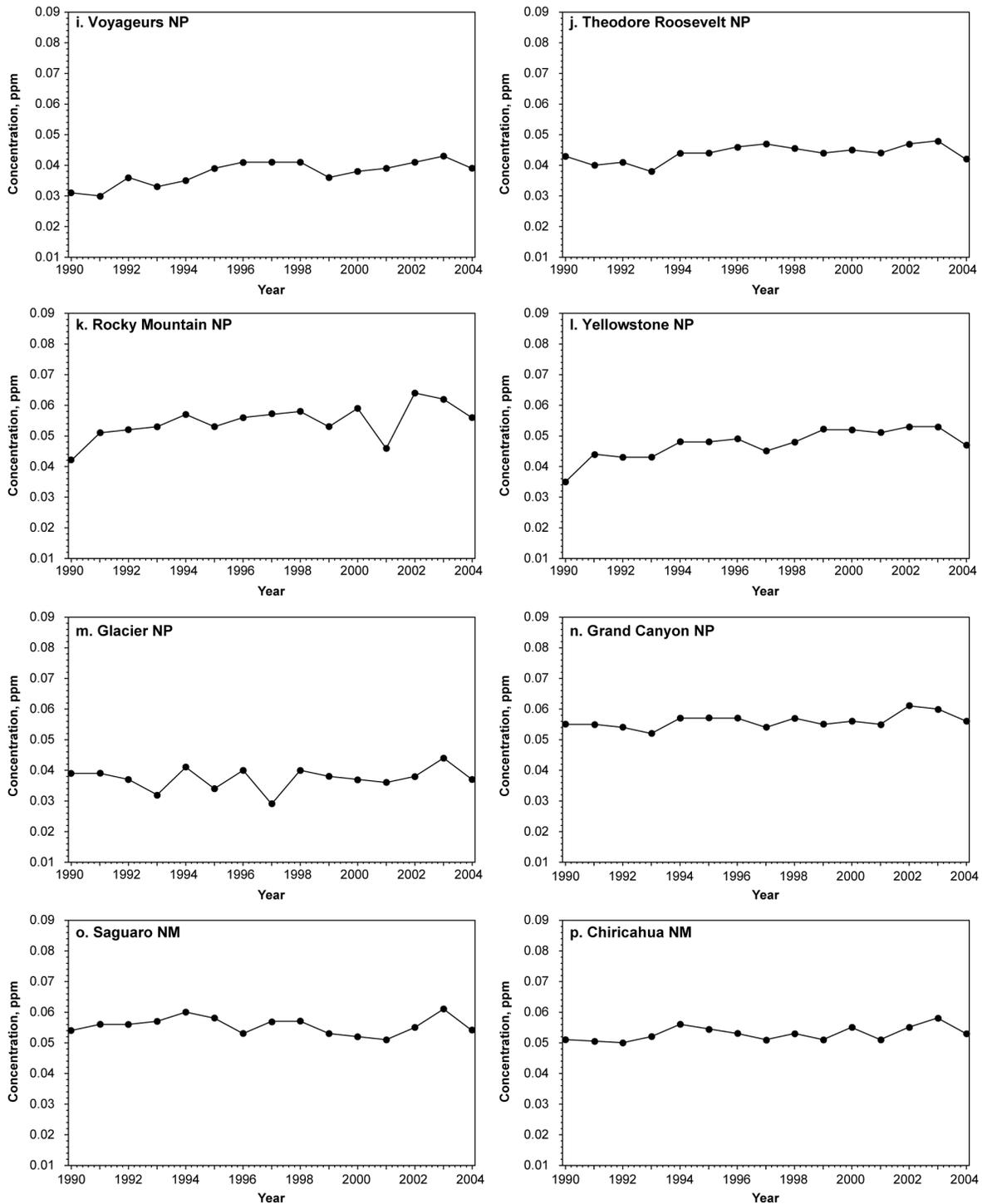


Figure AX3-66i-p. Year-to-year variability in mean daily maximum 8-h O₃ concentrations at selected national park (NP), national wildlife refuge (NWR), and national monument (NM) sites.

Source: Fitz-Simons et al. (2005).

May to September Mean of Daily Maximum 8-Hour Values, 1990 - 2004

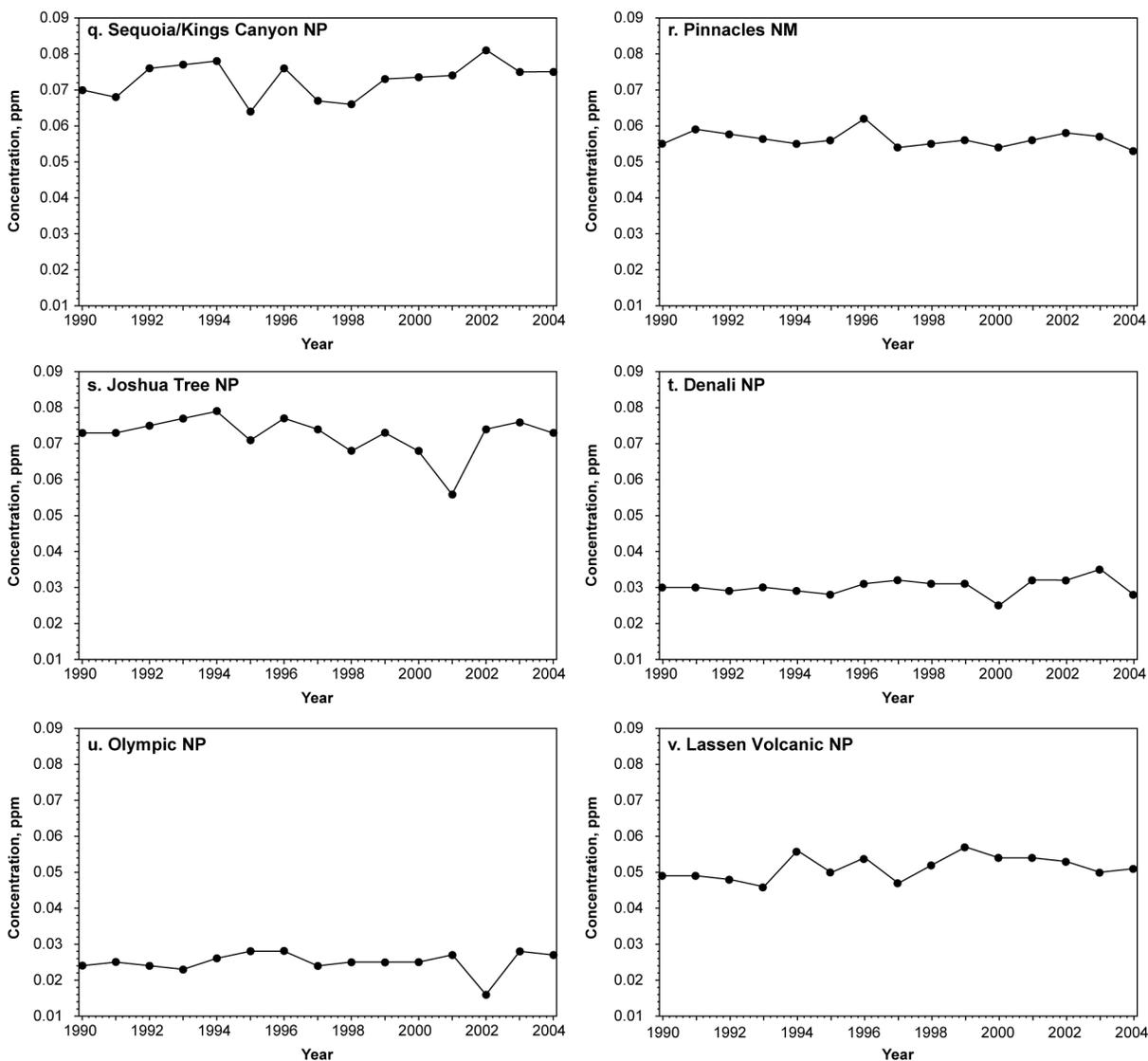


Figure AX3-66q-v. Year-to-year variability in mean daily maximum 8-h O₃ concentrations at selected national park (NP), national wildlife refuge (NWR), and national monument (NM) sites.

Source: Fitz-Simons et al. (2005).

obtained at these sites still provide valuable information about the variability in regional background concentrations, especially since the West has not been broken down into regions as has been done by Lehman et al. (2004) and shown in Figure AX3-7.

May to September 95th Percentile of Daily Maximum 8-Hour Values, 1990 - 2004

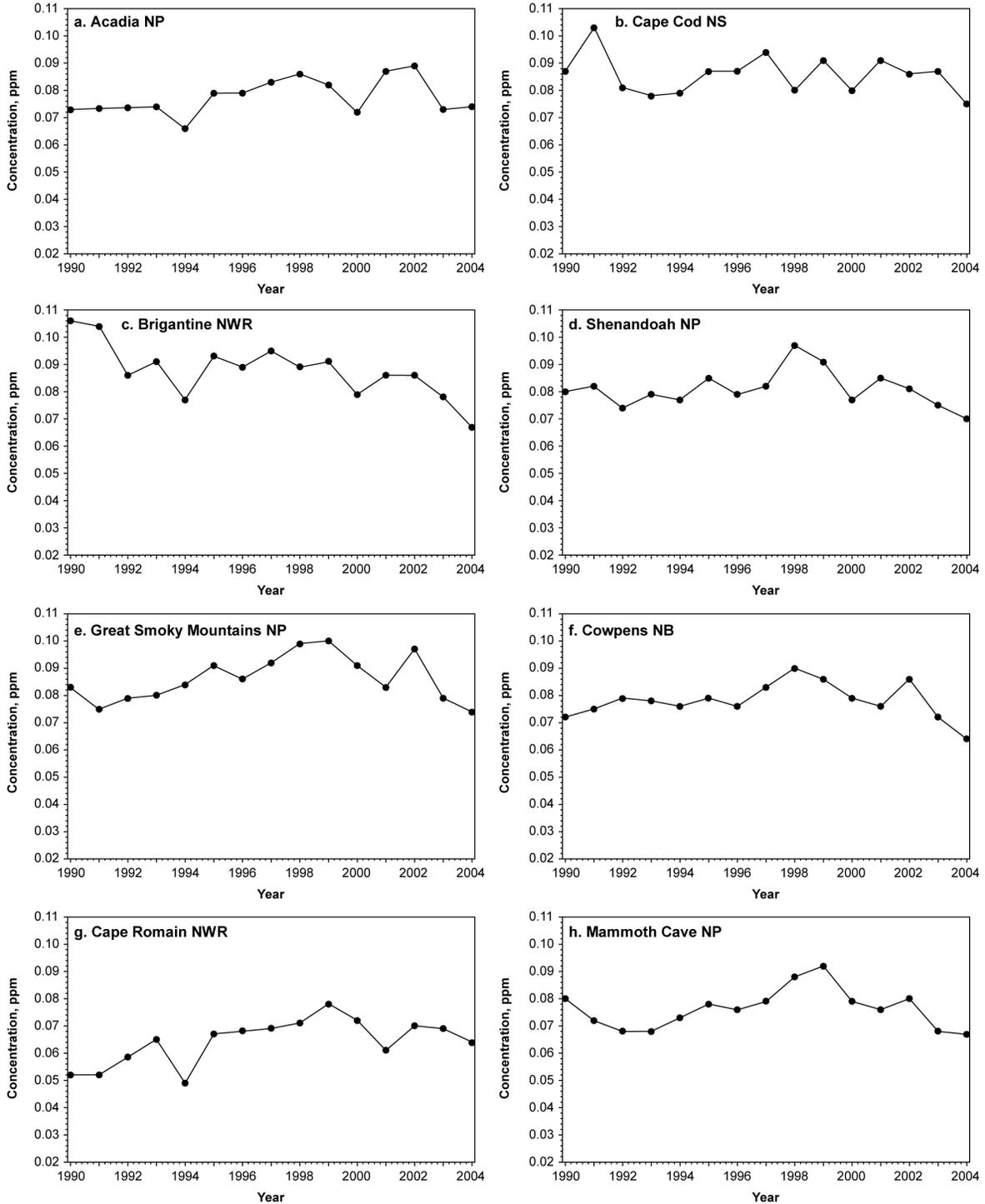


Figure AX3-67a-h. Year-to-year variability in 95th percentile of daily maximum 8-h O_3 concentrations at selected national park (NP), national wildlife refuge (NWR), and national monument (NM) sites.

Source: Fitz-Simons et al. (2005).

May to September 95th Percentile of Daily Maximum 8-Hour Values, 1990 - 2004

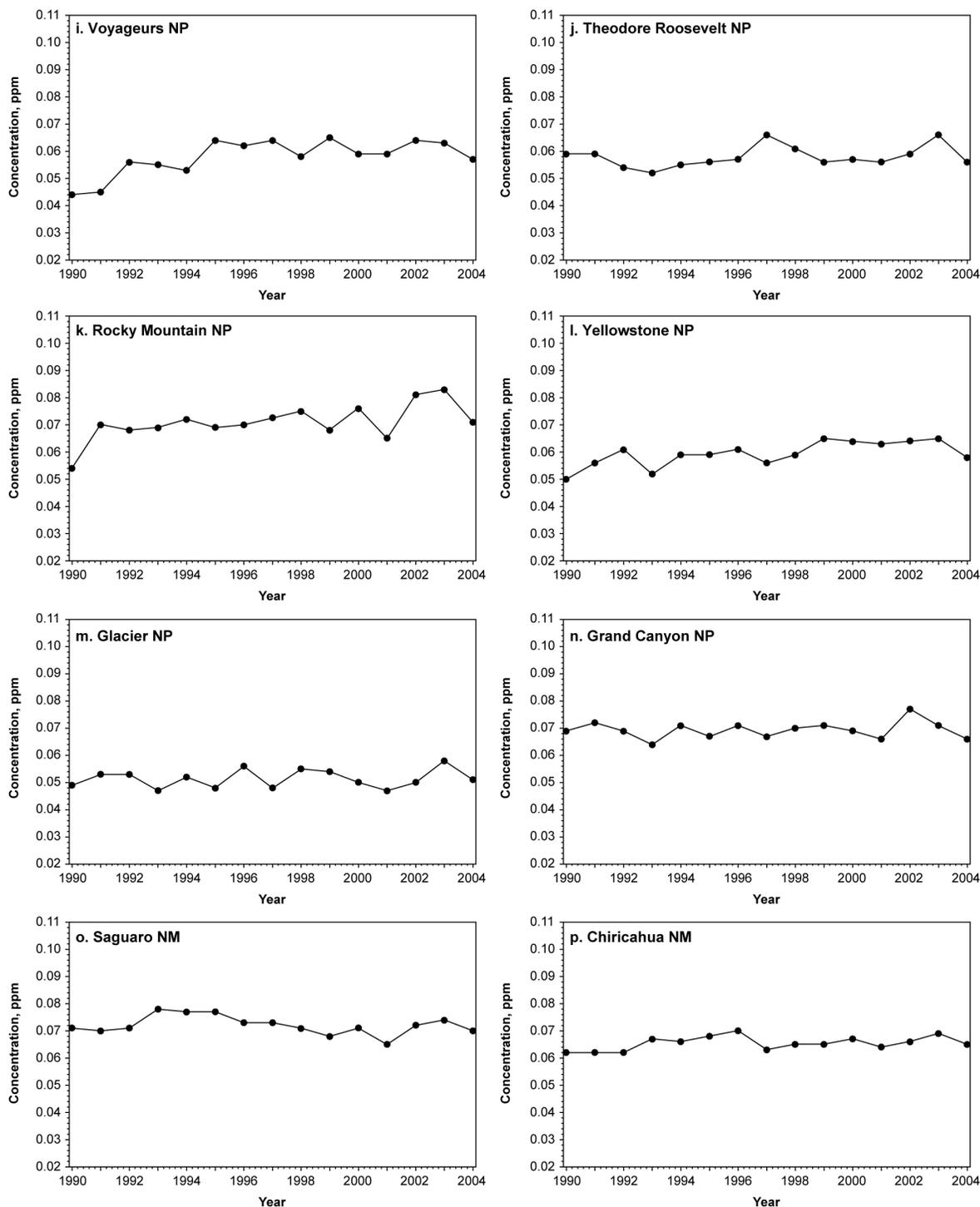


Figure AX3-67i-p. Year-to-year variability in 95th percentile of daily maximum 8-h O_3 concentrations at selected national park (NP), national wildlife refuge (NWR), and national monument (NM) sites.

Source: Fitz-Simons et al. (2005).

May to September 95th Percentile of Daily Maximum 8-Hour Values, 1990 - 2004

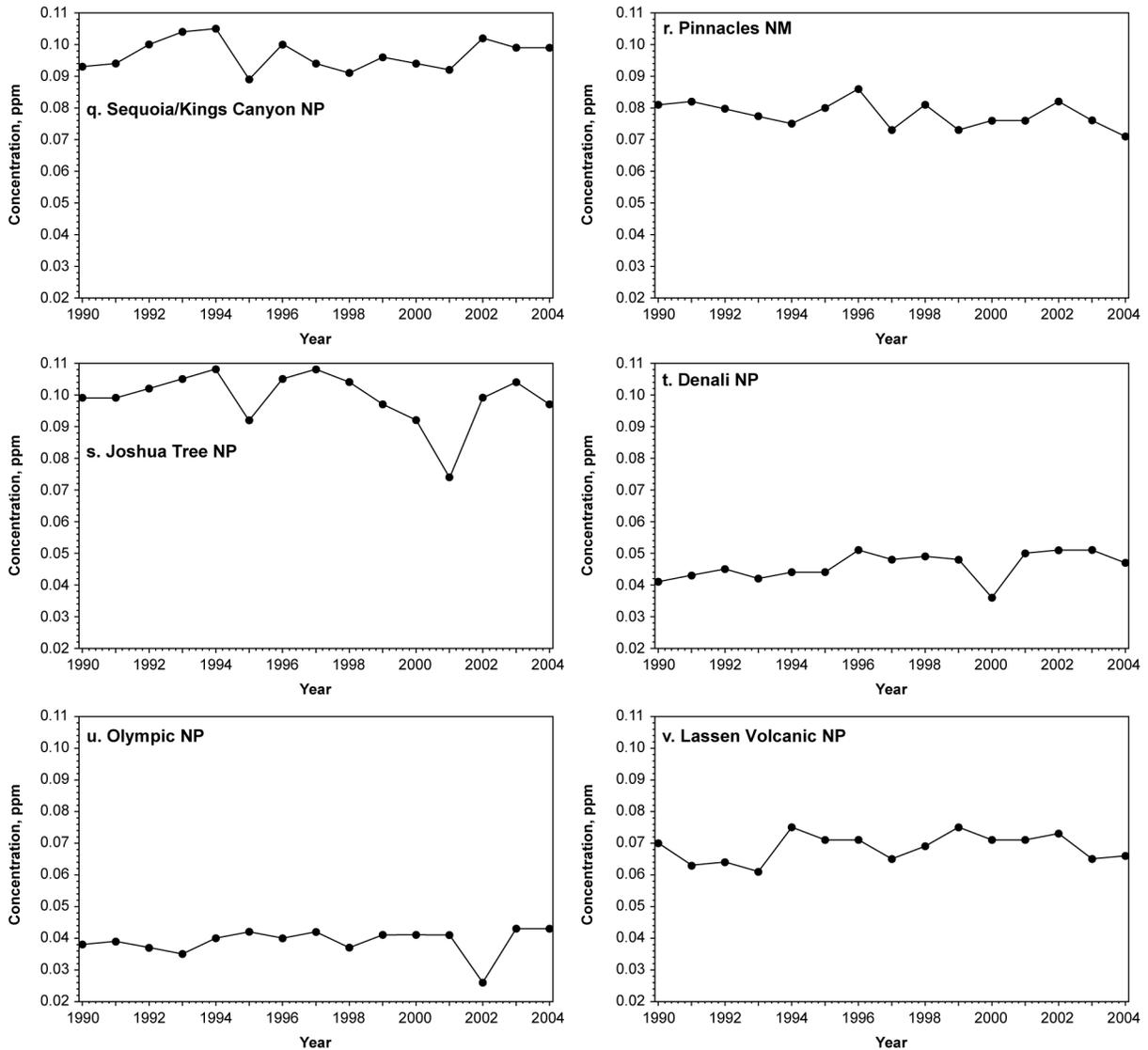


Figure AX3-67q-v. Year-to-year variability in 95th percentile of daily maximum 8-h O_3 concentrations at selected national park (NP), national wildlife refuge (NWR), and national monument (NM) sites.

Source: Fitz-Simons et al. (2005).

Caution should be exercised in using trends calculated at national parks to infer contributions from distant sources either inside or outside of North America, because of the influence of local and regional pollution. For example, using a 15-year record of O_3 from Lassen

Table AX3-9. Trends in Warm Season (May to September) Daily Maximum 8-h O₃ Concentrations at National Parks in the United States (1990 to 2004). Trends are given as ppb yr⁻¹.

Site	Mean		P 95		P 98	
	trend	p-value	trend	p-value	trend	p-value
Acadia NP (ME)	0.040 ¹	0.037	1.0 ¹	0.037	-0.2	0.349
Brigantine NWR (NJ)	-0.80 ²	0.014	-1.7 ²	0.004	-1.9 ²	0.003
Cape Cod NS (MA)	0	0.423	0	0.349	-0.5	0.19
Cape Romain NWR (SC)	0.7 ¹	0.046	1.0 ¹	0.01	1.0	0.07
Chiricahua NM (AZ)	0.22 ¹	0.046	0.2	0.084	0.15	0.218
Cowpens NB (SC)	0	0.423	0.1	0.349	0.4	0.349
Denali NP (AK)	0.17	0.12	0.6 ¹	0.01	0.6 ¹	0.002
Glacier NP (MT)	0	0.5	0.1	0.349	0.27	0.19
Grand Canyon NP (AZ)	0.25	0.07	0	0.5	0.13	0.218
Great Smoky Mountains NP (NC-TN)	0.29	0.248	0.9	0.19	0.4	0.423
Joshua Tree NP (CA) ³	—	—	—	—	—	—
Lassen Volcanic NP (CA)	0.25	0.141	0.2	0.19	0	0.5
Mammoth Cave NP (KY) ³	—	—	—	—	—	—
Olympic NP (WA)	0.14	0.141	0.3 ¹	0.037	0.2	0.19
Pinnacles NM (CA)	-0.1	0.218	-0.5	0.07	-0.56	0.057
Rocky Mountain NP (CO)	0.91 ¹	0.004	1.0 ¹	0.014	0.88	0.07
Saguaro NM (AZ)	-0.2	0.279	-0.3	0.19	-0.38	0.141
Sequoia/Kings Canyon NP (CA)	0.38	0.218	0	0.461	0	0.539
Shenandoah NP (VA)	0	0.461	-0.2	0.385	0.33	0.279
Theodore Roosevelt NP (ND)	0.38 ¹	0.023	0.2	0.19	0.2	0.141
Voyageurs NP (MN) ³	—	—	—	—	—	—
Yellowstone NP (WY) ³	—	—	—	—	—	—

¹ Upward trend, significant at p = 0.05 level.

² Downward trend, significant at p = 0.05 level.

³ Site moved. See text for details.

Volcanic National Park, a rural elevated site in northern California; data from two aircraft campaigns; and observations spanning 18 years from five U.S. West Coast, marine boundary layer sites, Jaffe et al. (2003) reported that O₃ in air arriving from the eastern Pacific in spring has increased by approximately 10 ppb from the mid-1980s. They concluded that this positive trend is due to increases of emissions of O₃ precursors in Asia. They found positive trends in O₃ in all seasons. They also noted that diurnal variations during summer were about 21 ppb, but only about 6 ppb during spring. Although Lassen Volcanic National Park site is not close to any major emission sources or urban centers, the site experiences maximum hourly average O₃ concentrations above 0.080 ppm during April to May and above 0.100 ppm during the summer (U.S. Environmental Protection Agency, 2003), suggesting local photochemical production, at least during summer. However, local springtime photochemical production cannot be ruled out. The authors suggested that the likely cause for the spring increases is transport from Asia, because emissions of precursors have decreased in California over the monitoring period. The springtime increases appears to be inconsistent with the summer increases, when there is evidence for the occurrence of more localized photochemical activity. Although emissions of O₃ precursors may have decreased in California as a whole over the monitoring period, there still may be regional increases in areas that could affect air quality in Lassen.

AX3.7 RELATIONS BETWEEN OZONE, OTHER OXIDANTS, AND OXIDATION PRODUCTS

Tables of measurements of PAN and peroxypropionyl nitrate (PPN, CH₃CH₂C(O)OONO₂) concentrations were given in the 1996 O₃ AQCD (U.S. Environmental Protection Agency, 1996a). Measurements were summarized for rural and urban areas in the United States, Canada, France, Greece, and Brazil. The use of measurements from aboard serve to illustrate or support certain U.S. results as well as to demonstrate the widespread presence of PANs in the atmosphere. Additional data for H₂O₂ were also presented in the 1996 O₃ AQCD. Data for these species are obtained as part of specialized field studies and not as part of routine monitoring operations and thus are highly limited in their ranges of applicability. As a result, it is difficult to relate the concentrations of O₃, other oxidants, and oxidation products on the basis of rather sparse data sets. This information is simply not available for a large number of environments.

Instead, it might be more instructive to examine the relations between O_3 and other products of atmospheric reactions on the basis of current understanding of atmospheric photochemical processes.

In order to understand co-occurrence between atmospheric species, an important distinction must be made between primary (directly emitted) species and secondary (photochemically produced) species. In general, it is more likely that primary species will be more highly correlated with each other, and that secondary species will be more highly correlated with each other than will species from mixed classes. By contrast, primary and secondary species are less likely to be correlated with each other. Secondary reaction products tend to correlate with each other, but there is considerable variation. Some species (e.g., O_3 and organic nitrates) are closely related photochemically and correlate with each other strongly. Others (e.g., O_3 and H_2O_2) show a more complex correlation pattern.

Although NO_2 is produced mainly by the reaction of directly emitted NO with O_3 with some contributions from direct emissions, in practice, it behaves like a primary species. The timescale for conversion of NO to NO_2 is fast (5 min or less), so NO and NO_2 ambient concentrations rapidly approach values determined by the photochemical steady state. The sum $NO + NO_2$ (NO_x) behaves like a typical primary species, while NO and NO_2 reflect some additional complexity based on photochemical interconversion. As a primary species, NO_2 generally does not correlate with O_3 in urban environments. In addition, chemical interactions among O_3 , NO and NO_2 have the effect of converting O_3 to NO_2 and vice versa, which can result in a significant anti-correlation between O_3 and NO_2 .

Organic nitrates consist of PAN, a number of higher-order species with photochemistry similar to PAN (e.g., PPN), and species such as alkyl nitrates with somewhat different photochemistry. These species are produced by a photochemical process very similar to that of O_3 . Photochemical production is initiated by the reaction of primary and secondary VOCs with OH radicals, the resulting organic radicals subsequently react with NO_2 (producing PAN and analogous species) or with NO (producing alkyl nitrates). The same sequence (with organic radicals reacting with NO) leads to the formation of O_3 .

In addition, at warm temperatures, the concentration of PAN forms a photochemical steady state with its radical precursors on a timescale of roughly 30 minutes. This steady state value increases with the ambient concentration of O_3 (Sillman et al., 1990). Ozone and PAN may

show different seasonal cycles, because they are affected differently by temperature. Ambient O_3 increases with temperature, driven in part by the photochemistry of PAN (see description above). By contrast, the photochemical lifetime of PAN decreases rapidly with increasing temperature. The ratio, O_3/PAN , should show seasonal changes, with highest ratios in summer, although there is no evidence from measurements. Measured ambient concentrations (Figures AX3-68a-d) show a strong nonlinear association between O_3 and PAN, and between O_3 and other organic nitrates (Pippin et al., 2001; Roberts et al., 1998). Moreover, the uncertainty in the relationship between O_3 and PAN grows as the level of PAN increases.

Individual primary VOCs are generally highly correlated with each other and with NO_x (Figure AX3-69). A summary of the results of a number of field studies of the concentrations of precursors including NO_x and nonmethane organic compounds (NMOCs) are summarized in the 1996 O_3 AQCD.

Formation of H_2O_2 takes place by self-reaction of photochemically generated HO_2 radicals, so that there is large seasonal variation of H_2O_2 concentrations and values in excess of 1 ppb are mainly limited to the summer months (Kleinman, 1991). Although H_2O_2 is produced from photochemistry that is closely related to O_3 , it does not show a consistent pattern of correlation with O_3 . Hydrogen peroxide is produced in abundance along with O_3 only when O_3 is produced under NO_x -limited conditions. When the photochemistry is NO_x -saturated much less H_2O_2 is produced. In addition, increasing NO_x tends to slow the formation of H_2O_2 under NO_x -limited conditions.

Measurements of gas phase peroxides in the atmosphere were reviewed by Lee et al. (2000). Ground level measurements of H_2O_2 taken during the 1970s indicated values of 180 ppb in Riverside, CA and 10 to 20 ppb during smog episodes in Claremont and Riverside, with values approaching 100 ppb in forest fire plumes. However, later surface measurements always found much lower values. For example, in measurements made in Los Angeles and nearby areas in the 1980s, peak values were always less than about 2 ppb and in a methods intercomparison study in Research Triangle Park, NC in June 1986, concentrations were <2.5 ppbv. Higher values ranging up to 5 ppb were found in a few other studies in Kinterbish, Alabama and Meadview, Arizona. Several of these studies found strong diurnal variations (typically about a factor three) with maximum values in the mid-afternoon and minimum values in the early

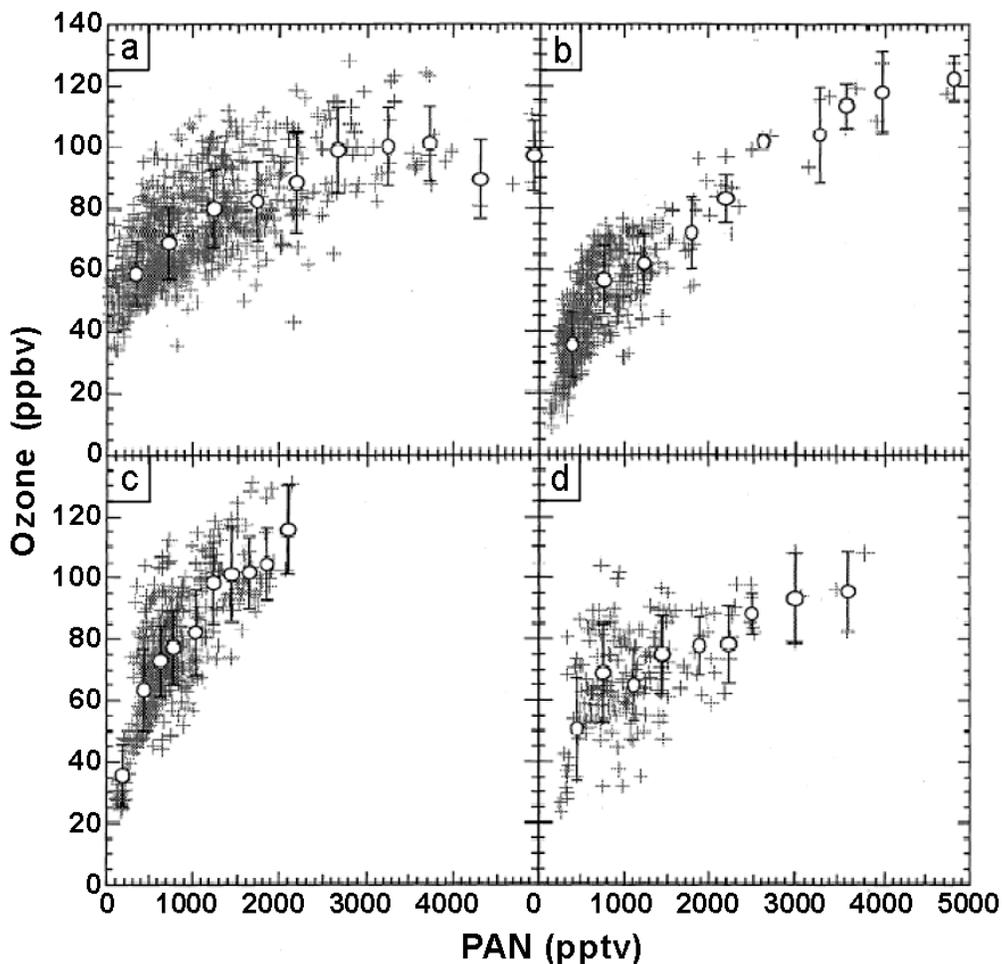


Figure AX3-68a-d. Measured O₃ (ppbv) versus PAN (pptv) in Tennessee, including (a) aircraft measurements, and (b, c, and d) suburban sites near Nashville.

Source: Roberts et al. (1998).

morning. Mean concentrations of organic hydroperoxides at the surface at Niwot Ridge, CO in the summer of 1988 and State Park, GA during the summer of 1991 were all less than a few ppb.

Early aircraft measurements of H₂O₂ over the eastern United States were reported by Heikes et al. (1987). More recent aircraft measurements of hydroperoxide (H₂O₂, CH₃OOH and HOCH₂OOH) concentrations were made as part of the Southern Oxidants Study intensive campaign in Nashville, TN in July 1995 (Weinstein-Lloyd et al., 1998). The median

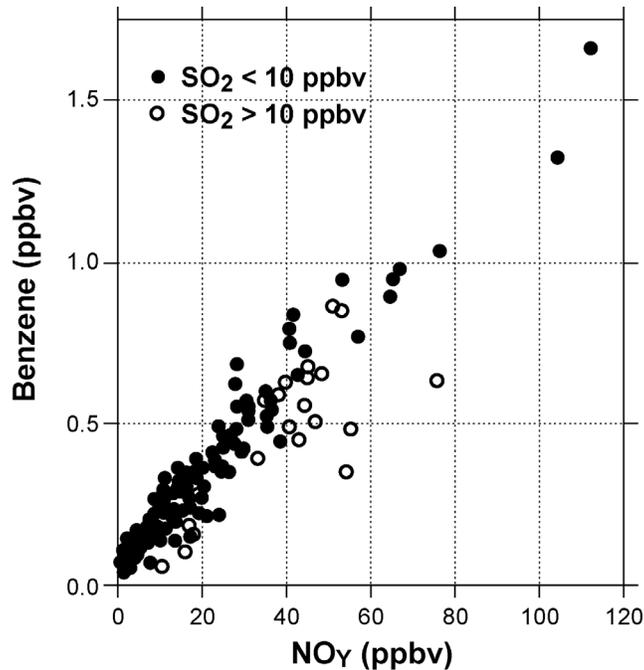


Figure AX3-69. Relationship between benzene and NO_y at a measurement site in Boulder, CO. Instances with $\text{SO}_2 > 10$ ppb are identified separately (open circles), because these may reflect different emission sources.

Source: Goldan et al. (1995).

concentration of total hydroperoxides in the boundary layer between 1100 and 1400 CDT was about 5 ppbv, with more than 50% contribution from organic hydroperoxides. Median O_3 was about 70 ppbv at the same time. The concentrations of the hydroperoxides depended strongly on wind direction. For example, values were about 40% lower when winds originated from the N/NW as opposed to the S/SW.

Elevated O_3 is generally accompanied by elevated HNO_3 , although the correlation is not as strong as between O_3 and organic nitrates. Ozone often correlates with HNO_3 , because they have the same precursor (NO_x). However, HNO_3 can be produced in significant quantities in winter, even when O_3 is low. The ratio between O_3 and HNO_3 also shows great variation in air pollution events, with NO_x -saturated environments having much lower ratios of O_3 to HNO_3 (Ryerson et al., 2001). Aerosol nitrate is formed primarily by the combination of nitrate (supplied by HNO_3) with ammonia, and may be limited by the availability of either nitrate or ammonia.

Nitrate is expected to correlate loosely with O₃ (see above), whereas ammonia is not expected to correlate with O₃.

In addition to nitrate, other oxidants are present in airborne cloud droplets, rain drops and particulate matter. Measurements of hydroperoxides, summarized by Reeves and Penkett (2003), are available mainly for hydrometeors, but are sparse for ambient particles. Venkatachari et al. (2005a) sampled the concentrations of total reactive oxygen species (ROS) in particles using a cascade impactor in Rubidoux, CA during July 2003. Although the species constituting ROS were not identified, the results were reported in terms of equivalent H₂O₂ concentrations. Unlike O₃ and gas phase H₂O₂ which show strong diurnal variability (i.e., about a factor of three variation between afternoon maximum and early morning minimum), the diurnal variation of particle phase ROS was found to be much weaker (i.e., less than about 20%) at least for the time between 8 a.m. and midnight. Because the ROS were measured in the fine aerosol size fraction, which has a lifetime with respect to deposition of much greater than a day, little loss is expected but their concentrations might also be expected to increase because of nighttime chemistry, perhaps involving NO₃ radicals. The concentration of ROS, expressed as equivalent H₂O₂ (5.2 to 6.1×10^{-7} M/m³, ranged from 20% to 100% that of O₃ (diurnal average: 30%), with highest values at night. The ratio was likely higher at the early morning minimum for O₃. In a companion study conducted in Queens, NY during January and early February 2004, Venkatachari et al. (2005b) found much lower concentrations of ROS of about 1×10^{-7} M/m³. However, O₃ levels were also substantially lower leading to ROS concentrations about 20% those of O₃. It is of interest to note that gas phase OH concentrations measured at the same time ranged from about 7.5×10^4 /cm³ to about 1.8×10^6 /cm³, implying the presence of significant photochemical activity even in New York City during winter.

Peroxyacetylnitrate (PAN) is produced during the photochemical oxidation of a wide range of VOCs in the presence of NO_x. It is removed by thermal decomposition and also by uptake to vegetation (Sparks et al., 2003; Teklemariam and Sparks, 2004). PAN is the dominant member of the broader family of peroxyacylnitrates (PANs), which includes as other significant atmospheric components peroxypropionyl nitrate (PPN) of anthropogenic origin and peroxyacrylic nitrate (MPAN) produced from oxidation of isoprene. Measurements and models show that PAN in the United States includes major contributions from both anthropogenic and biogenic VOC precursors (Horowitz et al., 1998; Roberts et al., 1998).

Measurements in Nashville during the 1999 summertime Southern Oxidants Study (SOS) showed PPN and MPAN amounting to 14% and 25% of PANs, respectively (Roberts et al., 2002). Measurements during the TexAQs 2000 study in Houston indicated PAN concentrations of up to 6.5 ppbv (Roberts et al., 2003). PAN measurements in southern California during the SCOS97-NARSTO study indicated peak concentrations of 5-10 ppbv, which can be contrasted to values of 60-70 ppbv measured back in 1960 (Grosjean, 2003). Vertical profiles measured from aircraft over the United States and off the Pacific coasts show PAN concentrations above the boundary layer of only a few hundred pptv, although there are significant enhancements associated with long-range transport of pollution plumes from Asia (Kotchenruther et al., 2001a; Roberts et al., 2004). Decomposition of this anthropogenic PAN as it subsides over North America can lead to significant O₃ production, enhancing the O₃ background (Kotchenruther et al., 2001b; Hudman et al., 2004).

Relations between primary and secondary components discussed above are illustrated by considering data for O₃ and PM_{2.5}. Ozone and PM_{2.5} concentrations observed at a monitoring site in Fort Meade, MD are plotted as binned means in Figure AX3-70. These data were collected between July 1999 and July 2001. As can be seen from the figure, PM_{2.5}, regarded as a function of O₃, increases to the left of the inflection point (at about 30 ppbv O₃) and also increases with O₃ to the right of the inflection point. Data to the left of the minimum in PM_{2.5} were collected mainly during the cooler months of the year, while data to the right of the minimum were collected during the warmer months. This situation arises because PM_{2.5} contains a large secondary component during the summer and has a larger primary component during winter. During the winter, O₃ comes mainly from the free troposphere, above the planetary boundary layer and, thus, may be considered a tracer for relatively clean air. Unfortunately, data for PM_{2.5} and O₃ are collected concurrently at relatively few sites in the United States throughout an entire year, so these results, while highly instructive are not readily extrapolated to areas where appreciable photochemical activity occurs throughout the year. Ito et al. (2005) showed the relation between PM₁₀ and O₃ on a seasonal basis in several urban areas (cf., Figure 7-24). Although PM₁₀ contains proportionately more primary material than does PM_{2.5}, relations similar to those shown in Figure AX3-70 are found, reflecting the dominant contribution from PM_{2.5} to PM₁₀.

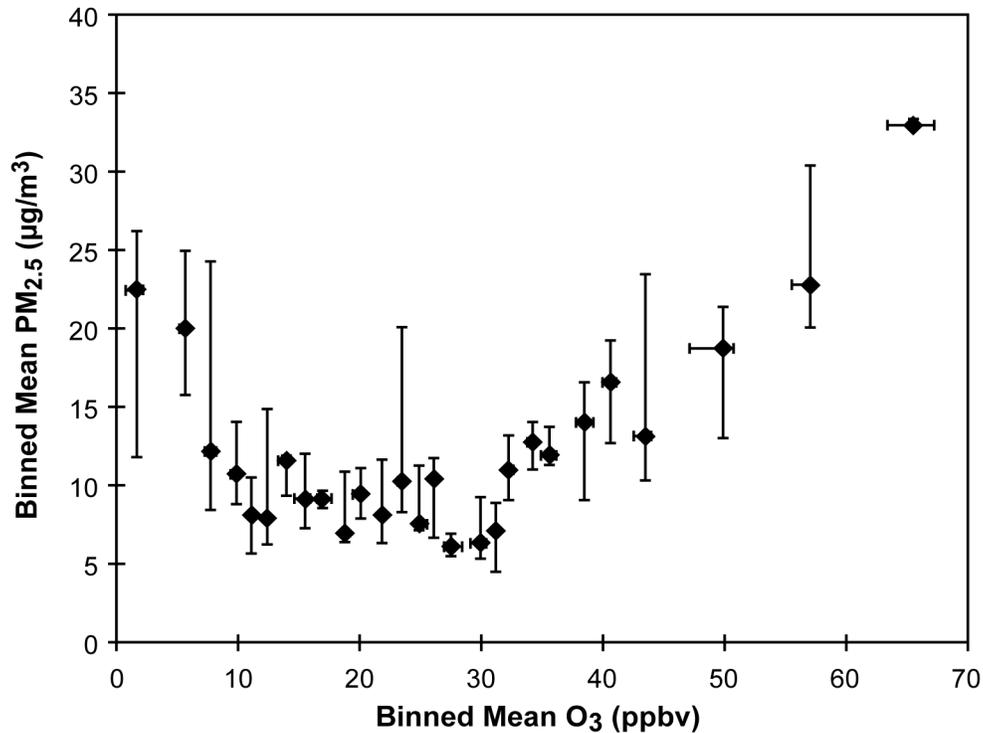


Figure AX3-70. Binned mean PM_{2.5} concentrations versus binned mean O₃ concentrations observed at Fort Meade, MD from July 1999 to July 2001.

Source: Chen (2002).

AX3.8 RELATIONSHIP BETWEEN SURFACE OZONE AND OTHER POLLUTANTS

AX3.8.1 Introduction

Several attempts have been made to characterize gaseous air pollutant mixtures (Lefohn and Tingey, 1984; Lefohn et al., 1987). The characterization of co-occurrence patterns under ambient conditions is important for relating human health and vegetation effects to controlled chamber studies and to ambient conditions. Lefohn et al. (1987) discussed the various patterns of pollutant exposures. Pollutant combinations can occur at or above a threshold concentration either together or temporally separated from one another. Patterns that show air pollutant pairs appearing at the same hour of the day at concentrations equal to or greater than a minimum

hourly mean value were defined as simultaneous-only daily co-occurrences. When pollutant pairs occurred at or above a minimum concentration during the 24-h period, without occurring during the same hour, a “sequential-only” co-occurrence was defined. During a 24-h period, if the pollutant pair occurred at or above the minimum level at the same hour of the day and at different hours during the period, the co-occurrence pattern was defined as “complex-sequential.”

For characterizing the different types of co-occurrence patterns for O₃/NO₂, O₃/SO₂, and NO₂/SO₂, Lefohn and Tingey (1984) used a 0.05 ppm threshold to identify the number of hourly simultaneous-only co-occurrences for the period May through September at a large number of air quality urban monitoring sites along with rural sites. The selection of a 0.05-ppm threshold concentration was based on vegetation effects considerations. Data used in the analysis included hourly averaged (1) Environmental Protection Agency Storage and Retrieval of Aerometric Data (SAROAD; now AQS) data for 1981, (2) EPRI-SURE and Eastern Regional Air Quality Study (ERAQS) data for 1978 and 1979, and (3) Tennessee Valley Authority (TVA) data from 1979 to 1982. Lefohn and Tingey (1984) concluded, for the pollutant combinations, that (1) the co-occurrence of two-pollutant mixtures lasted only a few hours per episode and (2) the time interval between episodes was generally large (weeks, sometimes months).

Lefohn et al. (1987), using a 0.03-ppm threshold, grouped air quality data from rural and RRMS (as characterized in the EPA database) within a 24-h period starting at 0000 hours and ending at 2359 hours. Data were analyzed for the May to September period. Data used in the analysis included hourly averaged (1) Environmental Protection Agency AQS (SAROAD) data from 1978 to 1982, (2) EPRI-SURE and –ERAQS data for 1978 and 1979, and (3) TVA data from 1979 to 1982. Patterns that showed air pollutant pairs appearing at the same hour of the day at concentrations equal to or greater than a minimum hourly mean value were defined as simultaneous-only daily co-occurrences. When pollutant pairs occurred at or above a minimum concentration during the 24-h period, without occurring during the same hour, a “sequential-only” co-occurrence was defined. During a 24-h period, if the pollutant pair occurred at or above the minimum level at the same hour of the day and at different hours during the period, the co-occurrence pattern was defined as “complex-sequential.” A co-occurrence was not indicated if one pollutant exceeded the minimum concentration just before midnight and the other pollutant exceeded the minimum concentration just after midnight. As will be discussed

below, studies of the joint occurrence of gaseous NO₂/O₃ and SO₂/O₃ reached two conclusions: (1) hourly simultaneous and daily simultaneous-only co-occurrences are fairly rare and (2) when co-occurrences are present, complex-sequential and sequential-only co-occurrence patterns predominate. The authors reported that year-to-year variability was found to be insignificant; most of the monitoring sites experienced co-occurrences of any type less than 12% of the 153 days.

Since 1999, monitoring stations across the United States have been routinely measuring the 24-h average concentrations of PM_{2.5}. Because of the availability of the PM_{2.5} data, daily co-occurrence of PM_{2.5} and O₃ over a 24-h period was characterized. Because PM_{2.5} data are mostly summarized as 24-h average concentrations in the AQS data base, a daily co-occurrence of O₃ and PM_{2.5} was subjectively defined as when an hourly average O₃ concentration ≥ 0.05 ppm and a PM_{2.5} 24-h concentration ≥ 40 $\mu\text{g}/\text{m}^3$ occurred over the same 24-h period.

For exploring the co-occurrence of O₃ and other pollutants (e.g., acid precipitation and acidic cloudwater), limited data are available. In most cases, routine monitoring data are not available from which to draw general conclusions. However, published results are reviewed and summarized for the purpose of assessing an estimate of the possible importance of co-occurrence patterns of exposure.

AX3.8.2 Co-Occurrence of Ozone with Nitrogen Oxides

Ozone occurs frequently at concentrations equal to or greater than 0.05 ppm at many rural and remote monitoring sites in the United States (U.S. Environmental Protection Agency, 1996a). Therefore, for many rural locations in the United States, the co-occurrence patterns observed by Lefohn and Tingey (1984) for O₃ and NO₂ were defined by the presence or absence of NO₂. Lefohn and Tingey (1984) reported that most of the sites analyzed experienced fewer than 10 co-occurrences (when both pollutants were present at an hourly average concentration ≥ 0.05 ppm). Figure AX3-71 summarizes the simultaneous co-occurrence patterns reported by Lefohn and Tingey (1984). The authors noted that several urban monitoring sites in the South Coast Air Basin experienced more than 450 co-occurrences. For more moderate areas of the country, Lefohn et al. (1987) reported that even with a threshold of 0.03 ppm O₃, the number of co-occurrences with NO₂ was small.

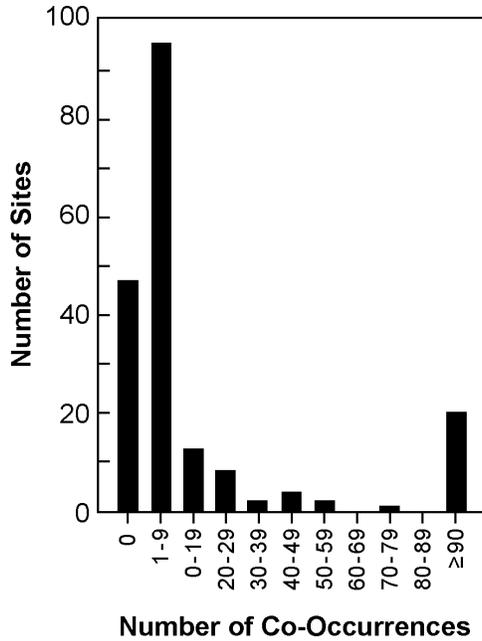


Figure AX3-71. The co-occurrence pattern for O₃ and NO₂.

Source: Lefohn and Tingey (1984).

Using 2001 data from the U.S. EPA AQS database, patterns that showed air pollutant pairs of O₃/NO₂ appearing at the same hour of the day at concentrations ≥ 0.05 ppm were characterized. The data were not segregated by location settings categories (i.e., rural, suburban, and urban and center city) or land use types (i.e., agricultural, commercial, desert, forest, industrial, mobile, or residential). Data capture was not a consideration in the analysis. The data were characterized over the EPA-defined O₃ season (Table AX3-1). In 2001, there were 341 monitoring sites that co-monitored O₃ and NO₂. Because of possible missing hourly average concentration data during periods when co-monitoring may have occurred, no attempt was made to characterize the number of co-occurrences in the 0 category. Thus, co-occurrence patterns were identified for those monitoring sites that experienced one or more co-occurrences.

Figure AX3-72 illustrates the results of the analysis. Similar to the analysis summarized by Lefohn and Tingey (1984), most of the collocated monitoring sites analyzed, using the 2001 data, experienced fewer than 10 co-occurrences (when both pollutants were present at an hourly average concentration ≥ 0.05 ppm).

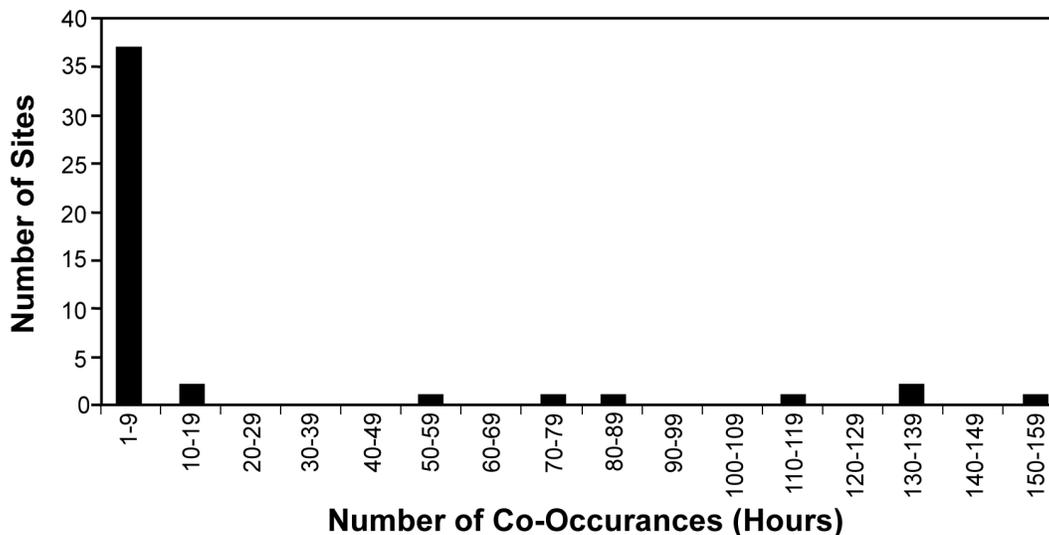


Figure AX3-72. The co-occurrence pattern for O₃ and NO₂ using 2001 data from the AQS.

AX3.8.3 Co-Occurrence of Ozone with Sulfur Dioxide

Because elevated SO₂ concentrations are mostly associated with industrial activities (U.S. Environmental Protection Agency, 1992), co-occurrence observations are usually associated with monitors located near these types of sources. Lefohn and Tingey (1984) reported that, for the rural and nonrural monitoring sites investigated, most sites experienced fewer than 10 co-occurrences of SO₂ and O₃. Lefohn et al. (1987) reported that even with a threshold of 0.03 ppm O₃, the number of co-occurrences with SO₂ was small. Figure AX3-73 illustrates the simultaneous co-occurrence results reported by Lefohn and Tingey (1984).

Meagher et al. (1987) reported that several documented O₃ episodes at specific rural locations appeared to be associated with elevated SO₂ levels. The investigators defined the co-occurrence of O₃ and SO₂ to be when hourly mean concentrations were ≥ 0.10 and 0.01 ppm, respectively.

The above discussion was based on the co-occurrence patterns associated with the presence or absence of hourly average concentrations of pollutant pairs. Taylor et al. (1992) have discussed the joint occurrence of O₃, nitrogen, and sulfur in forested areas using cumulative exposures of O₃ with data on dry deposition of sulfur and nitrogen. The authors concluded in

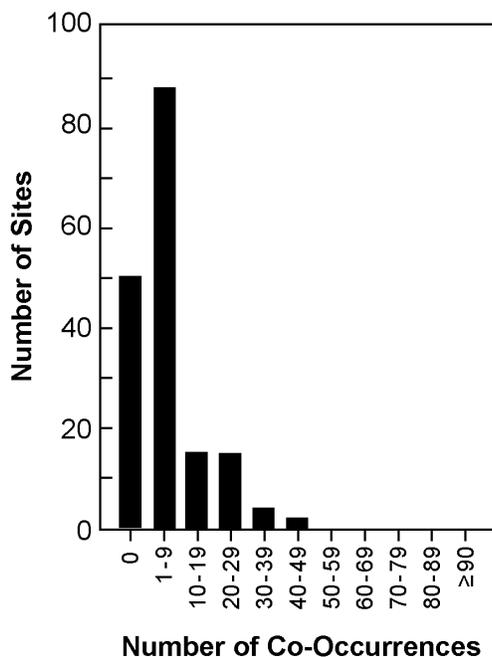


Figure AX3-73. The co-occurrence pattern for O₃ and SO₂.

Source: Lefohn and Tingey (1984).

their study that the forest landscapes with the highest loadings of sulfur and nitrogen via dry deposition tended to be the same forests with the highest average O₃ concentrations and largest cumulative exposure. Although the authors concluded that the joint occurrences of multiple pollutants in forest landscapes were important, nothing was mentioned about the hourly co-occurrences of O₃ and SO₂ or of O₃ and NO₂.

Using 2001 data from the EPA AQS database, patterns that showed air pollutant pairs of O₃/SO₂ appearing at the same hour of the day at concentrations ≥0.05 ppm were characterized. The data were not segregated by location settings categories (i.e., rural, suburban, and urban and center city) or land use types (i.e., agricultural, commercial, desert, forest, industrial, mobile, or residential). Data capture was not a consideration in the analysis. In 2001, there were 246 monitoring sites that co-monitored O₃ and SO₂. Because of possible missing hourly average concentration data during periods when co-monitoring may have occurred, no attempt was made to characterize the number of co-occurrences in the 0 category. Thus, co-occurrence patterns

were identified for those monitoring sites that experienced one or more co-occurrences. Figure AX3-74 shows the results from this analysis for the simultaneous co-occurrence of O₃ and SO₂. Similar to the analysis summarized by Lefohn and Tingey (1984), most of the collocated monitoring sites analyzed, using the 2001 data, experienced fewer than 10 co-occurrences (when both pollutants were present at an hourly average concentration ≥ 0.05 ppm).

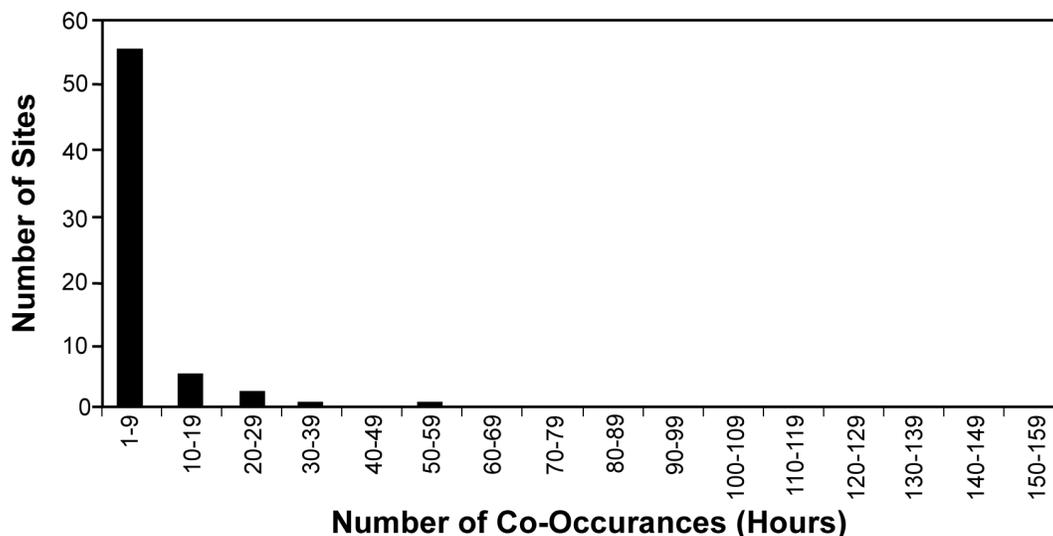


Figure AX3-74. The co-occurrence pattern for O₃ and SO₂ using 2001 data from AQS.

AX3.8.4 Co-Occurrence of Ozone and Daily PM_{2.5}

Using 2001 data from the EPA AQS, the daily co-occurrence of PM_{2.5} and O₃ over a 24-h period was characterized. There were 362 sites where PM_{2.5} and O₃ monitors were collocated. As described in the introduction selection of this annex, a daily co-occurrence of O₃ and PM_{2.5} is subjectively defined as an hourly average O₃ concentration ≥ 0.05 ppm and a PM_{2.5} 24-h concentration ≥ 40 $\mu\text{g}/\text{m}^3$ occurring over the same 24-h period. Figure AX3-75 illustrates the daily co-occurrence patterns observed. Using 2001 data from the AQS, the daily co-occurrence of PM_{2.5} and O₃ was infrequent.

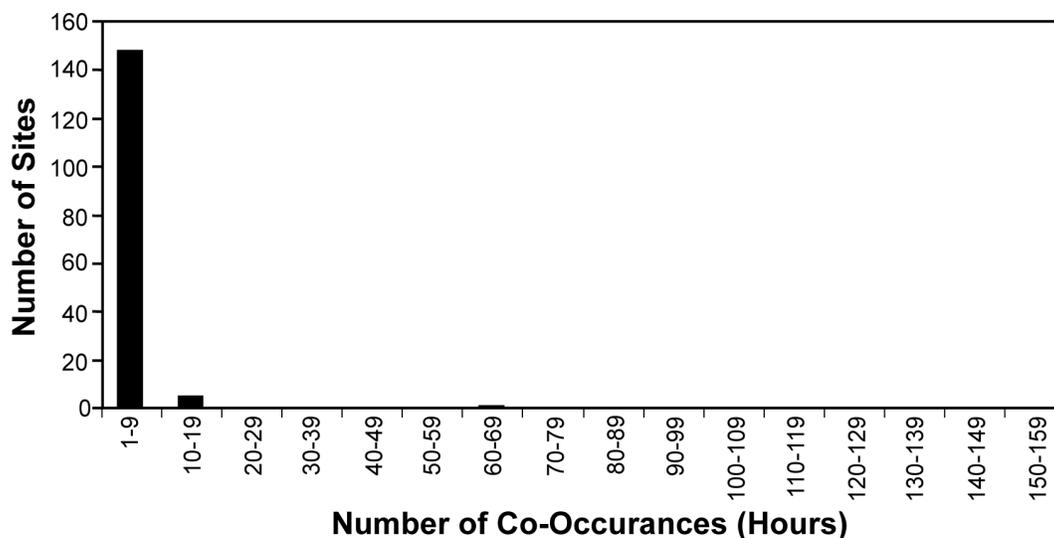


Figure AX3-75. The co-occurrence pattern for O₃ and PM_{2.5} using 2001 data from AQS.

AX3.8.5 Co-Occurrence of Ozone with Acid Precipitation

Concern has been expressed about the possible effects on vegetation from co-occurring exposures of O₃ and acid precipitation (Prinz et al., 1985; National Acid Precipitation Assessment Program, 1987; Prinz and Krause, 1989). Little information has been published concerning the co-occurrence patterns associated with the joint distribution of O₃ and acidic deposition (i.e., H⁺). Lefohn and Benedict (1983) reviewed the EPA SAROAD monitoring data for 1977 through 1980 and, using National Atmospheric Deposition Program (NADP) and EPRI wet deposition data, evaluated the frequency distribution of pH events for 34 NADP and 8 EPRI chemistry monitoring sites located across the United States. Unfortunately, there were few sites where O₃ and acidic deposition were co-monitored.

As a result, Lefohn and Benedict (1983) focused their attention on O₃ and acidic deposition monitoring sites that were closest to one another. In some cases, the sites were as far apart as 144 km. Using hourly O₃ monitoring data and weekly and event acidic deposition data from the NADP and EPRI databases, the authors identified specific locations where the hourly mean O₃ concentrations were ≥0.1 ppm and 20% of the wetfall daily or weekly samples were below pH 4.0. Elevated levels of O₃ were defined as hourly mean concentrations equal to or greater than 0.1 ppm. Although for many cases, experimental research results of acidic deposition on

agricultural crops show few effects at pH levels >3.5 (National Acid Precipitation Assessment Program, 1987), it was decided to use a pH threshold of 4.0 to take into consideration the possibility of synergistic effects between O_3 and acidic deposition.

Based on their analysis, Lefohn and Benedict (1983) identified five sites with the potential for agricultural crops to experience additive, less than additive, or synergistic (i.e., greater than additive) effects from elevated O_3 and H^+ concentrations. The authors stated that they believed, based on the available data, the greatest potential for interaction between acid rain and O_3 concentrations in the United States, with possible effects on crop yields, may be in the most industrialized areas (e.g., Ohio and Pennsylvania). However, they cautioned that, because no documented evidence existed to show that pollutant interaction had occurred under field growth conditions and ambient exposures, their conclusions should only be used as a guide for further research.

In their analysis, Lefohn and Benedict (1983) found no collocated sites. The authors rationalized that data from non-co-monitoring sites (i.e., O_3 and acidic deposition) could be used because O_3 exposures are regional in nature. However, work by Lefohn et al. (1988) has shown that hourly mean O_3 concentrations vary from location to location within a region, and that cumulative indices, such as the percent of hourly mean concentrations ≥ 0.07 ppm, do not form a uniform pattern over a region. Thus, extrapolating hourly mean O_3 concentrations from known locations to other areas within a region may provide only qualitative indications of actual O_3 exposure patterns.

In the late 1970s and the 1980s, both the private sector and the government funded research efforts to better characterize gaseous air pollutant concentrations and wet deposition. The event-oriented wet deposition network, EPRI/Utility Acid Precipitation Study Program, and the weekly oriented sampling network, NADP, provided information that can be compared with hourly mean O_3 concentrations collected at several co-monitored locations. No attempt was made to include H^+ cloud deposition information. In some cases, for mountaintop locations (e.g., Clingman's Peak, Shenandoah, Whiteface Mountain, and Whitetop Mountain), the H^+ cloud water deposition is greater than the H^+ deposition in precipitation (Mohnen, 1989), and the co-occurrence patterns associated with O_3 and cloud deposition will be different from those patterns associated with O_3 and deposition by precipitation.

Smith and Lefohn (1991) explored the relationship between O₃ and H⁺ in precipitation, using data from sites that monitored both O₃ and wet deposition simultaneously and within one-minute latitude and longitude of each other. The authors reported that individual sites experienced years in which both H⁺ deposition and total O₃ exposure were at least moderately high (i.e., annual H⁺ deposition $\geq 0.5 \text{ kg ha}^{-1}$ and an annual O₃ cumulative, sigmoidally weighted exposure (W126) value $\geq 50 \text{ ppm-h}$). With data compiled from all sites, it was found that relatively acidic precipitation (pH ≤ 4.31 on a weekly basis or pH ≤ 4.23 on a daily basis) occurred together with relatively high O₃ levels (i.e., W126 values $\geq 0.66 \text{ ppm-h}$ for the same week or W126 values $\geq 0.18 \text{ ppm-h}$ immediately before or after a rainfall event) approximately 20% of the time, and highly acidic precipitation (i.e., pH ≤ 4.10 on a weekly basis or pH ≤ 4.01 on a daily basis) occurred together with a high O₃ level (i.e., W126 values $\geq 1.46 \text{ ppm-h}$ for the same week or W126 values $\geq 0.90 \text{ ppm-h}$ immediately before or after a rainfall event) approximately 6% of the time. Whether during the same week or before, during, or after a precipitation event, correlations between O₃ level and pH (or H⁺ deposition) were weak to nonexistent. Sites most subject to relatively high levels of both H⁺ and O₃ were located in the eastern United States, often in mountainous areas.

AX3.8.6 Co-Occurrence of Ozone with Acid Cloudwater

In addition to the co-occurrence of O₃ and acid precipitation, results have been reported on the co-occurrence of O₃ and acidic cloudwater in high-elevation forests. Vong and Guttorp (1991) characterized the frequent O₃-only and pH-only, single-pollutant episodes, as well as the simultaneous and sequential co-occurrences of O₃ and acidic cloudwater. The authors reported that both simultaneous and sequential co-occurrences were observed a few times each month above the cloud base. Episodes were classified by considering hourly O₃ average concentrations $\geq 0.07 \text{ ppm}$ and cloudwater events with pH ≤ 3.2 . The authors reported that simultaneous occurrences of O₃ and pH episodes occurred two to three times per month at two southern sites (Mitchell, NC and Whitetop, VA) and the two northern sites (Whiteface Mountain, NY and Moosilauke, NH) averaged one episode per month. No co-occurrences were observed at the central Appalachian site (Shenandoah, VA), due to a much lower cloud frequency. Vong and Guttorp (1991) reported that the simultaneous occurrences were usually of short duration

(mean = 1.5 h/episode) and were followed by an O₃-only episode. As would be expected, O₃-only episodes were longer than co-occurrences and pH episodes, averaging an 8-h duration.

AX3.9 THE METHODOLOGY FOR DETERMINING POLICY RELEVANT BACKGROUND OZONE CONCENTRATIONS

AX3.9.1 Introduction

Background O₃ concentrations used for NAAQS-setting purposes are referred to as Policy Relevant Background (PRB) O₃ concentrations. Policy Relevant Background concentrations are those concentrations that would result in the United States in the absence of anthropogenic emissions in continental North America (the United States, Canada and Mexico). Policy Relevant Background concentrations include contributions from natural sources everywhere in the world and from anthropogenic sources outside these three countries. For the purposes of informing decisions about O₃ NAAQS, EPA assesses risks to human health and environmental effects to O₃ levels in excess of PRB concentrations. Issues concerning the methodology for estimating PRB O₃ concentrations are described in detail in Annex AX3, Section AX3.9.

Contributions to PRB O₃ include: photochemical interactions involving natural emissions of VOCs, NO_x, and CO; the long-range transport of O₃ and its precursors from outside North America; and stratospheric-tropospheric exchange (STE). Processes involved in STE are described in detail in Annex AX2.3. Natural sources of O₃ precursors include biogenic emissions, wildfires, and lightning. Biogenic emissions from agricultural activities are not considered in the formation of PRB O₃.

Most of the issues concerning the calculation of PRB O₃ center on the origin of springtime maxima in surface O₃ concentrations observed at monitoring sites in relatively unpolluted areas of the United States and on the capability of the current generation of global-scale, three-dimensional chemistry transport models to correctly simulate their causes. These issues are related to the causes of the occurrence of high O₃ values, especially those averaged over 1-h to 8-h observed at O₃ monitoring sites during late winter through spring (i.e., February to June). The issues raised do not affect interpretations of the causes of summertime O₃ episodes as strongly. Summertime O₃ episodes are mainly associated with slow-moving high-pressure

systems characterized by limited mixing between the planetary boundary layer and the free troposphere (Section AX2.3).

Springtime maxima are observed at national parks mainly in the western United States that are relatively clean (Section AX3.2.2; Figures AX3-76a,b) and at a number of other relatively unpolluted monitoring sites throughout the Northern Hemisphere. Spring maxima in tropospheric O₃ were originally attributed to transport from the stratosphere by Regener (1941) as cited by Junge (1963). Junge (1963) also cited measurements of springtime maxima in O₃ concentrations at Mauna Loa (elevation 3400 m) and at Arkosa, Germany (an alpine location, elevation 1860 m). Measurements of radioactive debris transported downward from the stratosphere as the result of nuclear testing during the 1960s also show springtime maxima (Ludwig et al., 1977). However, more recent studies (Lelieveld and Dentener, 2000; Browell et al., 2003) attribute the springtime maximum in tropospheric O₃ concentrations to tropospheric production rather than transport from the stratosphere. It should be noted here that O₃ in the free troposphere is subject to chemical loss on time scales much shorter than for decay of most radio-isotopes produced by nuclear testing that were used as tracers of stratospheric air such as ¹⁴C, ¹³⁷Cs and ⁹⁰Sr.

Springtime O₃ maxima were observed in low-lying surface measurements during the late 19th century. However, these measurements are quantitatively highly uncertain, and extreme caution should be exercised in their use. Concentrations of approximately 0.036 ppm for the daytime average and of 0.030 ppm for the nighttime averages were reported for Zagreb, Croatia using the Schonbein method during the 1890s (Lisac and Grubišić, 1991). Of the numerous measurements of tropospheric O₃ made in the 19th century, only the iodine catalyzed oxidation of arsenite has been verified with modern laboratory methods. Kley et al. (1988) reconstructed the apparatus used between 1876 and 1910 in Montsouris, outside Paris, and evaluated it for accuracy and specificity. They concluded that O₃ mixing ratios ranged from 5 to 16 ppb with uncertainty of ±2 ppb. Interferences from SO₂ were avoided as the Montsouris data were selected to exclude air from Paris, the only source of high concentrations of SO₂ at that time. Uncertainties in the humidity correction to the Schonbein reading will lead to considerable inaccuracies in the seasonal cycle established by this method (Pavelin et al., 1999). Because of the uncertainties in the earlier methods, it is difficult to quantify the differences between

Yellowstone National Park Maximum Hourly Concentration 1998-2001

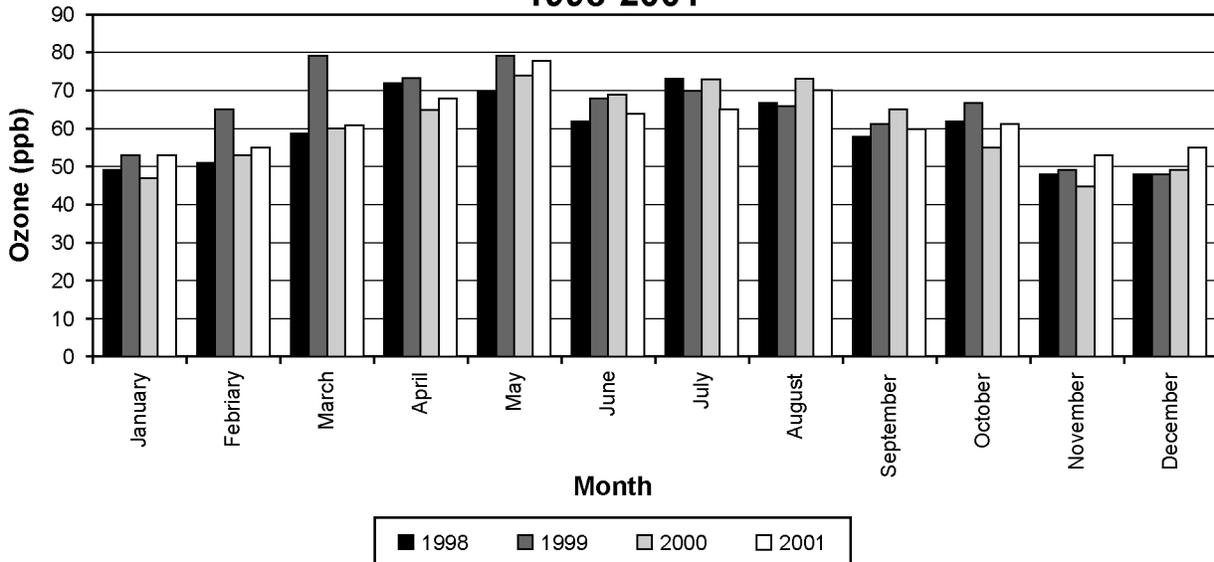


Figure AX3-76a. Monthly maximum hourly average O₃ concentrations at Yellowstone National Park, Wyoming in 1998, 1999, 2000, and 2001.

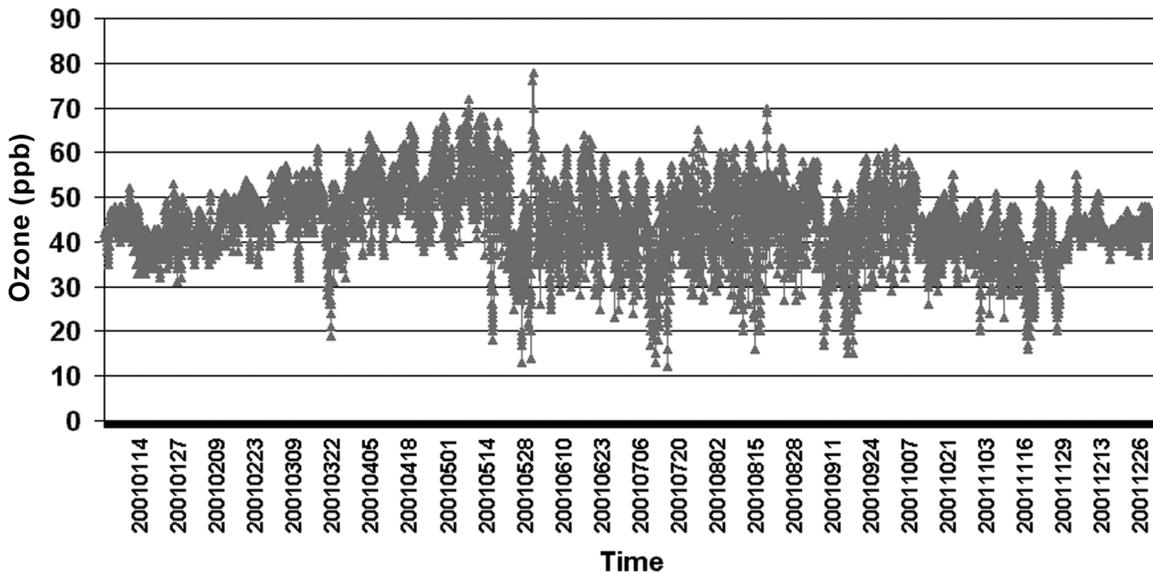


Figure AX3-76b. Hourly average O₃ concentrations at Yellowstone National Park, Wyoming for the period January to December 2001.

Source: U.S. Environmental Protection Agency (2003).

surface O₃ concentrations measured in the last half of the 19th century at certain locations in either Europe or North America with those currently monitored at remote locations in the world.

Observations of O₃ profiles at a large number of sites indicate a positive gradient in O₃ mixing ratios with increasing altitude in the troposphere and a springtime maximum in O₃ concentrations in the upper troposphere (Logan, 1999). As discussed in Section AX2.3.1, STE affects the middle and upper troposphere more than the lower troposphere. It is, therefore, reasonable to suppose that the main cause of this positive gradient is STE. However, deep convection transports pollutants upward and can result in an increase in the pollutant mixing ratio with altitude downwind of surface source regions as shown in Figure AX3-77. This effect can be seen in differences in ozonesonde profiles as one moves eastward across the United States (Newchurch et al., 2003). In addition, O₃ formed by lightning-generated NO_x also contributes to the vertical O₃ gradient (Lelieveld and Dentener, 2000). This O₃ could be either background or not, depending on the sources of radical precursors. Another contributing factor is the increase of O₃ lifetime with altitude (Wang et al., 1998). Free-tropospheric O₃ is not predominantly of stratospheric origin, nor is it all natural; it is mostly controlled by production within the troposphere and includes a major anthropogenic enhancement (e.g., Berntsen et al., 1997; Roelofs et al., 1997; Wild and Akimoto, 2001).

Stohl (2001), Wernli and Borqui (2002), Seo and Bowman (2002), James et al. (2003a,b), Sprenger and Wernli (2003), and Sprenger et al. (2003) addressed the spatial and temporal variability in stratosphere to troposphere transport. Both Stohl (2001) and Sprenger et al. (2003) produced 1-year climatologies of tropopause folds based on a 1° by 1° gridded meteorological model data set. They each found that the probability of deep folds (penetrating to the 800 hPa level) was maximum during winter (December through February) with the highest frequency of folding extending from Labrador down the east coast of North America. However, these deep folds occurred in <1% of the 6-h intervals for which meteorological data was assimilated for grid points in the continental United States, with a higher frequency in Canada. They observed a higher frequency of more shallow folds (penetrating to the upper troposphere) and medium folds (penetrating to levels between 500 and 600 hPa) of about 10% and 1 to 2%, respectively. These events occur preferentially across the subtropics and the southern United States. At higher latitudes, other mechanisms such as the erosion of cut-off lows and the breakup of stratospheric

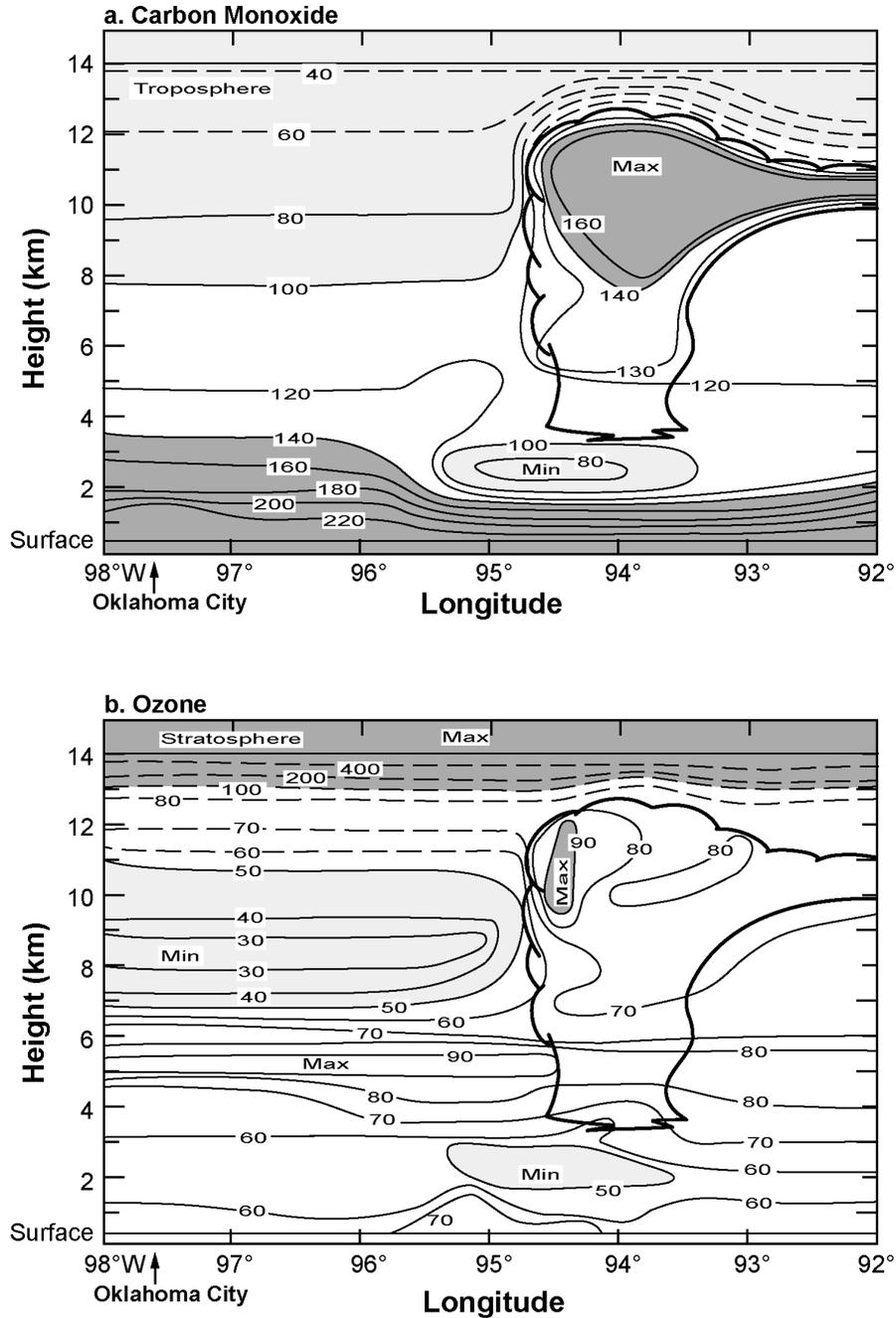


Figure AX3-77. (a) Contour plot of CO mixing ratios (ppbv) observed in and near the June 15, 1985, mesoscale convective complex in eastern Oklahoma. Heavy line shows the outline of the cumulonimbus cloud. Dark shading indicates high CO and light shading indicates low CO. Dashed contour lines are plotted according to climatology since no direct measurements were made in that area. (b) Same as (a) but for O₃ (ppbv).

Source: Dickerson et al. (1987).

streamers are likely to play an important role in STE. A 15-year model climatology by Sprenger and Wernli (2003) showed the consistent pattern of STE occurring over the primary storm tracks along the Asian and North American coasts. This climatology, and the one of James et al. (2003a,b) both found that recent stratospheric air associated with deep intrusions are relatively infrequent occurrences in these models. Thus, stratospheric intrusions are most likely to directly affect the middle and upper troposphere, not the planetary boundary layer. However, this O₃ can still exchange with the planetary boundary layer through convection or through large-scale subsidence as described later in this subsection and in Sections AX2.3.2, AX2.3.3, and AX2.3.4. These results are in accord with the observations of Ludwig et al. (1977) over the western United States. It should also be remembered that stratospheric O₃ injected into the upper troposphere is subject to chemical destruction as it is transported downward toward the surface.

Ozone concentrations measured at RRMS in the Northern Hemisphere have been compiled by Vingarzan (2004) and are reproduced here in Tables AX3-10, AX3-11, and AX3-12. Data for annual mean/median concentrations show a broad range, as do annual maximum 1-h concentrations. Generally, concentrations increase with elevation and the highest concentrations are found during spring. The overall average of the annual median O₃ concentrations at all sites in the continental United States is about 30 ppb and excluding higher elevation sites it is about 24 ppb. Maximum concentrations may be related to stratospheric intrusions, wildfires, and intercontinental or regional transport of pollution. However, it should be noted that all of these sites are affected by anthropogenic emissions to some extent making an interpretation based on these data alone problematic.

Daily 1-h maximum O₃ concentrations exceeding 50 or 60 ppb are observed during late winter and spring in southern Canada and at sites in national parks as shown in Tables AX3-13, AX3-14, and Figure AX3-78. That these high values can occur during late winter when there are low sun angles and cold temperatures may imply a negligible role for photochemistry and a major role for stratospheric intrusions. However, active photochemistry occurs even at high latitudes during late winter. Rapid O₃ loss, apparently due to multiphase chemistry involving bromine atoms (see Section 2.2.10) occurs in the Arctic marine boundary layer. The Arctic throughout much of winter is characterized by low light levels, temperatures, and precipitation, and can act as a reservoir for O₃ precursors such as PAN and alkyl nitrates,

Table AX3-10. Range of Annual (January-December) Hourly Ozone Concentrations (ppb) at Background Sites Around the World (CMDL, 2004)

Location	Elevation (m)	Period of Record	Range of Annual Means
Pt. Barrow, Alaska	11	1992-2001	23-29
Ny Alesund, Svalbard, Spitsbergen ^a	475	1989-1993	28-33 ^b
Mauna Loa, Hawaii ^c	3397	1992-2001	37-46 ^d

^aUniversity of Stockholm Meteorological Institute.

^bAnnual medians

^c10:00 - 18:00 UTC.

^dHigh elevation site.

Source: Vingarzan (2004).

Table AX3-11. Range of Annual (January-December) Hourly Median and Maximum Ozone Concentrations (ppb) at Background Stations in Protected Areas of the United States (CASTNet, 2004)

Location	Elevation (m)	Period of Record	Range of Annual Medians	Range of Annual Maxima
Denali NP, Alaska	640	1998-2001	29-34	49-68
Glacier NP, Montana	976	1989-2001	19-27	57-77
Voyageurs NP, Minnesota	429	1997-2001	28-35	74-83
Theodore Roosevelt NP, North Dakota	850	1983-2001	29-43	61-82
Yellowstone NP, Wyoming	2469	1996-2001	37-45 ^a	68-79 ^a
Rocky Mountain NP, Colorado	2743	1994-2001	40-47 ^a	68-102 ^a
Olympic NP, Washington	125	1998-2001	19-22	50-63
North Cascades NP, Washington	109	1996-2001	14-18	48-69
Mount Rainier NP, Washington	421	1995-2001	38-71	54-98
Lassen NP, California	1756	1995-2001	38-43 ^a	81-109 ^a
Virgin Islands NP, U.S. Virgin Islands	80	1998-2001	19-24	50-64

^aHigh elevation site.

Source: Vingarzan (2004).

Table AX3-12. Range of Annual (January-December) Hourly Median and Maximum Ozone Concentrations (ppb) at Canadian Background Stations (CAPMoN^a, 2003)

Location	Elevation (m)	Period of Record	Range of Annual Medians	Range of Annual Maxima
Kejimikujik, Nova Scotia ^b	127	1989-2001	25-34	76-116
Montmorency, Quebec	640	1989-1996	28-32	73-99
Algoma, Ontario ^a	411	1988-2001	27-33	76-108
Chalk River, Ontario	184	1988-1996	25-31	79-107
Egbert, Ontario ^a	253	1989-2001	27-32	90-113
E.L.A., Ontario	369	1989-2001	28-33	64-87
Bratt's Lake, Saskatchewan	588	1999-2001	26-29	63-68
Esther, Alberta	707	1995-2001	26-31	63-78
Saturna Island, British Columbia	178	1992-2001	23-27	65-82

^aCanadian Air and Precipitation Monitoring Network.

^bStations affected by long-range transport of anthropogenic emissions.

Source: Vingarzan (2004).

which build up and can then photolyze when sun angles are high enough during late winter and early spring. Long-range transport of total odd nitrogen species (NO_y) (defined in AX2.2.2) and VOCs to Arctic regions can occur from midlatitude-source regions. In addition, O₃ can be transported from tropical areas in the upper troposphere followed by its subsidence at mid and high latitudes (Wang et al., 1998).

Penkett (1983), and later Penkett and Brice (1986), first observed a spring peak in PAN at high northern latitudes and hypothesized that winter emissions transported into the Arctic would be mixed throughout a large region of the free troposphere and transformed into O₃ as solar radiation returned to the Arctic in the spring. Subsequent observations (Dickerson, 1985) confirmed the presence of strata of high concentrations of reactive nitrogen compounds at high latitudes in early spring. Bottenheim et al. (1990, 1993) observed a positive correlation between O₃ and NO₂ in the Arctic spring. Jaffe et al. (1991) found NO_y concentrations approaching 1 ppb in Barrow, Alaska, in the spring and attributed them to long-range transport.

**Table AX3-13. Number of Hours ≥ 0.05 ppm for Selected Rural O₃ Monitoring in the United States
by Month for the Period 1988 to 2001**

Site Name	Month	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
Denali National Park, Alaska	February	0	0	0	0	0	0	0	0		0	0	0	0	14
Denali National Park, Alaska	March	0	0	0	0	0	0	0	0	52	0	122	17	0	24
Denali National Park, Alaska	April	217	0	2	0	64	10	31	21	12	51	236	119	0	302
Denali National Park, Alaska	May	26	1	0	24	10	17	1	54	97	35	79	29	0	98
Denali National Park, Alaska	June	0	0	0	0	0	0	0	0	27	0	0	22	0	6
Yellowstone National Park, Wyoming	February	0		0	11	3	0	21	6	0	1	5	252	23	77
Yellowstone National Park, Wyoming	March	194		2	4	95	26	285	14	7	98	150	509	286	307
Yellowstone National Park, Wyoming	April	228		17	16	217	62	311	185	65	163	385	517	242	461
Yellowstone National Park, Wyoming	May	225		2	10	196	47	180	193	212	216	289	458	240	350
Yellowstone National Park, Wyoming	June	58		67	139	33	28	116	81	94	149	78	212	181	172

Table AX3-13 (cont'd). Number of Hours ≥ 0.05 ppm for Selected Rural O₃ Monitoring in the United States by Month for the Period 1988 to 2001

Site Name	Month	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
Glacier National Park, Montana	February			0	0	0	0	0	8	0	0	0	0	0	0
Glacier National Park, Montana	March			49	9	24	10	23	40	35	9	6	17	5	4
Glacier National Park, Montana	April			31	64	29	5	45	16	46	52	49	128	16	0
Glacier National Park, Montana	May			20	81	67	41	66	51	51	4	122	103	63	23
Glacier National Park, Montana	June			24	37	31	5	29	13	119	0	3	0	6	0
Voyageurs National Park, Minnesota	February	3	0	0	0	0	43	22	0	0	23	0	6	32	0
Voyageurs National Park, Minnesota	March	6	2	0	0	1	94	10	39	49	220	40	215	60	0
Voyageurs National Park, Minnesota	April	48	0	31	22	27	56	65	30	64	128	254	221	175	0
Voyageurs National Park, Minnesota	May	183	33	14	10	174	78	96	107	111	146	191	247	143	62
Voyageurs National Park, Minnesota	June	92		2	0	55	50	66	190	37	221	25	23	28	95

Table AX3-14. Number of Hours ≥ 0.06 ppm for Selected Rural O₃ Monitoring Sites in the United States by Month for the Period of 1988 to 2001

Site Name	Month	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
Denali National Park, Alaska	February	0	0	0	0	0	0	0	0		0	0	0	0	0
Denali National Park, Alaska	March	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Denali National Park, Alaska	April	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Denali National Park, Alaska	May	0	0	0	0	0	0	0	0	2	0	0	0	0	9
Denali National Park, Alaska	June	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Yellowstone National Park, Wyoming	February	0		0	0	0	0	0	0	0	0	0	6	0	0
Yellowstone National Park, Wyoming	March	37		0	0	0	0	0	0	0	1	0	120	1	4
Yellowstone National Park, Wyoming	April	59		0	0	29	0	20	4	0	0	64	158	11	77
Yellowstone National Park, Wyoming	May	20		0	0	61	3	42	24	38	26	54	169	49	139
Yellowstone National Park, Wyoming	June	8		7	18	2	1	13	0	0	22	4	27	43	18
Glacier National Park, Montana	February			0	0	0	0	0	0	0	0	0	0	0	0
Glacier National Park, Montana	March			1	0	0	0	0	0	0	0	0	0	0	0

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Table AX3-14 (cont'd). Number of Hours ≥ 0.06 ppm for Selected Rural O₃ Monitoring Sites in the United States by Month for the Period of 1988 of 2001

Site Name	Month	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
Glacier National Park, Montana	April			0	0	1	0	0	0	0	0	2	1	0	0
Glacier National Park, Montana	May			2	7	13	0	0	4	5	0	16	19	8	0
Glacier National Park, Montana	June			0	3	1	0	1	0	16	0	0	0	0	0
Voyageurs National Park, Minnesota	February	1	0	0	0	0	1	8	0	0	0	0	0	0	0
Voyageurs National Park, Minnesota	March	0	0	0	0	0	34	0	5	2	15	0	9	4	0
Voyageurs National Park, Minnesota	April	9	0	1	0	0	5	8	0	17	2	57	24	41	0
Voyageurs National Park, Minnesota	May	77	6	0	0	40	9	40	2	27	46	53	139	43	6
Voyageurs National Park, Minnesota	June	30		0	0	28	17	5	113	12	115	0	5	0	32

AX3-142

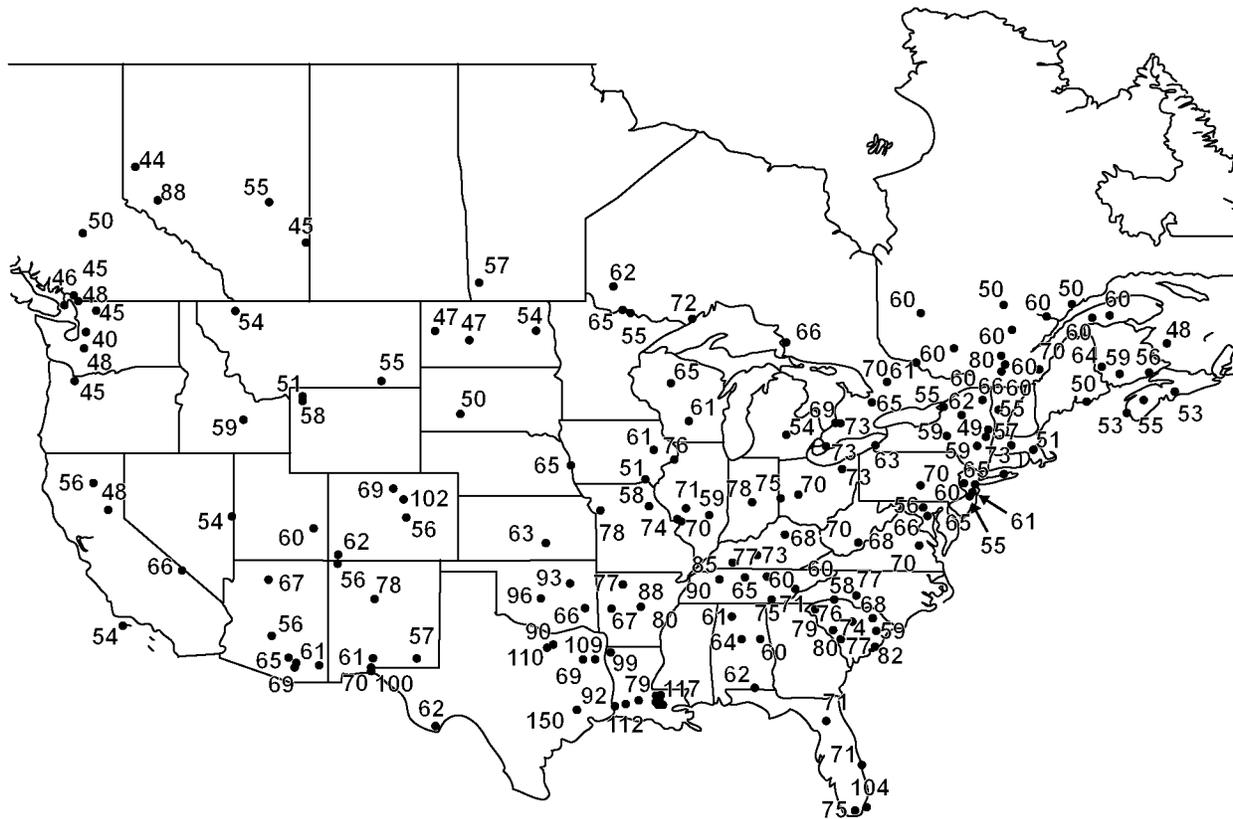


Figure AX3-78. Maximum hourly average O₃ concentrations at rural monitoring sites in Canada and the United States in February from 1980 to 1998.

Source: Lefohn et al. (2001).

Beine et al. (1997) and Honrath et al. (1996) measured O₃, PAN, and NO_x in Alaska and Svalbard, Norway and concluded that PAN decomposition can lead to photochemical O₃ production. At Poker Flat, Alaska, O₃ production was directly observable. Herring et al. (1997) tracked springtime O₃ maxima in Denali National Park, Alaska, an area one might presume to be pristine. They measured NO_x and hydrocarbons and concluded that, in the spring, O₃ was produced predominantly by photochemistry at a calculated rate of 1 to 4 ppb/day, implying that the O₃ observed could be produced on timescales ranging from about a week to a month. Solberg et al. (1997) tracked the major components of NO_y in remote Spitsbergen, Norway for the first half of the year 1994. They observed high concentrations of PAN (800 ppt) peaking simultaneously with O₃ (45 to 50 ppb) and attributed this to the long-range transport of pollution

and to photochemical smog chemistry. These investigators concluded, in general, that large regions of the Arctic store high concentrations of O₃ precursors in the winter and substantial quantities of O₃ are produced by photochemical reactions in the spring. Although reactions with high-activation-energy barriers may be ineffective, reactions with low- or no activation-energy barriers (such as radical-radical reactions) or negative temperature dependencies will still proceed. Indeed, active photochemistry is observed in the coldest regions of the stratosphere and mesosphere. While it is expected that photochemical production rates of O₃ will increase with decreasing solar zenith angle as one moves southward from the locations noted above, it should not be assumed that photochemical production of O₃ does not occur during late winter and spring at mid- and high-latitudes.

Perhaps the most thorough set of studies investigating causes of springtime maxima in surface O₃ has been performed as part of the AEROCE and NARE studies (cf., Sections AX2.3.4a,b) and TOPSE (Browell et al., 2003). These first two studies found that elevated or surface O₃ > 40 ppb at Bermuda, at least, arises from two distinct sources: the polluted North American continent and the stratosphere. It was also found that these sources mix in the upper troposphere before descending as shown in Figure AX3-79. (In general, air descending behind cold fronts contains contributions from intercontinental transport and the stratosphere.) These studies also concluded that it is impossible to determine sources of O₃ without ancillary data that could be used either as tracers of sources or to calculate photochemical production and loss rates. In addition, subsiding back trajectories do not necessarily imply a free-tropospheric or stratospheric origin for O₃ observed at the surface, since the subsiding conditions are also associated with strong inversions and clear skies that promote O₃ production within the boundary layer. Thus, it would be highly problematic to use observations alone as estimates of PRB O₃ concentrations, especially for sites at or near sea level.

The IPCC Third Assessment Report (TAR) (2001) gave a large range of values for terms in the tropospheric O₃ budget. Estimates of O₃ STE of O₃ ranged over a factor of three from 391 to 1440 Tg/year in the twelve models included in the intercomparison; many of the models included in that assessment overestimated O₃ STE. However, the overestimates likely reflected errors in assimilated winds in the upper troposphere (Douglass et al., 2003; Schoeberl et al., 2003; Tan et al., 2004; van Noije et al., 2004). The budgets of tropospheric O₃ calculated since the IPCC TAR are shown in Table AX3-15. Simulation of stratospheric intrusions is

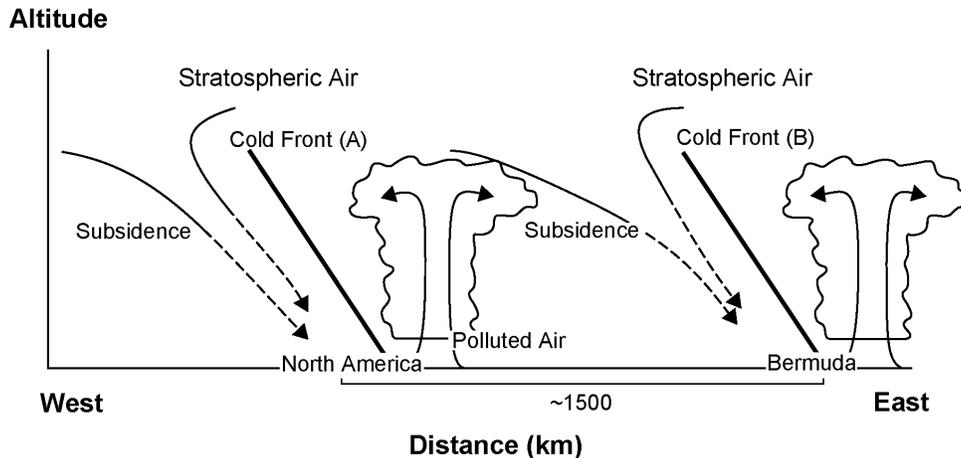


Figure AX3-79. Schematic diagram of a meteorological mechanism involved in high concentrations of O₃ found in spring in the lower troposphere off the American East Coast. Subsidence behind the first cold front meets convection ahead of a second cold front such that polluted air and O₃ from the upper troposphere/ lower stratosphere are transported in close proximity (or mixed) and advected over the North Atlantic Ocean. The vertical scale is about 10 km; the horizontal scale about 1500 km. (Note that not all cold fronts are associated with squall lines and that mixing occurs even in their absence.)

Source: Prados (2000).

notoriously difficult in global models, and O₃ STE is generally parameterized in these models. However, as can be seen from inspection of Table AX3-15, improvements in assimilation techniques have improved and narrowed estimates of STE. A model intercomparison looking at actual STE events found significant variations in model results that depended significantly on the type and horizontal resolution of the model (Meloan et al., 2003; Cristofanelli et al., 2003). In particular, it was found that the Lagrangian perspective (as opposed to the Eulerian perspective used in most global scale CTMs) was necessary to characterize the depths and residence times of individual events (Sprenger and Wernli, 2003; James et al., 2003a,b). A few studies of the magnitude of the O₃ STE have been made based on chemical observations in the lower stratosphere or combined chemistry and dynamics (e.g., 450 Tg/year net global [Murphy and Fahey, 1994]; 510 Tg/year net global extratropics only [Gettelman et al., 1997]; and 550 ± 140 Tg/year [Olsen et al., 2002]).

Table AX3-15. Global Budgets of Tropospheric Ozone (Tg year⁻¹) for the Present-day Atmosphere¹

Reference	Model	Stratosphere-Troposphere Exchange (STE)	Chemical Production ²	Chemical Loss ²	Dry Deposition	Burden (Tg)	Lifetime (days) ³
TAR ⁴	11 models	770 ± 400	3420 ± 770	3470 ± 520	770 ± 180	300 ± 30	24 ± 2
Lelieveld and Dentener (2000)		570	3310	3170	710	350	33
Bey et al. (2001a) ⁵	GEOS-CHEM	470	4900	4300	1070	320	22
Horowitz et al. (2003)	MOZART-2	340	5260	4750	860	360	23
Von Kuhlmann et al. (2003)	MATCH-MPIC	540	4560	4290	820	290	21
Shindell et al. (2003)	GISS	417	NR ⁶	NR	1470	349	NR
Park et al. (2004)	UMD-CTM	480	NR	NR	1290	340	NR
Rotman et al. (2004)	IMPACT	660	NR	NR	830	NR	NR
Wong et al. (2004)	SUNYA/UiO GCCM	600	NR	NR	1100	376	NR

¹ From global CTM simulations describing the atmosphere of the last decade of the 20th century.

² Chemical production and loss rates are calculated for the odd oxygen family, usually defined as $O_x = O_3 + O + NO_2 + 2NO_3 + 3N_2O_5 + HNO_4 +$ peroxyacynitrates (and sometimes HNO_3), to avoid accounting for rapid cycling of O_3 with short-lived species that have little implication for its budget. Chemical production is mainly contributed by reactions of NO with peroxy radicals, while chemical loss is mainly contributed by the $O(^1D) + H_2O$ reaction and by the reactions of O_3 with HO_2^* , $\bullet OH$, and alkenes. Several models in this table do not report production and loss separately (“NR” entry in the table), reporting instead net production. However, net production is not a useful quantity for budget purposes, because (1) it represents a small residual between large production and loss, (2) it represents the balance between STE and dry deposition, both of which are usually parameterized as a flux boundary condition.

³ Calculated as the ratio of the burden to the sum of chemical and deposition losses

⁴ Means and standard deviations from an ensemble of 11 CTM budgets reported in the IPCC TAR. The mean budget does not balance exactly because only 9 CTMs reported chemical production and loss statistics.

⁵ The Martin et al. (2003) more recent version of GEOS-CHEM gives identical rates and burdens.

⁶ Not reported.

Even if the magnitude of cross-tropopause O₃ fluxes in global CTMs are calculated correctly in an annual mean sense, it should be noted that stratospheric intrusions occur episodically following the passage of cold fronts at midlatitudes. Of major concern is the ability of global-scale CTMs to simulate individual intrusions and the effects on surface O₃ concentrations that may result during these events. As noted in Section AX2.3.1, these intrusions occur in “ribbons” ~ 200 to 1000 km long, 100 to 300 km wide, and 1 to 4 km thick. An example of a stratospheric intrusion occurred in Boulder, CO (EPA AQS Site 080130011; formally AIRS) on May 6, 1999 (Lefohn et al., 2001). At 1700 UTC (1000 hours LST) an hourly average concentration of 0.060 ppm was recorded and by 2100 UTC (1400 hours LST), the maximum hourly average O₃ concentration of 0.076 ppm was measured. At 0200 UTC on May 7, 1999 (1900 hours LST on May 6), the hourly average concentration declined to 0.059 ppm. Figure AX3-80 shows the O₃ vertical profile that was recorded at Boulder, CO on May 6, 1999, at 1802 UTC (1102 hours LST). The ragged vertical profile of O₃ at > 4 km reflects stratospheric air that has spiraled downward around an upper-level low and mixed with tropospheric air along the way. Thus, stratospheric air which is normally extremely cold and dry and rich in O₃, loses its characteristics as it mixes downward. This process was described in Section AX2.3.1 and illustrated in Figures AX2-7a, b, and c.

The dimensions given above imply that individual intrusions are not resolved properly in the current generation of global-scale CTMs (Figure AX3-80). However, as noted in Section AX2.3.1, penetration of stratospheric air directly to the planetary boundary layer rarely occurs in the continental United States. Rather, intrusions are more likely to affect the middle and upper troposphere, providing a reservoir for O₃ that can exchange with the planetary boundary layer. In this regard, it is important that CTMs be able to spatially and temporally resolve the exchange between the planetary boundary layer and the lower free troposphere properly.

AX3.9.2 Capability of Global Models to Simulate Tropospheric Ozone

The current generation of global CTMs includes detailed representation of tropospheric O₃-NO_x-VOC chemistry. Meteorological information is generally provided by global data assimilation centers. The horizontal resolution is typically a few hundred km, the vertical resolution is 0.1 to 1 km, and the effective temporal resolution is a few hours. These models can simulate most of the observed variability in O₃ and related species, although the coarse

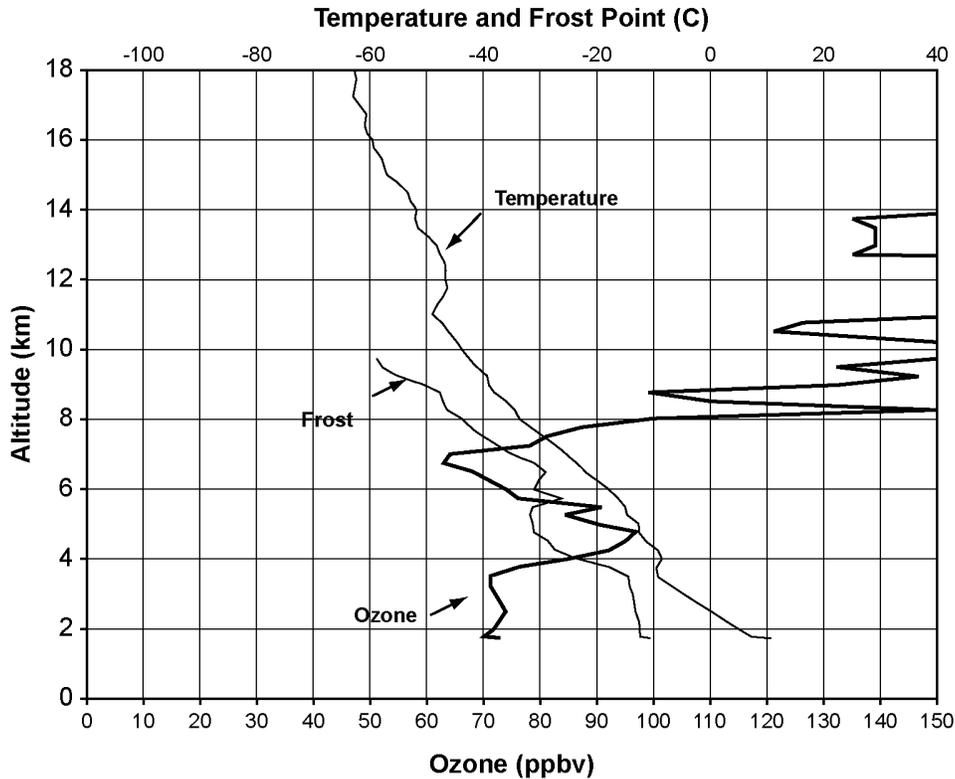


Figure AX3-80. Ozone vertical profile at Boulder, Colorado on May 6, 1999 at 1802 UTC (1102 LST).

Source: Lefohn et al. (2001).

resolution precludes simulation of fine-scale structures or localized extreme events. On the synoptic scale, at least, all evidence indicates that global models are adequate tools to investigate the factors controlling tropospheric O_3 . Stratosphere-troposphere exchange of O_3 in global models is generally parameterized. The parameterizations are typically constrained to match the global mean O_3 cross-tropopause flux, which is in turn constrained by a number of observational proxies ($550 \pm 140 \text{ Tg } O_3 \text{ year}^{-1}$ [Olsen et al., 2002]). The model simulations are routinely compared to ozonesonde observations in the middle and upper troposphere to test the simulation of stratospheric influence on tropospheric O_3 (Logan, 1999). Such evaluations show that the parameterized cross-tropopause O_3 flux in global models results in a good simulation of tropospheric O_3 , at least in a mean sense; and that the current generation of models can

reproduce the tropospheric ozonesonde climatology to within 5 to 10 ppbv, even at mid- and high-northern latitudes in winter, with the correct seasonal cycle.

Fiore et al. (2003a) used the GEOS-CHEM global tropospheric chemistry model to quantify PRB O₃ concentrations across the United States. A net global O₃ flux of 490 Tg O₃ year⁻¹ from the stratosphere to the troposphere is imposed in the GEOS-CHEM model, consistent with the range constrained by observations (Olsen et al., 2002). Previous applications of the model have demonstrated that it simulates the tropospheric ozonesonde climatology (Logan, 1999) generally to within 5 to 10 ppbv, including at mid- and high-latitudes (Bey et al., 2001a) over Bermuda in spring (Li et al., 2002) and at sites along the Asian Pacific rim (Liu et al., 2002). The phase of the seasonal cycle is reproduced to within 1 to 2 months (Bey et al., 2001a; Li et al., 2002; Liu et al., 2002). An analysis of the ²¹⁰Pb-⁷Be-O₃ relationships observed in three aircraft missions over the western Pacific indicates that the model does not underestimate the stratospheric source of O₃ (Liu et al., 2004). These studies and others (Li et al., 2001; Bey et al., 2001b; Fusco and Logan, 2003) demonstrate that the model provides an adequate simulation of O₃ in the free troposphere at northern midlatitudes, including the mean influence from the stratosphere. However, it cannot capture the structure and enhancements associated with stratospheric intrusions, leading to mean O₃ under-prediction in regions of preferred stratospheric downwelling.

Fiore et al. (2002a, 2003b) presented a detailed evaluation of the model simulation for O₃ and related species in surface air over the United States for the summer of 1995. They showed that the model reproduces important features of observations including the high tail of O₃ frequency distributions at sites in the eastern United States (although sub-grid-scale local peaks are underestimated), the O₃ to (NO_y - NO_x) relationships, and that the highest O₃ values exhibit the largest response to decreases in U.S. fossil fuel emissions from 1980 to 1995 (Lefohn et al., 1998). Empirical orthogonal functions (EOFs) for the observed regional variability of O₃ over the eastern United States are also well reproduced, indicating that GEOS-CHEM captures the synoptic-scale transport processes modulating surface O₃ concentrations (Fiore et al., 2003b). One model shortcoming relevant for the discussion below is that excessive convective mixing over the Gulf of Mexico and the Caribbean leads to an overestimate of O₃ concentrations in southerly flow over the southeastern United States. Comparison of GEOS-CHEM with the Multiscale Air Quality Simulation Platform (MAQSIP) regional air quality modeling system

(Odman and Ingram, 1996) at 36 km² horizontal resolution showed that the models exhibit similar skill at capturing the observed variance in O₃ concentrations with comparable model biases (Fiore et al., 2003b).

Simulations to Quantify Background Ozone Over the United States

The sources contributing to the O₃ background over the United States were quantified by Fiore et al. (2003a) with three simulations summarized in Table AX3-16: (1) a standard simulation, (2) a background simulation in which North American anthropogenic NO_x, NMVOC, and CO emissions are set to zero, and (3) a natural O₃ simulation in which global anthropogenic NO_x, NMVOC and CO emissions are set to zero and the CH₄ concentration is set to its 700 ppbv pre-industrial value. Anthropogenic emissions of NO_x, nonmethane volatile organic compounds (NMVOCs), and CO include contributions from fuel use, industry, and fertilizer application. The difference between the standard and background simulations represents regional pollution, i.e., the O₃ enhancement from North American anthropogenic emissions. The difference between the background and natural simulations represents hemispheric pollution, i.e., the O₃ enhancement from anthropogenic emissions outside North America. Methane and NO_x contribute most to hemispheric pollution (Fiore et al., 2002b). A tagged O₃ tracer simulation (Fiore et al., 2002a) was used to isolate the stratospheric contribution to the background and yielded results that were quantitatively consistent with those from a simulation in which O₃ transport from the stratosphere to the troposphere was suppressed (Fusco and Logan, 2003). All simulations were initialized in June 2000; results are reported for March through October 2001.

The standard and background simulations were conducted at 2° × 2.5° horizontal resolution, but the natural simulation was conducted at 4° × 5° resolution to save on computational time. There was no significant bias between 4° × 5° and 2° × 2.5° simulations (Fiore et al., 2002a), particularly for a natural O₃ simulation where surface concentrations were controlled by large-scale processes.

AX3.9.3 Mean Background Concentrations: Spatial and Seasonal Variation

The analysis of Fiore et al. (2003a) focused on the 2001 observations from the Clean Air Status and Trends Network (CASTNet) of rural and remote U.S. sites (Lavery et al., 2002)

**Table AX3-16. Description of Simulations Used for Source Attribution
(Fiore et al., 2003a)**

Simulation	Description	Horizontal Resolution
Standard	Present-day emissions as described in the text	2° × 2.5°
Background	North American anthropogenic NO _x , NMVOC, and CO emissions set to zero	2° × 2.5°
Natural	Global anthropogenic NO _x , NMVOC, and CO emissions set to zero and CH ₄ concentration set to its 700 ppbv preindustrial value	4° × 5°
Stratospheric	Tagged O ₃ tracer originating from the stratosphere in standard simulation	2° × 2.5°

(Figure AX3-81). Figure AX3-82 shows the mean seasonal cycle in afternoon (1300 to 1700 hours LT) O₃ concentrations averaged over the CASTNet stations in each U.S. quadrant. Measured O₃ concentrations (asterisks) are highest in April to May, except in the Northeast where they peak in June. Model results (triangles) are within 3 ppbv and 5 ppbv of the observations for all months in the Northwest and Southwest, respectively. Model results for the Northeast are too high by 5 to 8 ppbv when sampled at the CASTNet sites; the model is lower when the ensemble of grid squares in the region are sampled (squares). The model is 8 to 12 ppbv too high over the Southeast in summer for reasons discussed in Section AX3.9.2. Results from the background simulation (no anthropogenic emissions in North America; see Table AX3-16) are shown as diamonds in Figure AX3-82. Mean afternoon background O₃ ranges from 20 ppbv in the Northeast in summer to 35 ppbv in the Northwest in spring. It is higher in the West than in the East because of higher elevation, deeper mixed layers, and longer O₃ lifetimes due to the arid climate (Fiore et al., 2002a). It is also higher in spring than in summer, in part because of the seasonal maximum of stratospheric influence (Figure AX3-82) and in part because of the longer lifetime of O₃ (Wang et al., 1998).

Results from the natural O₃ simulation (no anthropogenic emissions anywhere; Table AX3-16) are shown as crosses in Figure AX3-82. Natural O₃ concentrations are also highest in the West and in spring when the influence of stratospheric O₃ on the troposphere peaks (e.g., Holton et al., 1995). Monthly mean natural O₃ concentration ranges are 18 to 23, 18 to 27, 13 to 20, and 15 to 21 ppbv in the Northwest, Southwest, Northeast, and Southeast,

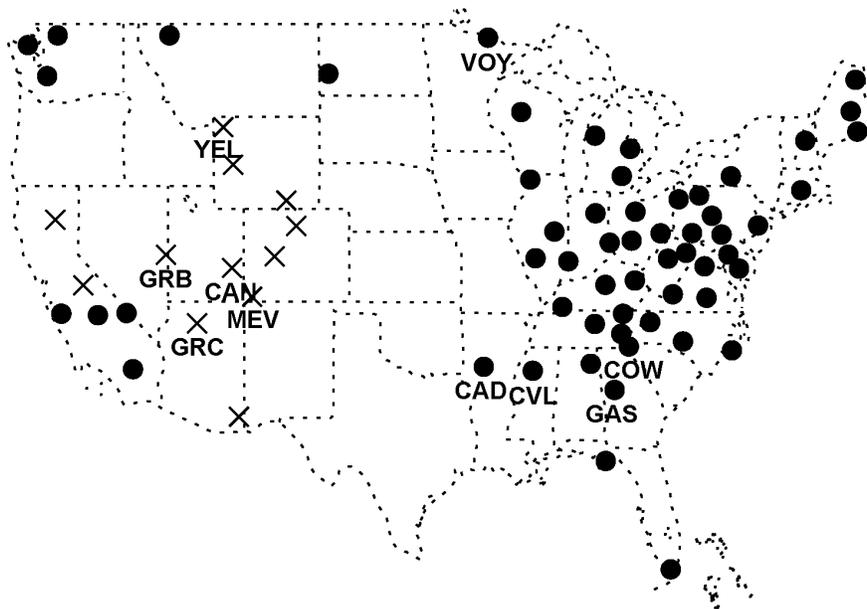


Figure AX3-81. CASTNet stations in the continental United States for 2001. Sites discussed in Section AX3.9.4 are labeled: VOY = Voyageurs NP, MI; COW = Coweeta, NC; YEL = Yellowstone NP, WY; CAD = Caddo Valley, AR; CVL = Coffeeville, MS; GAS = Georgia Station, GA; GB = Great Basin, NV; GRC = Grand Canyon, AZ; CAN = Canyonlands, UT; MEV = Mesa Verde, CO. Crosses denote sites > .5 km altitude.

Source: Fiore et al. (2003a).

respectively. The stratospheric contribution (X's) ranges from 7 ppbv in spring to 2 ppbv in summer.

The difference between the background and natural simulations in Figure AX3-82 represents the increases in monthly mean hemispheric pollution. This increase ranges from 5 to 12 ppbv depending on region and season. It peaks in spring due to a longer O₃ lifetime (Wang et al., 1998) and to efficient ventilation of pollution from the Asian continent (Liu et al., 2003). In contrast to hemispheric pollution, the regional pollution influence (O₃ produced from North American anthropogenic emissions, shown as the difference between the squares and diamonds) peaks in summer and is highest in the East. For the data in Figure AX3-82, it ranges from 8 ppbv in the northern quadrants in March to over 30 ppbv in the eastern quadrants in summer. Monthly mean observed O₃ concentrations are influenced by both regional and hemispheric pollution in all U.S. regions from March through October.

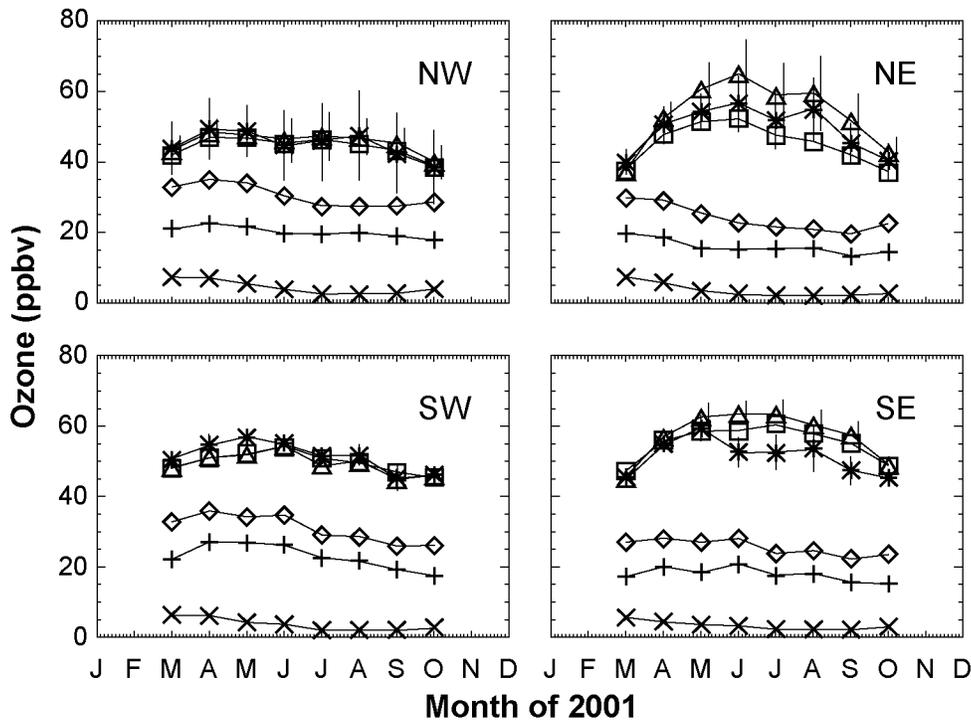


Figure AX3-82. Monthly mean afternoon (1300 to 1700 hours LT) concentrations (ppbv) in surface air averaged over the CASTNet stations (Figure AX3-81) in each U.S. quadrant for March to October 2001. Observations (asterisks) are compared with model values from the standard simulation sampled at the CASTNet sites (triangles) and sampled for the entire quadrant (squares). The vertical lines show the standard deviation in the observed and simulated values. Monthly mean model results for the background (diamonds), natural (crosses), and stratospheric (X's) contributions (Table AX3-16) to surface O_3 are shown. The U.S. quadrants are centered at 98.75° W and 37° N.

Source: Fiore et al. (2003a).

AX3.9.4 Frequency of High-Ozone Occurrences at Remote Sites

Lefohn et al. (2001) pointed out the frequent occurrence of high- O_3 events (>50 and 60 ppbv) at remote northern U.S. sites in spring. Fiore et al. (2003a) replicated the analysis of Lefohn et al. (2001) at the four CASTNet sites that they examined: Denali National Park (Alaska), Voyageurs National Park (Minnesota), Glacier National Park (Montana), and Yellowstone National Park (Wyoming). The number of times that the hourly O_3 observations at

the sites are >50 and 60 ppbv for each month from March to October 2001 were then calculated (see results in Table AX3-17) and compared with the same statistics for March to June 1988 to 1998 from Lefohn et al. (2001), to place the 2001 statistics in the context of other years. More incidences of O₃ above both thresholds occur at Denali National Park and Yellowstone National Park in 2001 than in nearly all of the years analyzed by Lefohn et al. (2001). The statistics at Glacier National Park, Montana indicate that 2001 had fewer than average incidences of high-O₃ events. At Voyageurs National Park in Minnesota, March and April 2001 had lower-than-average frequencies of high-O₃ events, but May and June were more typical. Overall, 2001 was considered to be a suitable year for analysis of high-O₃ events. Ozone concentrations >70 and 80 ppbv occurred most often in May through August in 2001 and were found to be associated with regional pollution by Fiore et al. (2003a).

Fiore et al. (2003a) focused their analysis on mean O₃ concentrations during the afternoon hours (1300 to 1700 LT), as the comparison of model results with surface observations is most appropriate in the afternoon when the observations are representative of a relatively deep mixed layer (Fiore et al., 2002a). In addition, the GEOS-CHEM model does not provide independent information on an hour-to-hour basis, because it is driven by meteorological fields that are updated every 6-h and then interpolated. Fiore et al. (2003a) tested whether an analysis restricted to these mean 1300 to 1700 LT surface concentrations captures the same frequency of O₃ >50 and 60 ppbv that emerges from an analysis of the individual hourly concentrations over 24 hours. Results are reproduced here in Table AX3-17, which shows that the percentage of individual afternoon (1300 to 1700 LT) hours when O₃ >50 and 60 ppbv at the CASTNet sites is always greater than the percentage of all hourly occurrences above these thresholds, indicating that elevated O₃ concentrations preferentially occur in the afternoon. Furthermore, Table AX3-17 shows that the frequency of observation of high-O₃ events is not diminished when 4-h average (1300 to 1700 LT) concentrations are considered, reflecting persistence in the duration of these events. Model frequencies of high-O₃ events from 1300 to 1700 LT at the CASTNet sites are similar to observations in spring, as shown in Table AX3-17, and about 10% higher in the summer, largely because of the positive model bias in the Southeast discussed in Section AX3.9.2.

Table AX3-17. Number of Hours with Ozone Above 50 or 60 ppbv at U.S. CASTNet Sites in 2001

Site	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct
Observations ≥ 50 ppbv								
Denali NP, Alaska (64° N, 149° W, 0.6 km)	24	302	98	6	0	0	0	0
Voyageurs NP, Minnesota (48° N, 93° W, 0.4 km)	0	0	62	95	14	17	33	0
Glacier NP, Montana (49° N, 114° W, 1.0 km)	4	0	23	0	6	12	0	0
Yellowstone NP, Wyoming (45° N, 110° W, 2.5 km)	307	461	350	172	140	261	173	77
All CASTNet sites (71)	5468 (11%)	15814 (32%)	17704 (36%)	16150 (33%)	14489 (29%)	15989 (32%)	9874 (20%)	5642 (11%)
All sites, 1300-1700 LT only (hourly data)	1817 (21%)	4684 (56%)	5174 (61%)	4624 (56%)	4613 (54%)	5075 (60%)	3343 (40%)	1945 (23%)
All sites, 1300-1700 LT mean (4-hour average)	435 (20%)	1153 (55%)	1295 (61%)	1147 (55%)	1161 (54%)	1283 (60%)	841 (40%)	478 (22%)
All sites, model 1300-1700 LT mean	254 (12%)	1249 (59%)	1527 (69%)	1505 (71%)	1475 (67%)	1500 (68%)	1080 (51%)	591 (27%)
Observations ≥ 60 ppbv								
Denali NP	0	0	9	2	0	0	0	0
Voyageurs NP	0	0	6	32	0	0	15	0
Glacier NP	0	0	0	0	0	0	0	0
Yellowstone NP	4	77	139	18	6	26	1	2
All sites	519 (1%)	4729 (10%)	8181 (16%)	8199 (17%)	5705 (11%)	7407 (15%)	3492 (7%)	2073 (4%)
All sites, 1300-1700 LT only	235 (3%)	1798 (22%)	2808 (33%)	2721 (33%)	2235 (26%)	2758 (33%)	1416 (17%)	878 (10%)
All sites, 1300-1700 LT mean	56 (3%)	428 (20%)	697 (33%)	671 (32%)	550 (26%)	677 (32%)	358 (17%)	214 (10%)
All sites, model 1300-1700 LT mean	13 (1%)	377 (18%)	834 (38%)	964 (45%)	910 (41%)	834 (38%)	502 (24%)	204 (9%)

Data from 71 U.S. CASTNet sites are included in this analysis: those in Figure AX3-105 plus Denali NP.

Percentages of total occurrences are shown in parentheses.

NP = National Park; LT = Local Time.

Reproduced from Fiore et al. (2003a).

NATURAL VERSUS ANTHROPOGENIC CONTRIBUTIONS TO HIGH-OZONE OCCURRENCES

Figure AX3-83, reproduced from Fiore et al. (2003a), shows probability distributions of daily mean afternoon (1300 to 1700 LT) O₃ concentrations in surface air at the CASTNet sites for March through October 2001. Model distributions for background, natural, and stratospheric O₃ (Table AX3-16) are also shown. The background (long-dashed line) ranges from 10 to 50 ppbv with most values in the 20 to 35 ppbv range. The full 10 to 50 ppbv range of background predicted here encompasses the previous 25 to 45 ppbv estimates shown in Table 3-8. However, background estimates from observations tend to be at the higher end of the range (25 to 45 ppbv), while these results, as well as those from prior modeling studies (Table 3-8) indicate that background O₃ concentrations in surface air are usually below 40 ppbv. The background O₃ concentrations derived from observations may be overestimated if observations at remote and rural sites contain some influence from regional pollution (as shown below to occur in the model), or if the O₃ versus NO_y - NO_x correlation is affected by different relative removal rates of O₃ and NO_y (Trainer et al., 1993). Natural O₃ concentrations (short-dashed line) are generally in the 10 to 25 ppbv range and never exceed 40 ppbv. The range of the hemispheric pollution enhancement (the difference between the background and natural O₃ concentrations) is typically 4 to 12 ppbv and only rarely exceeds 20 ppbv (< 1% total incidences). The stratospheric contribution (dotted line) is always less than 20 ppbv and usually below 10 ppbv. Time series for specific sites are presented below.

CASE STUDIES: INFLUENCE OF THE BACKGROUND ON ELEVATED OZONE EVENTS IN SPRING

High-O₃ events were previously attributed to natural processes by Lefohn et al. (2001) at: Voyageurs National Park, Minnesota in June and Yellowstone National Park, Wyoming in March through May. Fiore et al. (2003a) used observations from CASTNet stations in conjunction with GEOS-CHEM model simulations to deconstruct the observed concentrations into anthropogenic and natural contributions.

At Voyageurs National Park in 2001, O₃ concentrations >60 ppbv occurred frequently in June but rarely later in summer (Table AX3-17). A similar pattern was observed in 1995 and 1997 and was used to argue that photochemical activity was probably not responsible for these events (Lefohn et al. 2001). Figure AX3-84 from Fiore et al. (2003a) shows that GEOS-CHEM

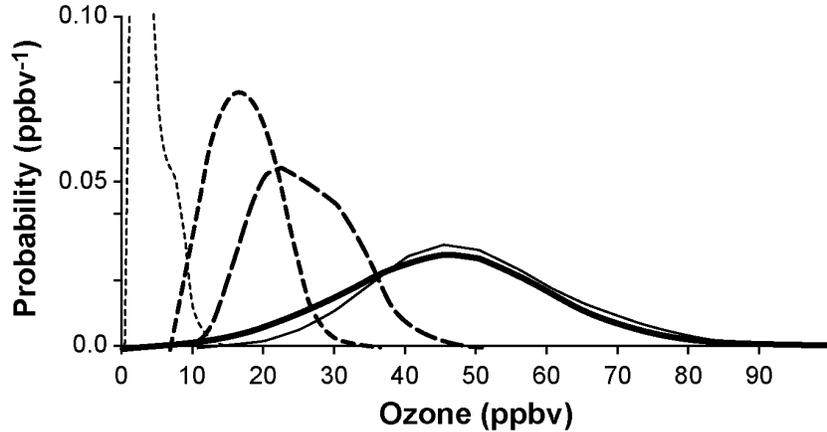


Figure AX3-83. Probability distributions of daily mean afternoon (1300 to 1700 LT) O_3 concentrations in surface air for March through October 2001 at U.S. CASTNet sites (Figure AX3-83): observations (thick solid line) are compared with model results (thin solid line). Additional probability distributions are shown for the simulated background (long-dashed line), natural (short-dashed line), and stratospheric (dotted line) contributions to surface O_3 (Table AX3-23).

Source: Fiore et al. (2003a).

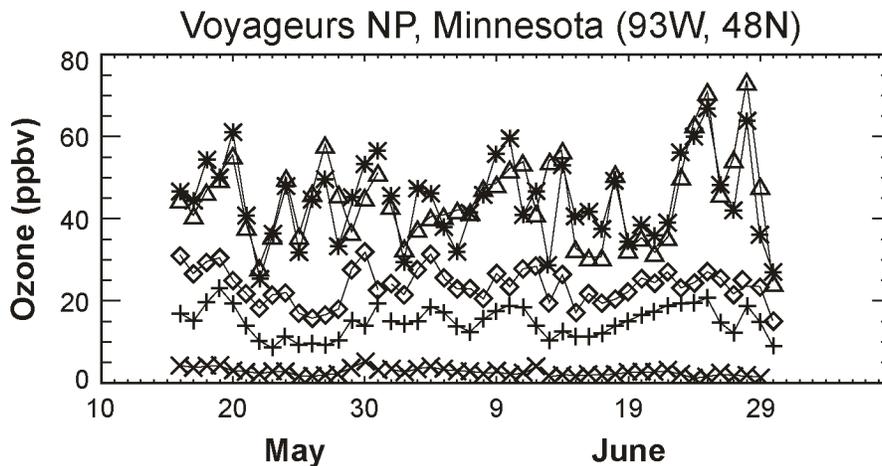


Figure AX3-84. Daily mean afternoon (13 to 17 LT) O_3 concentrations in surface air at Voyageurs National Park (NP), Minnesota in mid-May through June of 2001. Observations (asterisks) are compared with model values from the standard simulation (triangles). The simulated contributions from background (diamonds), natural (crosses), and stratospheric (X's) O_3 are also shown.

Source: Fiore et al. (2003a).

Figure AX3-84 shows that regional pollution drives most of the simulated day-to-day variability and explains all events above 50 captures much of the day-to-day variability in observed concentrations from mid-May through June, including the occurrence and magnitude of high-O₃ events. The simulated background contribution (diamonds) ranges from 15 to 36 ppbv with a 25 ppbv mean. The natural O₃ level (crosses) is 15 ppbv on average and varies from 9 to 23 ppbv. The stratospheric contribution (X's) is always < 7 ppbv. The dominant contribution to the high-O₃ events on June 26 and 29 is from regional pollution (44 and 50 ppbv on June 26 and 29, respectively, calculated as the difference between the triangles and diamonds in Figure AX3-84). The background contribution (diamonds) is < 30 ppbv on both days, and is composed of a 20 ppbv natural contribution (which includes 2 ppbv of stratospheric origin) and a 5 ppbv enhancement from hemispheric pollution (the difference between the diamonds and crosses). Beyond these two high-O₃ events, ppbv. In 2001, monthly mean observed and simulated O₃ concentrations are lower in July (37 and 42 ppbv, respectively) and August (35 and 36 ppbv) than in June (44 and 45 ppbv). Fiore et al. (2003a) hypothesized that the lower mean O₃ and the lack of O₃ >60 ppbv in July and August reflects a stronger Bermuda high-pressure system sweeping pollution from southern regions eastward before it could reach Voyageurs National Park.

Frequently observed concentrations of O₃ between 60 to 80 ppbv at Yellowstone NP in spring (Figures AX3-76a,b) have been attributed by Lefohn et al. (2001) to natural sources, because they occur before local park traffic starts and back-trajectories do not suggest influence from long-range transport of anthropogenic sources. More hours with O₃ >60 ppbv occur in April and May of 2001 (Table AX3-17) than in the years analyzed by Lefohn et al. (2001). Fiore et al. (2003a) used GEOS-CHEM to interpret these events; results are shown in Figure AX3-85. The mean background, natural, and stratospheric O₃ contributions in March to May are higher at Yellowstone (38, 22, and 8 ppbv, respectively) as compared to 27, 18, and 5 ppbv at the two eastern sites previously discussed. The larger stratospheric contribution at Yellowstone reflects the high elevation of the site (2.5 km). Fiore et al. (2003a) argued that the background at Yellowstone National Park should be considered an upper limit for U.S. PRB O₃ concentrations, because of its high elevation. While Yellowstone receives a higher background concentration than the eastern sites, the model shows that regional pollution from North American anthropogenic emissions (difference between the triangles and diamonds) contributes an

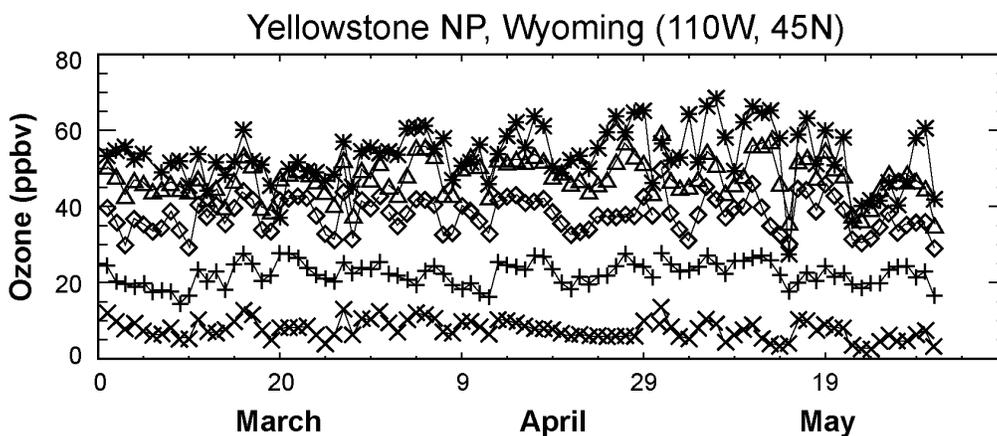


Figure AX3-85. Same as Figure AX3-84 but for Yellowstone National Park, Wyoming in March to May 2001. Observations (asterisks) are compared with model values from the standard simulation (triangles). The simulated contributions from background (diamonds), natural (crosses), and stratospheric (X's) O₃ are also shown.

Source: Fiore et al. (2003a).

additional 10 to 20 ppbv to the highest observed concentrations in April and May. One should not assume that regional photochemistry is inactive in spring.

Higher-altitude western sites are more frequent recipients of subsidence events that transport high concentrations of O₃ from the free troposphere to the surface. Cooper and Moody (2000) cautioned that observations from elevated sites are not generally representative of lower-altitude sites. At Yellowstone, the background O₃ rarely exceeds 40 ppbv, but it is even lower in the East. This point is illustrated in Figure AX3-86, from Fiore et al. (2003a), with time series at representative western and southeastern CASTNet sites for the month of March, when the relative contribution of the background should be high. At the western sites, the background is often near 40 ppbv but total surface O₃ concentrations are rarely above 60 ppbv. While variations in the background play a role in governing the observed total O₃ variability at these sites, regional pollution also contributes. Background concentrations are lower (often <30 ppbv) in the southeastern states where regional photochemical production drives much of the observed variability. Cooper and Moody (2000) have previously shown that the high O₃ concentrations at an elevated, regionally representative site in the eastern United States in spring coincide with

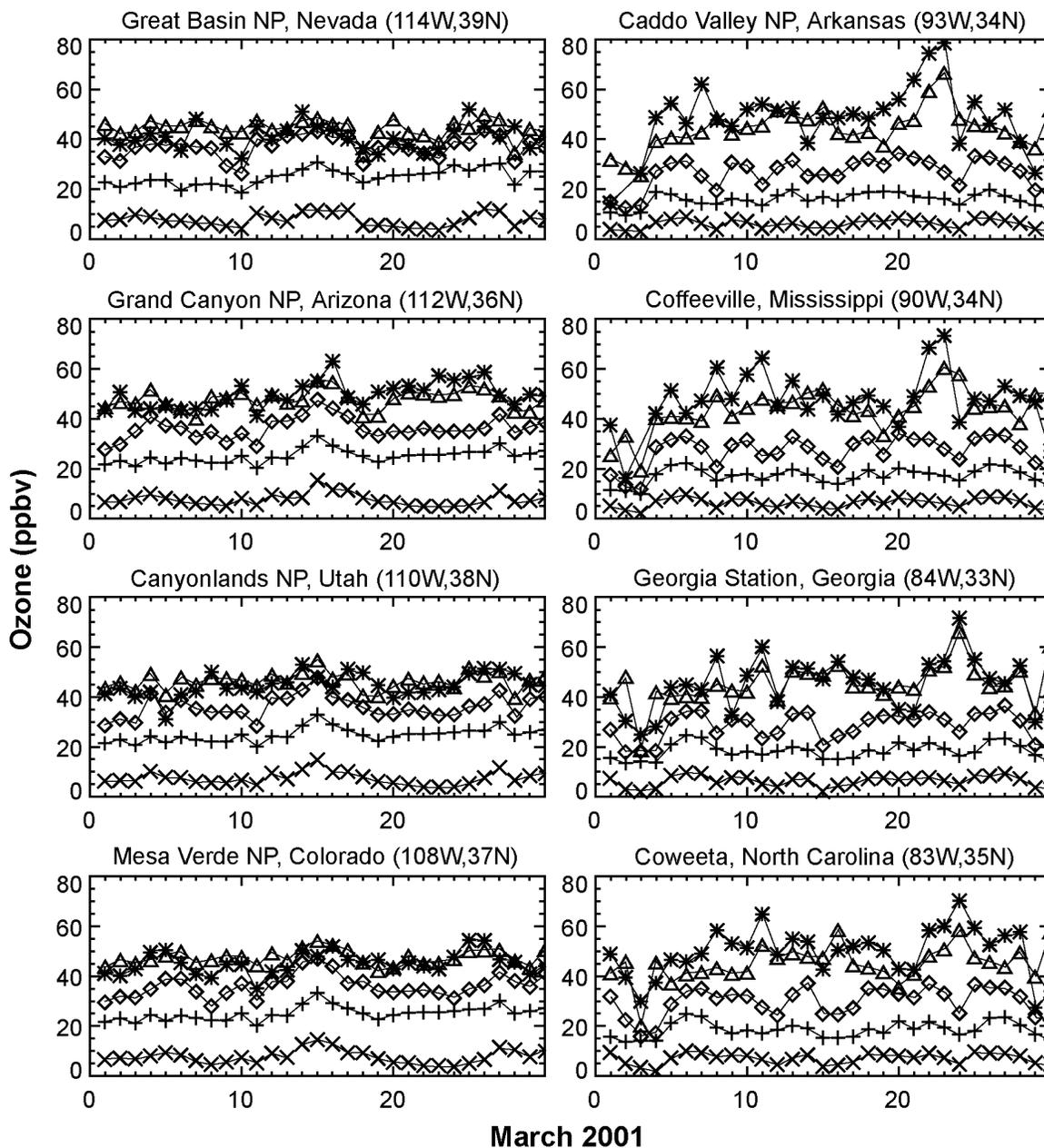


Figure AX3-86. Same as Figure AX3-84 but for March of 2001 at selected western (left column) and southeastern (right column) sites. Observations (asterisks) are compared with model values from the standard simulation (triangles). The simulated contributions from background (diamonds), natural (crosses), and stratospheric (X's) O₃ are also shown.

Source: Fiore et al. (2003a).

high temperatures and anticyclonic circulation, conditions conducive to photochemical O₃ production. Peak O₃ concentrations in this region, mainly at lower elevations, are associated with lower background concentrations because chemical and depositional loss during stagnant meteorological conditions suppress mixing between the boundary layer and the free troposphere (Fiore et al., 2002a). Surface O₃ concentrations >80 ppbv could conceivably occur when stratospheric intrusions reach the surface. However, based on information given in Section AX2.3.2, these events are rare.

AX3.10 OZONE EXPOSURE IN VARIOUS MICROENVIRONMENTS

AX3.10.1 Introduction

There are many definitions of exposure. Human exposure to O₃ and related photochemical oxidants are based on the measured O₃ concentrations in the individual's breathing zone as the individual moves through time and space. Epidemiological studies generally use the ambient concentrations as surrogates for exposure. Therefore, human exposure data and models provide the best link between ambient concentrations (from measurements at monitoring sites or estimated with atmospheric transport models), lung deposition and clearance, and estimates of air concentration-exposure-dose relationships.

This section discusses the current information on the available human exposure data and exposure model development. This includes information on (a) the relationships between O₃ measured at ambient monitoring sites and personal exposures and (b) factors that affect these relationships. The information presented in this section is intended to provide critical links between ambient monitoring data and O₃ dosimetry as well as between the toxicological and epidemiologic studies presented in Annexes AX4, AX5, AX6, and AX7 of this document.

AX3.10.2 Summary of the Information Presented in the Exposure Discussion in the 1996 Ozone Criteria Document

The 1996 O₃ AQCD (U.S. Environmental Protection Agency, 1996a), based on then currently available information, indicated that less emphasis should be placed on O₃ concentrations measured at ambient monitoring stations. Fixed monitoring stations are generally used for monitoring associated with air quality standards and do not provide a realistic

representation of individual exposures. Indoor/outdoor O₃ ratios reported in the literature were summarized for residences, hospitals, offices, art galleries, and museums. The differences in residential I/O were found to be a function of ventilation conditions. The I/O ratios were less than unity. In most cases, indoor and in-transit concentrations of O₃ were significantly different from ambient O₃ concentrations. Ambient O₃ varied from O₃ concentrations measured at fixed-site monitors. Very limited personal exposure measurements were available at the time the 1996 O₃ AQCD was published, so estimates of O₃ exposure or evaluated models were not provided. The two available personal exposure studies indicated that only 40% of the variability in personal exposures was explained by the exposure models using time-weighted indoor and outdoor concentrations. The discussion addressing O₃ exposure modeling primarily addressed work reported by McCurdy (1994) on population-based models (PBMs). Literature published since publication of the 1996 O₃ AQCD has also focused on PBMs. A discussion of individual-based models (IBMs) will be included in the description of exposure modeling in this document to improve our mechanistic understanding of O₃ source-to-exposure events and to evaluate their usefulness in providing population-based estimates.

AX3.10.3 Concepts of Human Exposure

Human exposure to O₃ and related photochemical oxidants occurs when individuals come in contact with the pollutant through “(a) the visible exterior of the person (skin and openings into the body such as mouth and nostrils) or (b) the so-called exchange boundaries where absorption takes place (skin, mouth, nostrils, lung, gastrointestinal tract)” (Federal Register, 1986). Consequently, exposure to a chemical, in this case O₃, is the contact of that chemical with the exchange boundary (U.S. Environmental Protection Agency, 1992). Therefore, inhalation exposure to O₃ is based on measurements of the O₃ concentration near the individual’s breathing zone that is not affected by exhaled air.

AX3.10.4 Quantification of Exposure

Quantification of inhalation exposure to any air pollutant starts with the concept of the variation in the concentration of the air pollutant in the breathing zone, unperturbed by exhaled breath, as measured by a personal exposure monitor as a person moves through time and space. Since the concentrations of O₃ and related photochemical oxidants vary with time and location

and since people move among locations and activities, the exposure and dose received changes during the day. Furthermore, the amount of pollutant delivered to the lung is dependent upon the person's minute ventilation rate. Thus, the level of exertion is an important consideration in determining the potential exposure and dose. Inhalation exposure has been defined as the integral of the concentration as a function of time over the time period of interest for each individual (Ott, 1982, 1985; Liroy, 1990):

$$E = \int_{t_1}^{t_2} c(t) dt \quad (\text{AX3-2})$$

where E is inhalation exposure, $c(t)$ is the breathing zone concentration as a function of time and t_1 and t_2 the starting and ending time of the exposure, respectively.

AX3.10.5 Methods to Estimate Personal Exposure

There are two approaches for measuring personal exposure; direct and indirect methods (Ott, 1982, 1985; Navidi et al., 1999). Direct approaches measure the contact of the person with the chemical concentration in the exposure media over an identified period of time. For the direct measurement method, a personal exposure monitor (PEM) is worn near the breathing zone for a specified time to either continually collect for subsequent analysis or directly measure the concentrations of the pollutant and the exposure levels. The indirect approach models concentrations of a pollutant in specific microenvironments. Both methods are subject to measurement error.

AX3.10.5.1 Direct Measurement Method

The passive monitors commonly used in the direct method provides integrated personal exposure information. The monitor's sensitivity to wind velocity, badge placement, and interference with other copollutants may result in measurement error.

Modified passive samplers have been developed for use in determining O_3 exposure. The difficulty in developing a passive O_3 monitor is in identifying a chemical or trapping reagent that can react with O_3 . Zhou and Smith (1997) evaluated the effectiveness of sodium nitrite, 3-methyl-2-benzothiazolinone acetone azine (MBTH), *p*-acetamidophenol (*p*-ATP), and indigo

carmine as O₃-trapping reagents. Only sodium nitrite and MBTH gave sensitive, linear responses at environmentally relevant concentrations. However, MBTH overestimated the O₃ concentrations significantly, suggesting an interference effect. Sodium nitrite was found to be a valid reagent when an effective diffusion barrier was used. Scheeren and Adema (1996) used an indigo carmine-coated glass-fiber filter to collect spectrophotometrically measured O₃. The detection limit was 23 ppb for a 1-h exposure, with no interfering oxidants identified. The reagent was valid for a relative humidity range of 20 to 80%. The uptake rate was wind velocity dependent. However, wind velocity dependencies was compensated for by using a small battery-operated fan that continuously blew air across the face of the monitor at a speed of 1.3 m/s. The overall accuracy of the sampler, after correcting for samples collected under low-wind conditions, was 11 ± 9% in comparison to a continuous UV-photometric monitor. Sample stability was > 25 days in a freezer. Bernard et al. (1999) employed a passive sampler consisting of a glass-fiber filter coated with a 1,2-di(4-pyridyl)ethylene solution. The sample was analyzed spectrophotometrically after color development by the addition of 3-methyl-2-benzothiazolinone hydrazone hydrochloride. The sampler was used at 48 sites in Montpellier, France. The correlation coefficient was $r = 0.9$, $p < 0.0001$. Detection limits were 17 ppb for 12-h and 8 ppb for 24-h samples with an overall variation coefficient of 5% for field-tested paired samples. The imprecision was estimated to be 1.0 ppb.

A series of studies have been conducted using a passive sampler developed by Koutrakis et al. (1993) at the Harvard School of Public Health. The sampler used sodium nitrate as the trapping reagent and included a small fan to assure sufficient movement of air across the face of the badge when sampling was done indoors. The passive sampler has been evaluated against the standard UV absorption technique used in studies in southern California (Avol et al., 1998a; Geyh et al., 1999, 2000; Delfino et al., 1996), Baltimore, MD (Sarnat et al., 2000), and Canada (Brauer and Brook, 1997).

In a study discussed later in this chapter, Avol et al. (1998a) used nitrite-coated passive samplers to measure O₃ air concentrations indoors and outdoors of 126 homes between February and December 1994 in the Los Angeles metropolitan area. The detection limit of the method was near 5 ppb. The inconsistent sampler response due to changes in wind pattern and changes in personal activity made the sampler unacceptable for widespread use.

Geyh et al. (1997, 1999) compared passive and active personal O₃ air samplers based on nitrite-coated glass-fiber filters. The active sampler was more sensitive allowing for the collection of short-term, 2.6-h samples. Comparison between the two samplers and UV photometric O₃ monitors demonstrated generally good agreement (bias for active personal sampler of ~6%). The personal sampler also had high precision (4% for duplicate analyses) and good compliance when used by children attending summer day camp in Riverside, CA.

AX3.10.5.2 Indirect Measurement Method

The indirect method determines and measures the concentrations in all of the locations or “microenvironments” a person encounters or determines the exposure levels through the use of models or biomarkers. The concept of microenvironments is critical for understanding human exposure and aids in the development of procedures for exposure modeling using data from stationary monitors (indoor and outdoor). Microenvironments were initially defined as individual or aggregate locations (and sometimes even as activities taking place within a location) where a homogeneous concentration of the pollutant is encountered for a specified period of time. Thus, a microenvironment has often been identified with an “ideal” (i.e., perfectly mixed) compartment of classical compartmental modeling. More recent and general definitions view the microenvironment as a “control volume,” indoors or outdoors, that can be fully characterized by a set of either mechanistic or phenomenological governing equations, when properly parameterized, given appropriate initial and boundary conditions. The boundary conditions typically reflect interactions with the ambient air and with other microenvironments. The parameterizations of the governing equations generally include the information on attributes of sources and sinks within each microenvironment. This type of general definition allows for the concentration within a microenvironment to be nonhomogeneous, provided its spatial profile and mixing properties can be fully predicted or characterized. By adopting this definition, the number of microenvironments used in a study is kept manageable, while existing variabilities in concentrations are still taken into account. The “control volume” variation could result in a series of microenvironments in the same location. If there are large spatial gradients within a location for the same time period, the space should be divided into the number of microenvironments needed to yield constant pollutant concentrations; the alternative offered by the control volume approach is to provide concentration as a function of location within it,

so that the appropriate value is selected for calculating exposure. Thus, exposure to a person in a microenvironment is calculated using a formula analogous to equation AX3-3, but as the sum of the discrete products of measured or modeled concentrations (specific to the receptor and/or activity of concern) in each microenvironment by the time spent there. The equation is expressed as:

$$E = \sum_{i=1}^n c_i \Delta t_i \quad (\text{AX3-3})$$

where i specifies microenvironments from 1 to n , c_i is the concentration in the i th microenvironment, and Δt_i is the duration spent in the i th microenvironment. The total exposure for any time interval for an individual is the sum of the exposures in all microenvironments encountered within that time interval. The concentration and time component in this approach can contribute to measurement error. However, this method should provide an accurate determination of exposure provided that all microenvironments that contribute significantly to the total exposures are included and the concentration assigned to the microenvironment is appropriate for the time period spent in those environments. Results from the error analysis models developed by Navidi et al. (1999) suggested that neither the microenvironmental nor personal sampling approach would give reliable health effect estimates when measurement errors were uncorrected. Using their error analysis models, nondifferential measurement error biased the effect estimates toward zero under the model assumptions. When the measurement error is correlated with the health response, a bias away from the null could result. These researchers proposed the use of bidirectional crossover and multi-level analytic statistical methods for estimating acute effects of environmental exposures.

Microenvironments typically used to determine O₃ exposures include indoor residences, other indoor locations, outdoors near roadways, other outdoor locations, and in-vehicles. Outdoor locations near roadways are segregated from other outdoor locations because N₂O emissions from automobiles alter O₃ and related photochemical oxidant concentrations compared to concurrent typical ambient levels. Indoor residences are typically separated from other indoor locations, because of the time spent there and potential differences between the residential environment and the work/public environment. A special concern for O₃ and related

photochemical oxidants is their diurnal weekly (weekday-weekend) and seasonal variability. Few indoor O₃ sources exist, but include electronic equipment, O₃ generators, and copying machines. Some secondary reactions of O₃ take place indoors that produce related photochemical oxidants that could extend the exposures to those species above the estimates obtained from O₃ alone. (See discussion on O₃ chemistry and indoor sources and concentrations later in this Annex.)

AX3.10.6 Ozone Exposure Models

Measurement efforts to assess population exposures or exposures of large numbers of individuals over long time periods is labor intensive and costly, so exposure modeling is often done for large populations evaluated over time. Predicting (or reconstructing) human exposure to O₃ through mechanistic models is complicated by the fact that O₃ (and associated photochemical oxidants) is formed in the atmosphere through a series of chemical reactions that are nonlinear and have a wide range of characteristic reaction timescales. Furthermore, these reactions require the precursors VOCs and NO_x that are emitted by a wide variety of both anthropogenic and natural (biogenic) emission sources. This makes O₃ a secondary pollutant with complex nonlinear and multiscale dynamics in time and space. Concentration levels experienced by individuals and populations exposed to O₃ are therefore affected by (1) emission levels and spatiotemporal patterns of the gaseous precursors: VOCs and NO_x, that can be due to sources as diverse as a power plant in a different state, automobiles on a highway five miles away, and the gas stove in one's own kitchen; (2) ambient atmospheric as well as indoor microenvironmental transport, removal and mixing processes (convective, advective, dispersive and molecular/diffusional); and (3) chemical transformations that take place over a multitude of spatial scales, ranging from regional/sub-continental (100 to 1000 km), to urban (10 to 100 km), to local (1 to 10 km), to neighborhood (< 1 km), and to microenvironmental/personal. These transformations depend on the presence of co-occurring pollutants in gas and aerosol phases, both primary and secondary, and on the nature of surfaces interacting with the pollutants.

Further, the strong temporal variability of O₃, both diurnal and seasonal, makes it critical that definitions of integrated or time-averaged exposure employ appropriate averaging times in order to produce scientifically defensible analyses for either causes of O₃ production or health effects that result from O₃ exposure. An understanding of the effect of temporal profiles of

concentrations and contacts with human receptors is essential. Short-term integrated metrics, such as hourly averages, 8-h running averages, etc., are needed to understand the relationship between O₃ exposure and observed health and other effects.

Health effects associated with O₃ have mostly been considered effects of acute exposures. Peak O₃ and related photochemical oxidants concentrations typically occur towards later in the day during the summer months. Elevated concentrations can last for several hours. Furthermore, O₃ participates in multiphase (gas/aerosol) chemical reactions in various microenvironments. Several recent studies show that O₃ reacts indoors with VOCs and NO_x in an analogous fashion to that occurring in the ambient atmosphere (Lee and Hogsett, 1999; Wainman et al., 2000; Weschler and Shields, 1997). These reactions produce secondary oxidants and other air toxics that could play a significant role in cumulative human exposure and health-related effects within the microenvironment.

Terminology

Models of human exposure to O₃ can be characterized and differentiated based upon a variety of attributes. For example, exposure models can be classified as (1) potential exposure models, typically maximum outdoor concentration versus “actual” exposure, including locally modified microenvironmental outdoor and indoor exposures; (2) population versus “specific individual”-based exposure models; (3) deterministic versus probabilistic models; and (4) observation versus mechanistic air quality model-driven estimates of spatial and temporal correlations.

Some points should be made regarding terminology and the directions of exposure modeling research (as related specifically to O₃ exposure assessments) before proceeding to discuss specific recent activities and developments. First, it must be understood that significant variation exists in the definitions for much of the terminology used in the published literature. The science of exposure modeling is an evolving field and the development of a “standard” and commonly accepted terminology is a process in evolution. Second, very often procedures/efforts listed in the scientific literature as “exposure models/exposure estimates,” may in fact address only a subset of the steps or components required for a complete exposure assessment. For example, some efforts focus solely on refining the subregional or local spatiotemporal dynamics of local O₃ concentrations starting from “raw” data representing monitor observations or regional

grid-based model estimates. It is recognized that ambient air concentrations are used as surrogates for exposure in some epidemiological studies. Nevertheless, such efforts are included in the discussion of the next subsection, as they can provide essential components of a complete exposure assessment. On the other hand, formulations that are identified as exposure models, but focus only on ambient air quality predictions, are not included in the discussion that follows, as they do not provide true exposure estimates. These models are reviewed in an earlier section of this annex. Third, O₃-exposure modeling is very often identified explicitly with population-based modeling, while models describing the specific mechanisms affecting the exposure of an individual to O₃, and possibly some of the co-occurring gas and/or aerosol phase pollutants, are usually associated with studies focusing on indoor chemistry modeling. Finally, in recent years, the focus of either individual- or population-based exposure modeling research has shifted from O₃ to other pollutants, mostly airborne toxics and particulate matter. However, many of the modeling components that have been developed in these efforts are directly applicable to O₃ exposure modeling and are, therefore, mentioned in the following discussion.

A General Framework for Assessing Exposure to Ozone

First, the individual and relevant activity locations for Individual Based Modeling, or the population and associated spatial (geographical) domain for Population Based Modeling are defined. The temporal framework of the analysis (period, resolution) and the comprehensive modeling of individual/population exposure to O₃ (and related pollutants) generally require several steps (or components, as some of them do not have to be performed in sequence). The steps represent a “composite” outline based on frameworks described in the literature over the last 20 years (Ott, 1982, 1985; Liroy, 1990; Georgopoulos and Liroy, 1994; U.S. Environmental Protection Agency, 1992, 1997) as well as on the structure of various existing inhalation exposure models (McCurdy, 1994; Johnson et al., 1992; Nagda et al., 1987; U.S. Environmental Protection Agency, 1996c; ICF Consulting, 2003; Burke et al., 2001; McCurdy et al., 2000; Georgopoulos et al., 2002a,b; Freijer et al., 1998; Clench-Aas et al., 1999; Künzli et al., 1997). The conceptual frameworks of the models are similar. Figures AX3-87a,b provides a conceptual overview of an exposure model. The steps involved in defining exposure models include (1) estimation of the background or ambient levels of O₃ through space-time analysis of fixed monitor data, or emissions-based, photochemical, air quality modeling; (2) estimation of

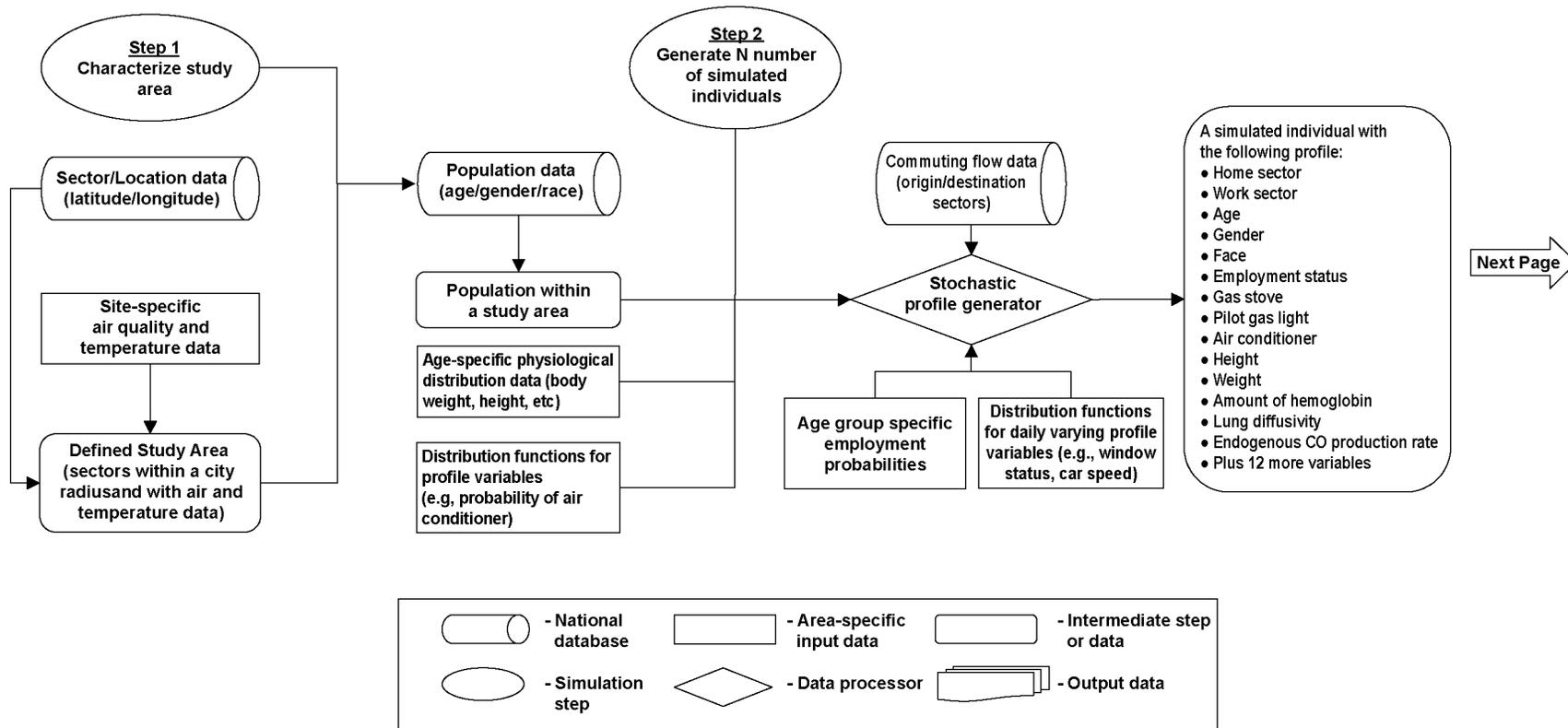


Figure AX3-87a. Detailed diagram illustrating components of an exposure model.

Source: ICF Consulting and ManTech Environmental Technology, Inc. (2003)

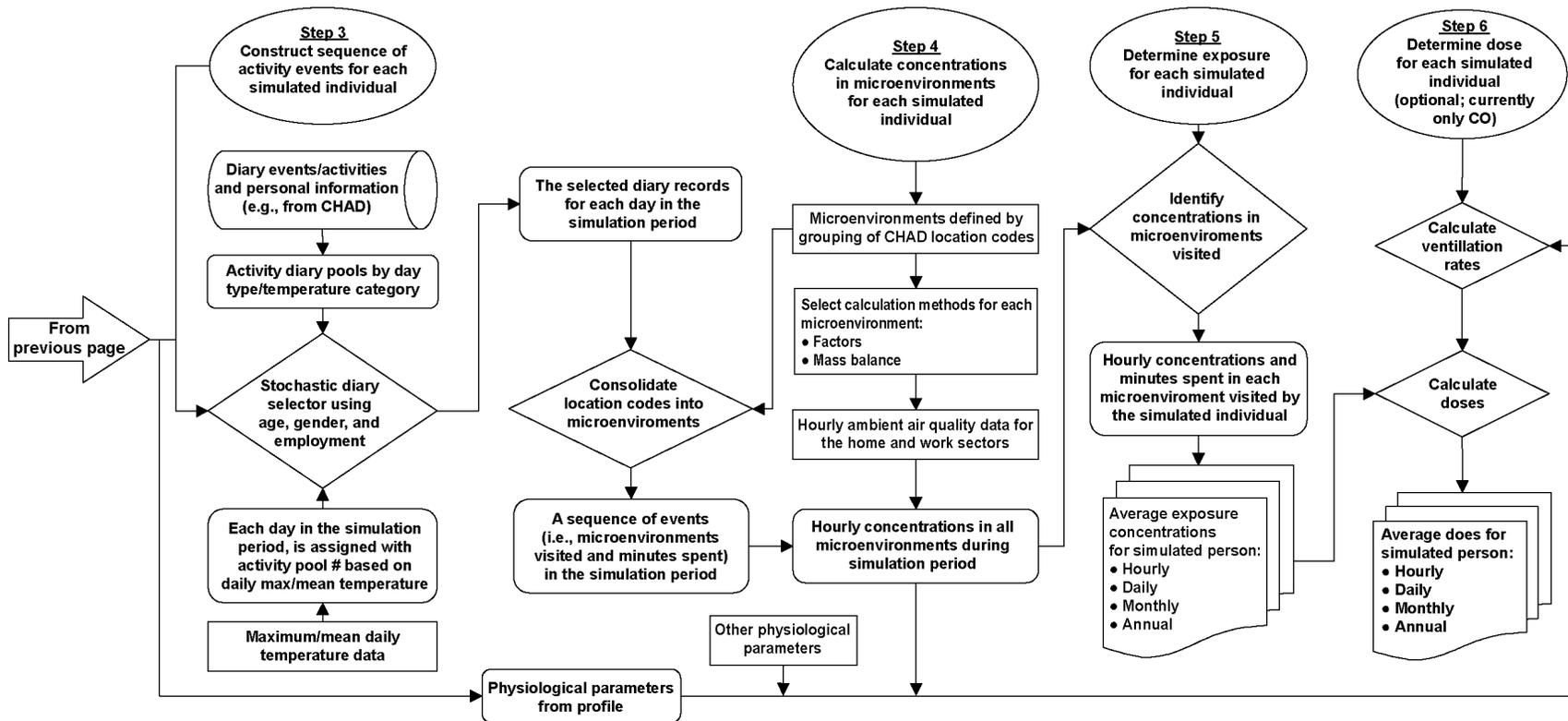


Figure AX3-87b. Detailed diagram illustrating components of an exposure model.

Source: ICF Consulting and ManTech Environmental Technology, Inc. (2003)

levels and temporal profiles of O₃ in various outdoor and indoor microenvironments such as street canyons, residences, offices, restaurants, vehicles, etc. through linear regression of available observational data sets, simple mass balance models, detailed (nonlinear) gas or gas/aerosol chemistry models, or detailed combined chemistry and computational fluid dynamics models; (3) characterization of relevant attributes of individuals or populations under study (age, gender, weight, occupation, etc.); (4) development of activity event (or exposure event) sequences for each member of the sample population or for each cohort for the exposure period; (5) calculation of appropriate inhalation (in general intake) rates for the individuals of concern, or the members of the sample population, reflecting/combining the physiological attributes of the study subjects and the activities pursued during the individual exposure events; (6) combination of intake rates and microenvironmental concentrations for each activity event to assess dose; (7) calculation of event-specific exposure and intake dose distributions for selected time periods (1-h and 8-h daily maximum, O₃ season averages, etc.); and (8) use of PBM to extrapolate population sample (or cohort) exposures and doses to the entire populations of interest. This process should aim to quantify, to the maximum extent feasible, variability and uncertainty in the various components, assessing their effects on the estimates of exposure.

Implementation of the above components of comprehensive exposure modeling has benefitted significantly from recent advances and expanded availability of computational technologies such as Relational Database Management Systems (RDBMS) and Geographic Information Systems (Purushothaman and Georgopoulos, 1997, 1999a,b).

AX3.10.6.1 Population Exposure Models

Existing comprehensive inhalation exposure models treat human activity patterns as sequences of exposure events in which each event is defined by a geographic location and microenvironment. The U.S. EPA has supported the most comprehensive efforts in this area, leading to the development of the National Ambient Air Quality Standard Exposure Model and Probabilistic National Ambient Air Quality Standard Exposure Model (NEM and pNEM) (Johnson, 2003) and the Modeling Environment for Total Risk Studies/Simulation of Human Exposure and Dose System (MENTOR/SHEDS) (McCurdy et al., 2000). The Total Risk Integrated Methodology Inhalation Exposure (TRIM.Expo) model, also referred to as the Air Pollutants Exposure (APEX) model, was developed by the U.S. EPA as a tool for estimating

human population exposure to criteria and air toxic pollutants. APEX serves as the human inhalation exposure model within the Total Risk Integrated Methodology (TRIM) framework (ICF Consulting and ManTech Environmental Technology, Inc. [2003]). APEX, a PC-based model derived from the probabilistic NAAQS Exposure Model (pNEM), was used in the last O₃ NAAQS review (Johnson et al., 1996a, 1996b). Over the past five years, APEX has undergone several significant improvements in the science reflected in the model and in the databases input to the model.

Recent European efforts have produced some formulations that have similar general attributes as the above models but generally involve major simplifications in some of their components. Examples of recent European models addressing O₃ exposures include the AirPEX (Air Pollution Exposure) model (Freijer et al., 1998), which basically replicates the pNEM approach, and the AirQUIS (Air Quality Information System) model (Clench-Aas et al., 1999).

The NEM/pNEM, APEX, and MENTOR/SHEDS families of models provide exposure estimates, defined by concentration and minute ventilation rate for each individual exposure event, and provide distributions of exposure and O₃ dose over any averaging period of concern from 1 h to an entire O₃ season. The above families of models also simulate certain aspects of the variability and uncertainty in the principal factors affecting exposure. pNEM divides the population of interest into representative cohorts based on the combinations of demographic characteristics (age, gender, employment), home/work district, residential cooking fuel, and then assigns activity diary records (Glen et al., 1997) to each cohort according to demographic characteristic, season, day-type (weekday/weekend), and temperature. APEX and MENTOR/SHEDS generates a population demographic file containing a user-defined number of person-records for each census tract of the population based on proportions of characteristic variables (age, gender, employment, housing) obtained for the population of interest, and then assigns the matching activity information based on the characteristic variables. A discussion of databases on time-activity data, and their influence on estimates of long-term ambient O₃ exposure, can be found in Künzli et al. (1997), McCurdy (2000), and McCurdy et al. (2000).

More recent exposure models are designed (or have been redesigned) to obtain such information from CHAD (Consolidated Human Activities Database; www.epa.gov/chadnet1; see Table AX3-18). There are now about 22,600 person-days of sequential daily activity pattern data in CHAD. All ages of both genders are represented in CHAD. The data for each subject

Table AX3-18. Activity Pattern Studies Included in the Consolidated Human Activity Database (CHAD)

Study Name	Calendar Time Period of the Study	Age ¹	Days ²	Diary		Rate ⁵	Documentation or Reference	Notes
				Type ³	Time ⁴			
Baltimore	Jan-Feb 1997 Jul-Aug 1998	65+	391	Diary; 15-min blocks	24-h Standard	No	Williams et al. (2000a,b)	Multiple days, varying from 5-15; part of a PM _{2.5} PEM study
CARB: Adolescents and Adults	Oct 1987-Sept 1988	12-94	1762	Retrospective	24-h Standard	No	Robinson et al. (1991) Wiley et al. (1991a)	
CARB: Children	Apr 1989-Feb 1990	0-11	1200	Retrospective	24-h Standard	No	Wiley et al. (1991b)	
Cincinnati (EPRI)	Mar-Apr and Aug 1985	0-86	2614	Diary	24 h; nominal 7 pm-7 am	Yes	Johnson (1989)	3 consecutive days; 186 P-D removed ⁷
Denver (EPA)	Nov 1982-Feb 1983	18-70	805	Diary	24 h; nominal 7 pm-7 am	No	Akland et al. (1985) Johnson (1984)	Part of CO PEM ⁶ study; 2 consec. days; 55 P-D removed ⁷
Los Angeles: Elem. School Children	Oct 1989	10-12	51	Diary	24-h Standard	Yes	Spier et al. (1992)	7 P-D removed ⁷
Los Angeles: High School Adoles.	Sept-Oct 1990	13-17	43	Diary	24-h Standard	Yes	Spier et al. (1992)	23 P-D removed ⁷
National: NHAPS-A ⁸	Sept 1992-Oct 1994	0-93	4723	Retrospective	24-h Standard	No ⁹	Klepeis et al. (1995) Tsang and Klepeis (1996)	A national random-probability survey
National: NHAPS-B ⁸	As above	0-93	4663	Retrospective	24-h Standard	No ⁹	As above	As above
University of Michigan: Children	Feb-Dec 1997	0-13	5616	Retrospective	24-h Standard	No	Institute for Social Research (1997)	2 days of data: one is a weekend day
Valdez, AK	Nov 1990-Oct 1991	11-71	401	Retrospective	Varying 24-h period	No	Goldstein et al. (1992)	4 P-D removed ⁷
Washington, DC (EPA)	Nov 1982-Feb 1983	18-98	699	Diary	24 h; nominal 7 pm-7 am	No	Akland et al. (1985) Hartwell et al. (1984)	Part of a CO PEM ⁶ study; 6 P-D removed ⁷

¹ All studies included both genders. The age range depicted is for the subjects actually included; in most cases, there was not an upper limit for the adult studies. Ages are inclusive. Age 0 = babies < 1 year old.

² The actual number of person-days of data in CHAD after the “flagging” and removal of questionable data. See the text for a discussion of these procedures.

³ Retrospective: a “what did you do yesterday” type of survey; also known as an ex post survey. Diary: a “real-time” paper diary that a subject carried as he or she went through the day.

⁴ Standard = midnight to midnight.

⁵ Was activity-specific breathing rate data collected?

⁶ PEM = a personal monitoring study. In addition to the diary, a subject carried a small CO or PM_{2.5} monitor throughout the sampling period.

⁷ P-D removed = The number of person-days of activity pattern data removed from consolidated CHAD because of missing activity *and* location information; completeness criteria are listed in the text.

⁸ National Human Activity Pattern Study; A = the air version; B = the water version. The activity data obtained on the two versions are identical.

⁹ A question was asked regarding which activities (within each 6-h time block in the day) involved “heavy breathing,” lifting heavy objects, and running hard.

Source: U.S. Environmental Protection Agency (2004a)

consist of one or more days of sequential activities, in which each activity is defined by start time, duration, activity type (140 categories), and microenvironment classification (110 categories). Activities vary from 1 min to 1 h in duration. Activities longer than 1 h are subdivided into clock-hour durations to facilitate exposure modeling. A distribution of values for the ratio of oxygen uptake rate to body mass (referred to as metabolic equivalents or METs) is provided for each activity type listed. The forms and parameters of these distributions were determined through an extensive review of the exercise and nutrition literature. The primary source of distributional data was Ainsworth et al. (1993), a compendium developed specifically to “facilitate the coding of physical activities and to promote comparability across studies.” Other information on activity patterns has been reported by Klepeis et al. (1996, 2001); Avol et al. (1998b); Adams (1993); Shamoo et al. (1994); Linn et al. (1996); Künzli et al. (1997). Use of the information in CHAD provides a rational way for incorporating realistic intakes into exposure models by linking inhalation rates to activity information. As mentioned earlier, an exposure event sequence derived from activity-diary data is assigned to each population unit (cohort for pNEM- or REHEX-type models, or individual for APEX or MENTOR/SHEDS-type models). Each exposure event is typically defined by a start and duration time, a geographic location and microenvironment, and activity level. The most recent pNEM, APEX, and MENTOR/SHEDS models have defined activity levels using the activity classification coding scheme incorporated into CHAD. A probabilistic module within the APEX and MENTOR/SHEDS-type models converts the activity classification code of each exposure event to an energy expenditure rate, which in turn is converted into an estimate of oxygen uptake rate. The oxygen uptake rate is then converted into an estimate of ventilation rate (\dot{V}_E), expressed in L/min. Johnson (2001) reviewed the physiological principles incorporated into the algorithms used in pNEM and APEX to convert each activity classification code to an oxygen uptake rate and describes the additional steps required to convert oxygen uptake to \dot{V}_E .

McCurdy (1997a,b, 2000) recommended that ventilation rate be estimated as a function of energy expenditure rate. The energy expended by an individual during a particular activity can be expressed as:

$$EE = (\text{MET})(\text{RMR}) \tag{AX3-4}$$

where EE is the average energy expenditure rate (kcal/min) during the activity, MET (metabolic equivalent of work) is a ratio specific to the activity and is dimensionless, and RMR is the resting metabolic rate of the individual expressed in terms of number of energy units expended per unit of time (kcal/min). If RMR is specified for an individual, then the above equation requires only an activity-specific estimate of MET to produce an estimate of the energy expenditure rate for a given activity. McCurdy et al. (2000) developed MET distributions for the activity classifications appearing in the CHAD database.

An important source of uncertainty in existing exposure modeling involves the creation of multiday, seasonal, or year long exposure activity sequences based on 1- to 3-day activity data for any given individual from CHAD. Currently, appropriate longitudinal data are not available and the existing models use various rules to derive longer-term activity sequences using 24-h activity data from CHAD.

The pNEM family of models used by the EPA has evolved considerably since the introduction of the first NEM model in the 1980s (Biller et al., 1981). The first such implementations of pNEM/O₃ in the 1980s used a reduced form of a mass balance equation to estimate indoor O₃ concentrations from outdoor concentrations. The second generation of pNEM/O₃ was developed in 1992 and used a simple mass balance model to estimate indoor O₃ concentrations. Subsequent enhancements to pNEM/O₃ and its input databases included revisions to the methods used to estimate equivalent ventilation rates (ventilation rate divided by body surface), to determine commuting patterns, and to adjust ambient O₃ levels to simulate attainment of proposed NAAQS. During the mid-1990s, the EPA applied updated versions of pNEM/O₃ to three different population groups in nine selected urban areas (Chicago, Denver, Houston, Los Angeles, Miami, New York, Philadelphia, St. Louis, and Washington): (1) the general population of urban residents, (2) outdoor workers, and (3) children who tended to spend more time outdoors than the average child. Reports by Johnson et al. (1996a,b,c) describe these versions of pNEM/O₃ and summarize the results of the application of the model to the nine urban areas. These versions of pNEM/O₃ used a revised probabilistic mass balance model to determine O₃ concentrations over 1-h periods in indoor and in-vehicle microenvironments (Johnson, 2003). The model assumed that there are no indoor sources of O₃, that the outdoor O₃ concentration and AER during the clock hour is constant at a specified value, and that O₃ decays at a rate proportional to the outdoor O₃ concentration and the indoor O₃ concentration.

The new pNEM-derived model, APEX, differs from earlier pNEM models in that the probabilistic features of the model are incorporated into a Monte Carlo framework. Instead of dividing the population of interest into a set of cohorts, APEX generates individuals as if they were being randomly sampled from the population. APEX provides each generated individual with a demographic profile that specifies values for all parameters required by the model. The values are selected from distributions and databases that are specific to the age, gender, and other specifications stated in the demographic profile. The APEX model has not been evaluated, however, the pCNEM, a Canadian conceptual version of the NEM model, has been evaluated for estimation of PM₁₀. Since pCNEM is similar to the pNEM/NEM, the APEX model should work as well as pCNEM. (See discussion on pCNEM later in this section.) The EPA plans to develop future versions of APEX applicable to O₃ and other criteria pollutants.

The latest version of APEX allows for finer geographical units such as census tracts and automatically assigns population to the nearest monitor within a cutoff distance. Exposure district-specific temperatures can be specified and the user can select the variables that affect each parameter (e.g., the AER parameter in certain indoor microenvironments may depend on air conditioning status or window position). The mass balance algorithms have been enhanced to allow window position or vehicle speed to also be considered in determining AERs.

The APEX model simulates individual movement through time and space to provide an estimate of exposure to a given pollutant in the indoor, outdoor, and in-vehicle microenvironments. The model is highly versatile, allowing input data for specific applications. APEX provides a good balance in terms of precision and resource expenditure compared with the more narrowly focused site-specific model and the broadly applicable national screening-level models.

A key strength of APEX is its ability to estimate hourly exposures and doses for all simulated individuals in the sampled population. APEX is capable of estimating exposures of workers in the geographic area where they work, in addition to the geographic area where they live. APEX is able to represent much of the variability in the exposure estimates resulting from the variability of the factors affecting human exposure by incorporating stochastic processes representing the natural variability of personal profile characteristics, activity patterns, and microenvironment parameters.

A limitation of APEX is that uncertainty in the predicted distributions has not been addressed. Certain aspects of the personal profiles are held constant (e.g., age) which could be an issue for simulations with long timeframes. The combined data set for activity patterns (CHAD) are from a number of different studies and may not constitute a representative sample. However, the largest portion of CHAD (about 40 percent) is from a study of national scope and research has shown that activity patterns are generally similar once you take into account age, gender, day of week, and season/temperature. The commuting data addresses only home-to-work travel and may not accurately reflect current commuting patterns. The population not employed outside the home is assumed to always remain in the residential census tract. Although several of the APEX microenvironments account for time spent in travel, the travel is assumed to always occur in basically a composite of the home and work tract. Seasonal or year long sequences for a simulated individual are created by sampling human activity data from more than one subject, possibly causing an underestimation of the variability from person to person and an overestimation of the day to day variability for any given individual. The model does not capture certain correlations among human activities that can impact microenvironmental concentrations (e.g., cigarette smoking leading to an individual opening a window, which in turn affects the amount of outdoor air penetrating the residence).

MENTOR/SHEDS estimates the population distribution of pollutant exposure by randomly sampling from various input distributions. MENTOR/SHEDS is capable of simulating individuals exposures in eight microenvironments (outdoors, residence, office, school, store, restaurant, bar, and vehicles) using spatial concentration data for each census tract for outdoor pollutant concentrations. The indoor and in-vehicle pollutant concentrations are calculated using specific equations for the microenvironment and ambient pollutant concentration relationship. Model simulations use demographic data at the census tract level. Randomly selected characteristics for a fixed number of individual are selected to match demographics within the census tract for age, gender, employment status, and housing type. Smoking prevalence statistics by gender and age is randomly selected for each individual in the simulation. Diaries for activity patterns are matched for the simulated individual by demographic characteristics. The essential attributes of some of the O₃ exposure models and approaches are summarized in Table AX3-19.

Table AX3-19. Personal and Population Exposure Models for Ozone

Model Name	Model Type	Microenvironments or Predictors	Notes	Reference
pNEM	Probabilistic	General population, outdoor workers, outdoor children	Provides estimates of exposure within a defined population for a specified period of time. Uses activity records from CHAD and CADS	Johnson et al. (1996a,b,c)
APEX	PC-based	Outdoors, indoor residence, in-vehicle	Simulates movement through time and space. Estimates hourly exposures and doses. Uncertainties in predicted distributions have not been addressed.	ICF Consulting and ManTech Environmental Technology, Inc. (2003)
Mentor/SHEDS	Probabilistic	General population, outdoors, indoors, in-vehicle	Employees detailed person oriented exposure approach that includes personal activity data, physiology, and microenvironmental conditions. Allows calculation of exposure and dose for each activity event.	Georgopoulos et al. (2005)
REHEX		General population	Provides estimates of exposure for 1-day to 3 yrs. Can represent variability in activities of the population to capture extremes in exposure distributions.	Lurmann and Colome (1991)

Zidek et al. (2000, 2005) described a methodology for predicting human exposure to environmental pollutants. The methodology builds on earlier models such as SHEDS and pNEM/NEM and provides a WWW platform for developing a wide variety of models. pCNEM, a platform model developed from this methodology, is a Canadian PC version of NEM. pCNEM was used to estimate a conditional predictive exposure distribution for PM₁₀ in London. An important feature of pCNEM is its ability to estimate the effects of reductions in ambient levels of pollutants.

Rifai et al. (2000) compared applications of an updated version of REHEX, REHEX-II. The applications used NHAPS data for the southern states and the 48-state NHAPS or the Houston-specific time-activity pattern data. The results indicated a sensitivity to the specificity of the activity data: using Houston-specific data resulted in higher estimates of human exposure in some of the scenarios. For example, using NHAPS data lead to an estimated 275 thousand-exposure-hours between 120 to 130 ppb, while use of the Houston-specific activity data lead to an estimated 297 thousand-exposure-hours between 120 and 130 ppb (8% higher). Using the Houston-specific activity data in the model resulted in about 2,400 person-exposure-hours above 190 to 200 ppb O₃ while no exposure above this threshold was estimated when the NHAPS activity were used in the model.

Of the above families of models only NEM/pNEM implementations have been extensively applied to O₃ studies. However, it is anticipated that APEX will be useful as an exposure modeling tool for assessing both criteria and hazardous air pollutants in the future. The 1996 O₃ AQCD (U.S. Environmental Protection Agency, 1996a) focused on the pNEM/O₃ family of models, referring to the review by McCurdy (1994) for the fundamental principles underlying its formulation and listing, in addition to the “standard” version, three pNEM/O₃-derived models (the Systems Applications International NEM [SAI/NEM]; the Regional Human Exposure Model [REHEX]; and the Event Probability Exposure Model [EPEM]).

AX3.10.6.2 Ambient Concentrations Models

As mentioned earlier, background and regional outdoor concentrations of pollutants over a study domain may be calculated either through emissions-based mechanistic modeling or through ambient-data-based modeling. Emissions-based models calculate the spatiotemporal fields of the pollutant concentrations using precursor emissions and meteorological conditions as

inputs. The ambient-data-based models typically calculate spatial or spatiotemporal distributions of the pollutant through the use of interpolation schemes, based on either deterministic or stochastic models for allocating monitor station observations to the nodes of a virtual regular grid covering the region of interest. (See later discussion on population exposure models). Kriging, a geostatistical technique, provides standard procedures for generating an interpolated O₃ spatial distribution for a given time period, using data from a set of observation points. The kriging approach, with parameters calculated specifically for each hour of the period of concern, was compared to the Urban Airshed Model (UAM-IV), a comprehensive photochemical grid-based model for deriving concentration fields. The concentration fields were then linked with corresponding population data to calculate potential outdoor population exposure. Higher exposure estimates were obtained with the photochemical grid-based model when O₃ concentrations were <120 ppb, however, the situation was reversed when O₃ concentrations exceeded 120 ppb. The authors concluded that kriging O₃ values at the locations studied can reconstruct aspects of population exposure distributions (Georgopoulos et al., 1997a,b).

Carroll et al. (1997a,b) developed a spatial-temporal model, with a deterministic trend component, to model hourly O₃ levels with the capacity to predict O₃ concentrations at any location in Harris County, Texas during the time period between 1980 and 1993. A fast model-fitting method was developed to handle the large amount of available data and the substantial amount of missing data. Ozone concentration data used consisted of hourly measurements from 9 to 12 monitoring stations for the years 1980 to 1993. Using information from the census tract, the authors estimated that exposure of young children to O₃ declined by approximately 20% over the analysis period. The authors also suggested that the O₃ monitors are not sited in locations to adequately measure population exposures. Several researchers have questioned the suitability of the model for addressing spatial variations in O₃ (Guttorp et al., 1997; Cressie, 1997; Stein and Fang, 1997).

Spatiotemporal distributions of O₃ concentrations have alternatively been obtained using methods of the “Spatio-Temporal Random Field” (STRF) theory (Christakos and Vyas, 1998a,b). The STRF approach interpolates monitoring data in both space and time simultaneously. This method can analyze information on “temporal trends,” which cannot be incorporated directly in purely spatial interpolation methods such as standard kriging. Further,

the STRF method can optimize the use of data that are not uniformly sampled in either space or time. The STRF theory was further extended in the Bayesian Maximum Entropy (BME) framework and applied to O₃ interpolation studies (Christakos and Hristopulos, 1998; Christakos and Kolovos, 1999; Christakos, 2000). The BME framework can use prior information in the form of “hard data” (measurements), probability law descriptors (type of distribution, mean and variance), interval estimation (maximum and minimum values) and even constraint from physical laws. According to these researchers, both STRF and BME were found to successfully reproduce O₃ fields when adequate monitor data are available.

Zidek et al. (1998, 2002), Sun et al. (1998, 2000), Le et al. (1997), and Li et al. (1999, 2001) used a hierarchical Bayesian approach to predict average hourly concentrations of ambient O₃ and PM₁₀ when monitoring data was not available. A trend model and the Gaussian stochastic residual was used at the primary level to model the logarithmic field. Space-time modeling occurs at the second level of the hierarchical prior model so that uncertainty about the model parameters is expressed at the first level. A special feature of this method is that it does not require all sites to monitor the same set of pollutants. Also, the model can be updated as new data become available.

AX3.10.6.3 Microenvironmental Concentration Models

Once specific ambient/local spatiotemporal O₃ concentration patterns have been derived, microenvironments that can represent either outdoor or indoor settings must be characterized. This process can involve modeling of various local sources and sinks as well as interrelationships between ambient/local and microenvironmental concentration levels. Three approaches have been used in the past to model microenvironmental concentrations: empirical, mass balance, and detailed computational fluid dynamics (CFD).

The empirical fitting approach has been used to summarize the findings of recent field studies (Liu et al., 1995, 1997; Avol et al., 1998a). These empirical relationships could provide the basis for future, “prognostic” population exposure models.

Mass balance modeling has ranged from very simple formulations, assuming ideal (homogeneous) mixing and only linear physicochemical transformations with sources and sinks, to models that take into account complex multiphase chemical and physical interactions and nonidealities in mixing. Mass balance modeling is the most common approach used to model

pollutant concentrations in enclosed microenvironments. As discussed earlier, the simplest microenvironmental setting is a homogeneously mixed compartment in contact with possibly both outdoor/local environments as well as with other microenvironments. The air quality of this idealized microenvironment is affected primarily by transport processes (including infiltration of outdoor air into indoor air compartments, advection between microenvironments, and convective transport); sources and sinks (local outdoor emissions, indoor emissions, surface deposition); and local outdoor and indoor gas and aerosol phase chemistry transformation processes (such as the formation of secondary organic and inorganic aerosols).

Numerous indoor air quality modeling studies have been reported in the literature; however, depending on the modeling scenario, only a limited number address physical and chemical processes that affect O₃ concentrations indoors (Nazaroff and Cass, 1986; Hayes, 1989, 1991). An example of a mass balance indoor air model for O₃ and benzene can be found in the work of Freijer and Bloemen (2000). They used outdoor O₃ measurements to parameterize a simplified linearized formulation of transport, transformation, and sources and sinks in the indoor microenvironment.

The pNEM/O₃ model includes a sophisticated mass balance model for enclosed (indoor and vehicle) microenvironments. The general form of this mass balance model is a differential equation that accounts for outdoor concentration, AER, penetration rate, decay rate, and indoor sources. To address uncertainty, each of these parameters is represented by a probability distribution or by a dynamic relationship to other parameters that may change according to time of day, temperature, air conditioning status, window status, or other factors (Johnson, 2003). The simplest form of the model is represented by the following differential equation for a perfectly mixed microenvironment without an air cleaner:

$$\frac{dC_{IN}}{dt} = vC_{OUT} + \frac{S}{V} - vC_{IN} \quad (\text{AX3-5})$$

where dC_{IN} is the indoor pollutant concentration (mass/volume), t is time in hours, v is the air exchange rate, C_{OUT} is the outdoor pollutant concentration (mass/volume), V is the volume of the microenvironment, and S is the indoor source emission rate.

Nazaroff and Cass (1986) extended the mass balance model to include multiple compartments and interactions between different compounds. The extended model takes into account the effects of ventilation, filtration, heterogeneous removal, direct emission, and photolytic and thermal and chemical reactions. A more in-depth discussion of the mass balance model may be found in Shair and Heitner (1974) and in Nazaroff and Cass (1986).

Freijer and Bloemen (2000) used the one-compartment mass balance model to examine the relationship between O₃ I/O ratios as influenced by time patterns in outdoor concentrations, ventilation rate, and indoor emissions. The microenvironment was 250 m³. Three different ventilation patterns with the same long-term average AER (0.64 h⁻¹) were used. A source pattern (direct emissions) of zero was used, because O₃ sources are not common. The time series for outdoor O₃ concentrations consisted of 100-day periods during the summer, with hourly measured concentrations. The following assumptions were made: (1) O₃ concentration in the air that enters the microenvironment is equal to the concentration of the outside air minus the fraction removed by filtration, (2) the O₃ concentration that leaves the microenvironment equals the O₃ concentration in the microenvironment, (3) the decay processes in the microenvironment are proportional to the mass of the pollutant, and (4) addition or removal of O₃ in the microenvironment also may occur through independent sources and sinks.

Figure AX3-88 represents the measured outdoor O₃ concentrations and modeled indoor O₃ concentrations. The indoor modeled O₃ concentrations were found to equal approximately 33% of the outdoor monitored concentrations.

Few indoor air models have considered detailed nonlinear chemistry, which, however, can have a significant effect on the indoor air quality, especially in the presence of strong indoor sources. Indeed, the need for more comprehensive models that can take into account the complex, multiphase processes that affect indoor concentrations of interacting gas phase pollutants and particulate matter has been recognized and a number of formulations have appeared in recent years. For example, the Exposure and Dose Modeling and Analysis System (EDMAS) (Georgopoulos et al., 1997a) included an indoor model with detailed gas-phase atmospheric chemistry. This indoor model accounts for interactions of O₃ with indoor sinks and sources (surfaces, gas releases) and with entrained gas. The indoor model was dynamically coupled with the outdoor photochemical air quality models, UAM-IV and UAM-V (Urban Airshed Models), which provided the gas-phase composition of entrained air, and with a

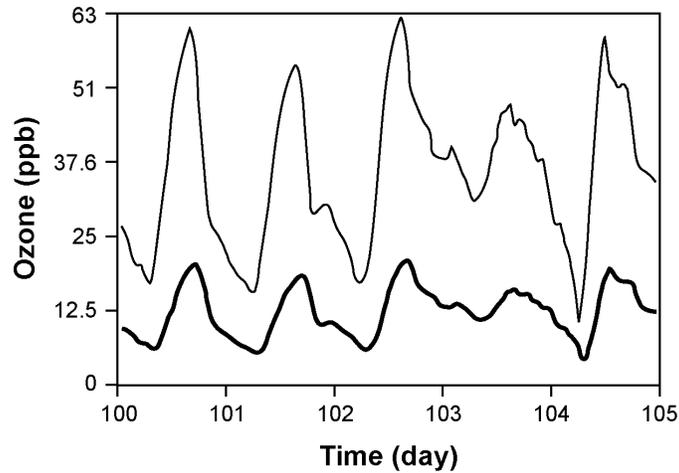


Figure AX3-88. Measured outdoor O₃ concentrations (thin line) and modeled indoor concentrations (bold line).

Source: Adapted from Freijer and Bloemen (2000).

physiologically based O₃ uptake and dosimetry model. Subsequent work (Isukapalli et al., 1999) expanded the framework and features of the EDMAS model to incorporate alternative representations of gas-phase chemistry as well as multiphase O₃ chemistry and gas/aerosol interactions. The new model is a component of the integrated Modeling Environment for Total Risk studies (MENTOR).

Sarwar et al. (2001, 2002) modeled estimates of indoor hydroxyl radical concentrations using a new indoor air quality model, Indoor Chemistry and Exposure Model (ICEM). The ICEM uses a modified SAPRC-99 atmospheric chemistry mechanism to simulate indoor hydroxyl radical production and consumption from reactions of alkenes with O₃. It also allows for the simulation of transport processes between indoor and outdoor environments, indoor emissions, chemical reactions, and deposition. Indoor hydroxyl radicals, produced from O₃ that penetrates indoors, can adversely impact indoor air quality through dark chemistry to produce photochemical oxidants.

Sørensen and Weschler (2002) used CFD modeling to examine the production of a hypothetical product from an O₃-terpene reaction under two different ventilation scenarios. The computational grid used in the model was nonuniform. There were significant variations in the concentrations of reactants between locations in the room, resulting in varying reaction rates.

Because the “age of the air” differed at different locations in the room, the time available for reactions to occur also differed between locations.

Very few studies have focused on mechanistic modeling of outdoor microenvironments. Fraigneau et al. (1995) developed a simple model to account for fast NO-O₃ reaction/dispersion in the vicinity of a motorway. Proyou et al. (1998) applied a simple three-layer photochemical box model to an Athens street canyon. However, the adjustments of O₃ levels for sources, sinks, and mixing in outdoor microenvironments are done in a phenomenological manner in existing exposure models, driven by limited available observations. Ongoing research is evaluating approaches for quantifying local effects on outdoor O₃ chemistry in specific settings.

Finally, one issue that should be mentioned is that of evaluating comprehensive prognostic exposure modeling studies, for either individuals or populations, with field data. Attempts had been made to evaluate pNEM/O₃-type models using personal exposure measurements (Johnson et al., 1990). Although databases that would be adequate for performing a comprehensive evaluation are not expected to be available any time soon, a number of studies are building the necessary information base, as discussed previously. Some of these studies report field observations of personal, indoor, and outdoor O₃ concentrations and describe simple semiempirical personal exposure models that are parameterized using observational data and regression techniques.

AX3.10.7 Measured Exposures and Monitored Concentrations

AX3.10.7.1 Personal Exposure Measurements

Passive O₃ monitors have been used in several field studies to determine average daily O₃ exposure as well as in scripted studies to evaluate O₃ exposures over one to several-hour time periods. Table AX3-20 lists the results of O₃ exposure studies. Delfino et al. (1996) measured 12-h personal daytime O₃ exposures in asthmatic patients in San Diego from September through October 1993. They found that the mean personal exposures were 27% of the mean outdoor concentrations. Individual exposure levels among the 12 asthmatic subjects aged 9 to 16 years varied greatly. Mean personal O₃ exposure levels were lower on Friday, Saturday, and Sunday than on other days of the week (10 versus 13 ppb), while the ambient air concentrations were higher Friday through Sunday. The authors suggested that the differences were due to higher weekday NO emissions from local traffic which titrated the ambient O₃ levels. The lower

Table AX3-20. Personal Exposure Measurements

Location, Population, Sample Duration	n	Personal Exposure Mean^a (range) (ppb)	Reference
San Diego, CA, Asthmatics ages 9-18 years, 12 hour	12	12 ± 12 (0-84) 10 weekend 12 weekday	Delfino et al. (1996)
Vancouver, Canada, Adult Workers, Daily High indoor time Moderate indoor time Only outdoor	585	(ND-9) (ND-12) (2-44)	Brauer and Brook (1997)
Southern California, Subjects 10-38 years Spring Fall	24	13.6 ± 2.5 (- to 80) 10.5 ± 2.5 (- to 50)	Liu et al. (1997)
Montpellier, France, Adults, Hourly Winter Summer	16	34.3 ± 17.6 (6.5-88) 15.4 ± 7.7 (6.5-40) 44.1 ± 18.2(11-88)	Bernard et al. (1999)
Souther California, Children 6-12 years, ≥ 6 days Upland - winter - summer Mountain - winter - summer	169	6.2 ± 4.7 (0.5-41) 19 ± 18 (0.5-63) 5.7 ± 4.2 (0.5-31) 25 ± 24 (0.5-72)	Geyh et al. (2000)
Baltimore, MD, Technician, Hourly ^b Winter Summer	1	3.5 ± 7.5 (ND-49) 15 ± 18 (ND-76)	Chang et al. (2000)
Baltimore, MD, Adults 75 ± 7 years, Daily Winter Summer	20	3.5 ± 3.0 (ND-9.9) 0. ± 1.8 (ND-2.8)	Sarnat et al. (2000)

^aND = not detected.

^bMeasurements made following scripted activities for 15 days.

personal exposure levels on Friday, Saturday, and Sunday may have been an artifact of greater noncompliance, with the badges remaining indoors and, therefore, being exposed to lower O₃ concentrations. The overall correlation between the personal exposure concentrations between any two individuals and with the outdoor stationary site was only moderate (r = 0.45; range: 0.36 to 0.69). The O₃ concentrations at the stationary site exceeded the personal levels by an average of 31 ppb. Avol et al. (1998b) observed a poor correlation between personal exposure and fixed-site monitoring concentrations (r = 0.28, n = 1336 pairs) for a cohort of children

(healthy, wheezy, and asthmatic). Personal exposure measurements were generally lower than integrated hourly data. Sarnat et al. (2000) measured personal O₃ exposures during a 12-day longitudinal study of 20 older adults (>64 years) in Baltimore, MD. The subjects spent >94% of the time indoors. Ten subjects participated in the summer and winter exposures and the remaining 10 participated in either the summer or winter exposure. No statistically significant overall correlations were identified between the personal and the ambient O₃ concentrations during either the winter or summer. Only a single individual (n = 14 summer and 13 winter) had a significant correlation with outdoor concentrations. Geyh et al. (2000) measured indoor and outdoor concentration and personal O₃ exposures in 169 elementary school children from 116 homes during a year-long sampling protocol in 2 communities in southern California (Upland and Mountain communities). Samples were collected for 1 week per month. Boys had higher O₃ exposure than girls, probably reflecting the greater amount of time boys spent outdoors compared to girls (3.8 versus 3.2 h for the spring/summer and 2.9 versus 2.2 h for the fall/winter). The average personal O₃ exposures were lower than the levels measured at the nearest monitor stations retrieved from the AQS. There was no significant difference in the O₃ exposure for both groups during the non-O₃ season (6.2 and 5.7 ppb for Upland and the mountain communities, respectively), however, children in the mountainous region were exposed to 35% more O₃ than children in Upland during the O₃ season (18.8 and 25.4 ppb for Upland and the mountain communities) (two-tailed *t*-test, *p* < 0.01). During the O₃ season, differences were found in indoor concentrations and personal O₃ exposures between the two communities participating in the study based on ambient air concentrations and differences in air exchange rates in the homes.

Brauer and Brook (1997) conducted personal exposure evaluations in three groups in Frazer Valley, Vancouver, Canada. The groups were divided by the amount of time spent outdoors: (1) the majority of the workday was spent indoors or commuting (25 medical clinic workers), (2) an intermediate amount of time was spent outdoors (25 overnight camp staff members), and (3) the entire exposure monitoring period was outdoors (15 adult farm workers). Time-activity data were collected for the first two groups to assess the proportion of time spent outdoors. For groups 1 and 2, the lowest quartile of participants based on the fraction of time spent outdoors (0 to 25% and 7.5 to 45%, respectively) had significantly lower O₃ exposure (mean personal exposure to outdoor concentration ratio = 0.18 and 0.35, respectively) compared to

those in the upper quartile (mean ratio = 0.51 and 0.58, respectively; $p < 0.05$; Bonferroni multiple range test). The mean ratio was 0.96 with values ranging from near 0 to 2 for group 3, the group that spent the entire exposure-monitoring period outdoors. The authors attributed the extreme low ratios to random measurement error at low O₃ air concentrations (estimated at 35%), local variability in O₃ concentrations, and to differences between ground-level concentrations (where the personal samples were collected) 3-m above ground level (where the continuous monitors were located). The highest ratios may be due to either locale variability in O₃ concentrations or to an interference affecting the personal O₃ samplers, particularly at the lower concentration range, leading to a small positive error. Temporal plots of O₃ for the mean daily personal exposures and ambient concentrations showed the same general trend with general agreement between the personal exposures and ambient air concentrations for group 3. However, for groups 1 and 2, the day-to-day variability of the personal exposures and ambient O₃ concentrations had consistent patterns, suggesting that the ambient air was the primary source for O₃ exposure. The day-to-day variability in personal and continuous measurements was 0.60, 0.42, and 0.64 for groups 1 through 3, respectively. The actual O₃ concentrations measured in the personal air space were always considerably lower than the ambient concentrations. Bernard et al. (1999) assessed O₃ personal exposure and in the home and outdoor O concentration for up to 110 subjects. Measurements were conducted over 5-day periods between June 1995 and October 1996. As anticipated, O₃ concentrations were higher during the warmer months. Mean O₃ concentrations for 70 subjects were 22, 35, 17.4, 40.5, and 18 ppb for personal, outdoor home, indoor home, outdoor work, and indoor work, respectively for measurements made during the warmer months.

In a study by Liard et al. (1999), 55 mild to moderate asthmatic adults (18 to 65 y old) and 39 children (7 to 15 y old) were monitored for O₃ exposure. Subjects were monitored during three periods, 4 days per monitoring period and asked to keep a diary of time spent outdoors and in a car. Many of the study subjects O₃ exposures were often below the level of detection for the method used. Ozone exposure levels correlated with the hours spent outdoors. Ozone personal exposure correlated poorly with the ambient monitoring measurements, however, the mean values for all subjects correlated with those measurements from the ambient monitoring site ($r = 0.83$, $p < 0.05$). Linn et al. (1996) estimated short-term O₃ exposures in 269 children from three communities in the Los Angeles Basin by monitoring air at head level in school class

rooms, on the roof of one level school buildings, and in personal microenvironments of selected individuals. Monitoring was carried out for six weeks in the fall, winter, and spring, two successive weeks per season at each of three schools. Each subject was monitored for one week in each season over a two year period. According to the authors there were meaningful associations between personal exposures and central monitoring site O₃ measurements ($r = 0.61$). Based on information reported in the questionnaires, outdoor activity increased slightly in communities/seasons with higher pollution.

Lee et al. (2004) found that personal O₃ exposure was positively correlated with time spent outdoors ($r = 0.19$, $p < 0.01$) and negatively correlated with time spent indoors ($r = -0.17$, $p < 0.01$) in elementary school children. Thirty-three elementary school children from two Nashville, TN area school districts participated in a six week long O₃ monitoring study during the summer vacation. The study participants maintained a dairy of daily activities during the study period. An additional 62 children from the same school completed a telephone interview on time/activity at least eight times during the study period. Study participants wore a passive sampler during their non-sleep time and the sampler was placed near their bed at night. A passive monitor also was placed outside and inside of the home. Personal exposure correlated with the amount of time spent outdoors. Exposures ranged from 0.0013 to 0.0064 ppm for indoor concentrations compared to ambient concentrations of 0.011 to 0.042 ppm O₃.

AX3.10.7.2 Monitored Ambient Concentrations

Ozone has been measured more extensively than the other photochemical oxidants. Ambient monitors have been established in most areas of the country, with extensive monitoring in regions that have been in noncompliance with the previous 1-h daily NAAQS. Monitoring station-measured hourly concentrations also have been used as surrogates of exposure in epidemiological studies and in evaluating exposure-related health effects. According to the Guideline on Ozone Monitoring Site Selection (U.S. Environmental Protection Agency, 1998), when designing an O₃ monitoring network, consideration should be given to (1) proximity to combustion emission sources, (2) distance from primary emission sources, and (3) the general wind direction and speed to determine the primary transport pathways of O₃ and its precursors. Finally, the 1-h daily maximum and 8-h average O₃ concentrations can have different spatial patterns with elevated daily 8-h O₃ concentrations typically being over a wider spatial area.

Therefore, O₃ monitoring networks should determine the highest concentrations expected to occur in the area, representative concentrations for high population density areas, the impact of sources or source categories on air pollution levels, and general background concentration levels (U.S. Environmental Protection Agency, 1998).

The guideline also states that the monitor's O₃ inlet probe should be placed at a height and location that best approximates where people are usually found. However, complicating factors (e.g., security considerations, availability) sometimes result in the probe placement being elevated 3 to 15 m above ground level, a different location than the breathing zone (1 to 2 m) of the populace. Although there are some commonalities in the considerations for the sampling design for monitoring and for determining population exposures, differences also exist. These differences between the location and height of the monitor compared to the locations and breathing zone heights of people can result in different O₃ concentrations between what is measured at the monitor and exposure and, therefore, should be considered when using ambient air monitoring data as a surrogate for exposure in epidemiological studies and risk assessments. Further, since most people spend the majority of their time indoors, where O₃ levels tend to be much lower than outdoor ambient levels, the use of ambient monitoring data to determine exposure generally overestimates true personal O₃ exposure, resulting in exposure estimates biased towards the null. Information on monitored ambient concentrations of O₃ and other photochemical oxidants appears earlier in this chapter.

AX3.10.7.3 Ozone Concentrations in Microenvironments

The 1996 O₃ AQCD for Ozone (U.S. Environmental Protection Agency, 1996a) reported O₃ I/O ratios for a variety of indoor environments including homes, office/laboratories, a hospital, museums, a school room, and automobiles and other vehicles. Ozone I/O ratios ranged from 0.09 to 1.0 for residences, 0.19 to 0.8 for offices/laboratories, hospital and school rooms, and 0.03 to 0.87 for museums and art galleries. The higher O₃ ratios were generally noted in indoor environments with high AERs or 100% outside air intake. Studies published since completion of the 1996 O₃ AQCD are discussed in this section. The findings of the more recent studies on O₃ I/O ratios are included in Table AX3-21.

Northeast States for Coordinated Air Use Management (NESCAUM, 2002) monitored levels of O₃ inside and outside of nine schools located in the New England states. The schools

Table AX3-21. Indoor/Outdoor Ozone Ratios

Location and Ventilation Conditions	Indoor/Outdoor Ratio Mean (range)	Comments	Reference
Toronto, Canada, Homes			
Winter – weekly (68)	0.07 ± 0.10 (ND - 0.63)	Electrostatic air cleaners were present in about 50% of the homes. Air conditioners were present in about 80% of the homes, most were central units that used recycled air. Air conditioners used in only 13 of the 40 homes on a daily basis. Measurements were made both inside and outside of the homes for 5 consecutive 24-h periods. Homes with electrostatic air cleaners had higher I/O ratios during the winter months. The mean average weekly AER for all homes during the winter months was 0.69 ± 0.88 h ⁻¹ with 50% of the homes with an AER of less than 0.41 h ⁻¹ . For the summer months, the mean average AER was 1.04 ± 1.28 h ⁻¹ with 50% of the homes with an AER of less than 0.52 h.	Liu et al. (1995)
Summer – weekly (38)	0.40 ± 0.29 (ND - 1.15)		
Summer – 12 h/day (128)	0.30 ± 0.32 (ND - 1.42)		
– 12 h/night (36)	0.43 ± 0.54 (ND - 2.89)		
Boston, MA, Homes (26)			
Winter – continuously 24 h	0.30 ± 0.42 (ND - 1.31)	Study examined the potential for O ₃ to react with VOCs to form acid aerosols. Carbonyls were formed. No clear trend of O ₃ with AERs. The average AER was 0.9 h ⁻¹ during the winter and 2.6 h ⁻¹ during the summer. Four residences in winter and nine in summer with 24 h average concentrations. Air concentrations varied from 0-34.2 ppb indoors and 4.4-40.5 ppb outdoors.	Reiss et al. (1995)
Summer – continuously 24 h	0.22 ± 0.25 (ND - 0.88)		
Mexico City, School			
Windows/Doors Open (27)	0.73 ± 0.04	Study conducted over 4-day period during winter months. Two-min averaged measurements were taken both inside and outside of the school every 30 min from 10 a.m. to 4 p.m. Estimated air exchange rates were 1.1, 2.1, and 2.5 h ⁻¹ for low, medium, and high flow rates. Ozone concentrations decreased with increasing relative humidity.	Gold et al. (1996)
Windows/Doors Closed, cleaner off (41)	0.17 ± 0.02		
Windows/Doors Closed, cleaner on (47)	0.15 ± 0.02		
Los Angeles, CA			
Homes (95)	0.28	Study conducted in September. Monitored O ₃ concentrations consisted of twenty-one 24-h periods beginning at 7 p.m. and ending at 7 p.m. on the following day. Ozone concentrations were higher at the fixed monitoring sites during the afternoon. The weather was sunny and the temperature was high. I/O ratio was lower when windows were closed. The effect of air conditioning on the I/O was varied.	Johnson (1997)
Other locations (57)	0.18		

Table AX3-21 (cont'd). Indoor/Outdoor Ozone Ratios

Location and Ventilation Conditions	Indoor/Outdoor Ratio Mean (range)	Comments	Reference
Mexico City Homes (237) Schools (59)	0.20 ± 0.18 (0.04 - 0.99) 0.1 - 0.3 0.3 - 0.4	Ozone monitoring occurred between September and July. Study included 3 schools and 145 homes. Most of the homes were large and did not have air conditioning. Ninety-two percent of the homes had carpeting, 13% used air filters, and 84% used humidifiers. Thirty-five percent opened windows frequently, 43% sometimes, and 22% never between 10 a.m. and 4 p.m. Ozone was monitored at the schools sites from 8 a.m. to 1 p.m. daily for 14 consecutive days. Homes were monitored for continuous 24-h periods for 14 consecutive days. I/O based on 1-h average concentrations.	Romieu et al. (1998)
Los Angeles, Homes (239) Summer Winter	0.37 ± 0.25 (0.06 - 1.5) 0.43 ± 0.29 0.32 ± 0.21	Four hundred and eighty-one samples collected inside and immediately outside of home from February to December. Ratios based on 24-h average O ₃ concentrations indoors and outdoors. Low outdoor concentrations resulted in low indoor concentrations. However, high outdoor concentrations resulted in a range of indoor concentrations and ratios. I/O ratios were highest during the summer months.	Avol et al. (1998a)
California Homes no AC, window opened (20) AC, windows closed (3)	0.68 (n = 20) 0.09 (n = 3)	I/O ratio was determined for 20 homes. Only 3 of the homes operated the air conditioning. I/O ratios based on 24-h continuous ambient concentrations and 0.5-1 h average indoor concentrations.	Lee et al. (1999)
Munich Germany Office Gymnasium Classroom Residence Bedroom Livingroom Hotel room Car	0.4 - 0.9 0.49 - 0.92 0.54 - 0.77 0.47 - 1.0 0.74 - 1.0 0.02 0.4 - 0.6	Indoor concentrations were dependent on the type of ventilation.	Jakobi and Fabian (1997)
La Rochelle, France	0 - 0.45	I/O ratio determined for 8 schools. Monitoring conducted for a 2-wk period. Schools located in various areas with different ambient O ₃ concentrations, types of ventilation systems, and the presumed air-tightness of building envelop. Building air-tightness and ambient O ₃ concentration influenced indoor O ₃ I/O.	Blondeau et al. (2005)

Table AX3-21 (cont'd). Indoor/Outdoor Ozone Ratios

Location and Ventilation Conditions	Indoor/Outdoor Ratio Mean (range)	Comments	Reference
Montpellier, France, Homes (110)	0.41	Ozone measurements were made over 5-day periods in and outside of 21 homes during the summer and winter months. The winter I/O ratio was 0.31 compared to 0.46 during the summer months.	Bernard et al. (1999)
Southern CA, Homes Upland Mountains	0.68 ± 0.18 (windows open) 0.07 - 0.11 (AC used)	Ozone measurements were taken at 119 homes (57 in Upland and 62 in towns located in the mountains) during April and May. I/O ratios were based on average monthly outdoor concentrations and average weekly indoor concentrations. I/O ratio was associated with the home location, number of bedrooms, and the presence of an air conditioner. I/O ratios based on subset of the homes.	Geyh et al. (2000); Lee et al. (2002)
Krakow, Poland Museums (5)	0.13 - 0.42	Ozone continuously monitored at five museums and cultural centers. Monitoring conducted during the summer months for 21-46 h or 28-33 days at each of the sites. The I/O was found to be dependent on the ventilation rate, i.e., when the ventilation rate was high, the I/O ratio approached unity, while in rooms sequestered from the outdoor air or where air was predominantly recycled through charcoal filters, the O ₃ levels indoors were greatly reduced resulting in low I/O ratios.	Salmon et al. (2000)
Buildings, Greece Thessaloniki Athens	0.24 ± 0.18 (0.01 to 0.75)	There was no heating/air conditioning system in the building at Thessaloniki. Windows were kept closed during the entire monitoring period. Complete air exchange took place every 3 h. I/O ratio ranged from 0.5-0.90, due to low deposition velocity on indoor surfaces. The air conditioning system in continuous use at the Athens site recirculated the air. Complete air exchange was estimated to be 1 h. Monitoring lasted for 30 days at each site, but only the 7 most representative days were used for calculation of the I/O ratio.	Drakou et al. (1998)
Southern California, Museum	0.19 ± 0.05	Measurements made over a 2-wk period (24-h avg). Ratio for concentrations at the buffer zone with the roll-up door closed.	Hisham and Grosjean (1991)

ND = not detectable.

represented a variety of environmental conditions in terms of ambient O₃ concentration, sources, geographic location, population density, traffic patterns, and building types. Schools were monitored during the summer months to establish baseline O₃ concentrations and again during the fall after classes started. A monitor was placed directly outside of the school entrance and 50 feet away from the entrance in the hall. Where available, monitors were placed at locations identified as “problem” classrooms, classrooms with carpeting, or in rooms close to outdoor sources of O₃. As expected, outdoor concentrations of O₃ were higher than those found indoors. Averaged O₃ concentrations were low during the early morning hours (7:30 a.m.) but peaked to approximately 25 and 40 ppb around 1:30 p.m. indoors and outdoors, respectively.

Gold et al. (1996) compared indoor and outdoor O₃ concentrations in classrooms in Mexico City under three different ventilation conditions: windows/doors open, air cleaner off; windows/doors closed, air cleaner off; and windows/doors closed, air cleaner on. Two-minute averaged outdoor O₃ levels varied between 64 and 361 ppb, while indoor O₃ concentrations ranged from 0 to 247 ppb. The highest indoor O₃ concentrations were noted when the windows/doors were open. The AERs were estimated to be 1.1, 2.1, and 2.5 h⁻¹ for low, medium, and high air flow rates, respectively. The authors indicated that the indoor levels, and therefore O₃ exposure to students in schools, can be reduced to < 80 ppb by closing windows and doors even when ambient O₃ levels reach 300 ppb.

In a second Mexico City study, Romieu et al. (1998) measured O₃ concentrations inside and outside of 145 homes and three schools. Measurements were made between November and June. Most of the homes were large and did not have air conditioning. Ninety-five percent of the homes had carpeting, 13% used air filters, and 84% used humidifiers. Thirty-five percent of the homeowners reported that they opened windows frequently between the hours of 10 a.m. and 4 p.m., while 43% opened windows sometimes and 22% reported that they never opened windows during that time period. Homes were monitored for continuous 24-h periods for 14 consecutive days. Schools were monitored from 8 a.m. to 1 p.m. or continuously for 24 h. During the school monitoring periods the windows were frequently left open and the doors were constantly being opened and closed. The mean indoor and outdoor O₃ concentrations during 5-h measurements at the schools were 22 ppb and 56 to 73 ppb, respectively. The mean indoor and outdoor O₃ concentrations for measurements made over a 7- and 14-day period at the test homes were 5 and 27 ppb and 7 and 37 ppb, respectively. Ozone concentrations inside of homes were

dependent on the presence of carpeting, the use of air filters, and whether the windows were open or closed. Air exchange rates were not reported.

Reiss et al. (1995) compared indoor and outdoor O₃ concentrations for residences in the Boston, MA area. Four residences were monitored during the winter months and nine residences during the summer months. Outside monitors were placed ~1 m away from the house. Monitoring was conducted over a continuous 24-h period. There were no indoor sources of O₃. Indoor O₃ concentrations were higher during the summer months, with concentrations reaching 34.2 ppb. Indoor O₃ concentrations reached as high as 3.3 ppb during the winter monitoring period. In one instance, O₃ concentrations were higher indoors than outdoors. The authors attributed that finding to analytical difficulties. Outdoor O₃ concentrations were generally higher during the summer monitoring period, with concentrations reaching 51.8 ppb. Indoor concentrations were dependent on the outdoor O₃ concentrations and AER. Indoor and outdoor O₃ concentrations, including the AERs at the times of the monitoring are included in Table AX3-22.

Avol et al. (1998a) monitored 126 home in the Los Angeles metropolitan area during February and December. Uniformly low ambient O₃ concentrations were present during the non-O₃ seasons. Indoor O₃ concentrations were always below outdoor O₃ concentrations. The mean indoor and outdoor O₃ concentrations over the sampling period were 13 ± 12 ppb and 37 ± 19 ppb, respectively. There was a correlation between indoor O₃ concentration and ambient temperatures. The effect was magnified when the windows were open. When a central refrigerant recirculating air conditioner was used, indoor O₃ concentrations declined. The authors were able to predict indoor O₃ levels with nearly the same accuracy using measurements made at regional stations coupled with window conditions as with measurements made directly outside the homes coupled with window conditions, suggesting that monitoring station data may be useful in helping to reduce errors associated with exposure misclassification. The authors cautioned that varying results may occur at different locations with different housing stock or at different times of the year.

Lee et al. (2002) reported indoor and outdoor O₃ concentrations in 119 homes of school children in two communities in southern California: Upland and San Bernadino county. Measurements were made over one year. Outdoor and indoor O₃ concentrations were based on

Table AX3-22. Indoor and Outdoor O₃ Concentrations in Boston, MA

Residence	Indoor Ozone (ppb)	Outdoor Ozone (ppb)	AER (h ⁻¹)	Indoor Data		Outdoor Data	
				Relative Humidity (%)	Temp. (°F)	Relative Humidity (%)	Temp. (°F)
<i>Winter</i>							
1 - Day 1	3.3	11.2	1	25-45	67-75	88	25
1 - Day 2	0	15	0.8	22-40	65-76	62	27
2 - Day 1	2.6	24.4	1	3-19	67-71	44	17
2 - Day 2	1.7	4.4	1	3-8	55-70	40	17
3 - Day 1	20.4	15.6	1	8-24	62-69	33	36
3 - Day 2	3.1	24.5	0.9	13-19	64-70	51	38
4 - Day 1	2.2	11.4	0.7	26-37	60-72	57	39
4 - Day 2	0.3	20.7	0.7	29-38	61-70	77	36
<i>Summer</i>							
1 - Day 1	5.6	32.4	3	28-44	71-74	44	65
1 - Day 2	0.6	13.4	2.3	37-44	70-74	59	60
2 - Day 1	0.8	14.3	2.4	48-54	73-79	54	70
2 - Day 2	5	24.1	2.1	46-60	72-78	64	73
3 - Day 1	34.2	38.9	4.6	48-63	64-80	52	71
3 - Day 2	6.9	14	3.1	45-53	65-69	52	62
4 - Day 1	4.3	30	1.4	37-60	66-75	51	67
4 - Day 2	4.9	40.5	1.8	38-68	67-79	64	67
5 - Day 1	1.4	17.5	5.1	30-50	69-74	54	58
5 - Day 2	1.9	19	3.5	39-63	N/A	40	64
6 - Day 1	0.8	8.2	0.5	59-73	74-77	76	72
6 - Day 2	1.7	18.6	0.7	43-66	76-78	47	76
7 - Day 1	3.9	40.1	1.1	57-70	70-77	51	75
7 - Day 2	0	33.9	1.1	58-73	72-75	64	72
8 - Day 1	22.9	51.8	3.2	66-81	71-77	75	75
8 - Day 2	23.5	31.6	6.3	43-67	66-79	48	72
9 - Day 1	1.6	20.9	2.1	N/A	N/A	37	70
9 - Day 2	1.2	25	1.7	33-52	75-79	70	66

N/A = not available

Adapted from: Reiss et al. (1995)

cautioned that varying results may occur at different locations with different housing stock or at different times of the year.

Lee et al. (2002) reported indoor and outdoor O₃ concentrations in 119 homes of school children in two communities in southern California: Upland and San Bernadino county. Measurements were made over one year. Outdoor and indoor O₃ concentrations were based on monthly and weekly averages, respectively. Housing characteristics were not found to affect indoor O₃ concentrations. Indoor O₃ concentrations were significantly lower than outdoor O₃ concentrations. Average indoor and outdoor O₃ concentrations were 14.9 and 56.5 ppb. Homes with air conditioning had lower O₃ concentrations, suggesting decreased ventilation or greater O₃ removal.

Chao (2001) evaluated the relationship between indoor and outdoor levels of various air pollutants, including O₃, in 10 apartments in Hong Kong during May to June. Air monitoring was conducted over a 48-h period. All participants had the habit of closing the windows during the evenings and using the air conditioner during the sleep hours. Windows were partially open during the morning. The air conditioners were off during the working hours. Indoor O₃ concentrations were low in all of the monitored apartments, ranging from 0 to 4.9 ppb with an average of 2.65 ppb. Outdoor O₃ concentrations ranged from 1.96 to 15.68 ppb. Table AX3-23 provides information on the indoor and outdoor O₃ concentrations and the apartment characteristics.

Drakou et al. (1995) demonstrated the complexity of the indoor environment. Measurements of several pollutants, including O₃, were made inside and outside of two nonresidential buildings in Thessaloniki and Athens, Greece. The building in Thessaloniki was a 58-m³ metal structure. The ceiling and walls were covered with colored corrugated plastic sheeting, and the flooring was plastic tile. There was no heating/air conditioning system and the building was closed during the monitoring period. The AER ranged from 0.3 to 0.35 h⁻¹. The building in Athens was a 51-m³ concrete structure. The air conditioning system (recirculated air) worked continuously during the monitoring period. A window was opened slightly to accommodate the monitors' sampling lines. The AER was approximately 1 h⁻¹. Monitoring lasted for 30 days at both locations, however, only data from the 7 most representative days were reported. Indoor O₃ concentrations closely followed the outdoor concentrations at the Thessaloniki building. The averaged 7-day indoor and outdoor O₃ concentrations were 9.39 and

Table AX3-23. Indoor and Outdoor O₃ Concentrations in Hong Kong

Apartment No.	Floor Area	Floor No.	Window Opening Frequency	AER (h ⁻¹)	Indoor O ₃ Conc.	Outdoor O ₃ Conc.
1	40	14	Seldom	1.44	0	1.96
2	47	13	Sometimes	1.97	4.96*	6.01*
3	140	2	Sometimes	0.83	1.0*	6.96*
4	67	5	Seldom	5.27	4.96*	8.76*
5	86	11	Sometimes	1.64	3.0*	7.80*
6	43	32	Sometimes	15.83	4.01*	8.76*
7	47	9	Always	15.91	0	3.0*
8	30	6	Seldom	3.25	2.05*	3.0*
9	26	35	Sometimes	2.1	4.9	15.68
10	20	15	Seldom	5.5	4.01*	4.96*

*Estimated Concentration.

Adapted from Chao (2001).

15.48 ppb, respectively. The indoor O₃ concentrations at the Athens location were highly variable compared to the outdoor concentration. The authors suggested that a high hydrocarbon intrusion may be the reason for the variability in O₃ concentrations noted at this site. The averaged 7-day indoor and outdoor O₃ concentrations were 8.14 and 21.66 ppb, respectively.

Weschler et al. (1994) reported that indoor O₃ concentrations closely tracked outdoor O₃ concentrations at a telephone switching station in Burbank, CA. The switching building was flat-roofed, two-story (first floor and basement), uncarpeted, with unpainted brick walls. Each floor was 930 m² with a volume of 5095 m³. Indoor O₃ concentrations were measured on the first floor using a perfluorocarbon tracer or an UV photometric analyzer. The AER were obtained by dividing the volumetric flow to the first floor by the volume of the first floor space or by perfluorocarbon tracer techniques. The AER ranged from 1.0 to 1.9 h⁻¹.

The major source of O₃ at the switching station was transport from outdoors. Indoor O₃ concentrations closely tracked outdoor concentrations, measuring from 30 to 70% of the outdoor concentrations. Indoor O₃ concentrations frequently exceed 50 ppb during the summer months,

but seldom exceeded 25 ppb during the winter. During the early spring through late fall, indoor O₃ concentrations peaked during the early afternoon and approach zero after sunset. Ozone sinks included a surface removal rate between 0.8 and 1.0 h⁻¹ and reactions with NO_x.

Figures AX3-89 and AX3-90 compare the outdoor and indoor O₃ concentrations, including the AER, for two 1-week periods during the study.

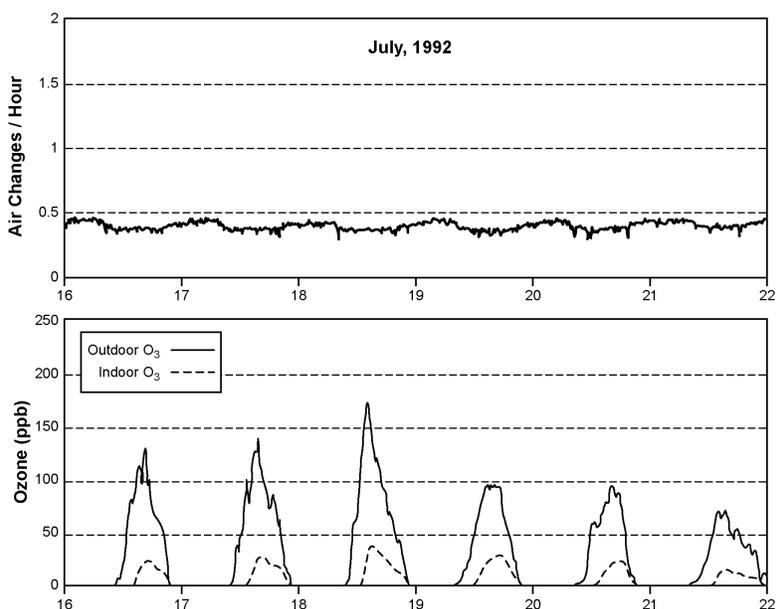


Figure AX3-89. Air exchange rates and outdoor and indoor O₃ concentrations during the summer at a telephone switching station in Burbank, CA.

Source: Weschler et al. (1994).

The relationships between indoor and outdoor O₃ concentrations in five museums and cultural centers (Wawel Castle, Matejko Museum, National Museum, Collegium Maius, and Cloth Hall) in Krakow, Poland were reported by Salmon et al. (2000). Measurements were made for up to 46 h and up to 33 days. Air exchange measurements were only made for the Matejko Museum and Wawel Castle. Both were naturally ventilated. However, the summertime AER for the Matejko Museum was more than twice that of the Wawel Castle site, 1.26 to 1.44 h⁻¹ compared to 0.56 to 0.66 h⁻¹. The highest indoor O₃ concentrations were noted at the

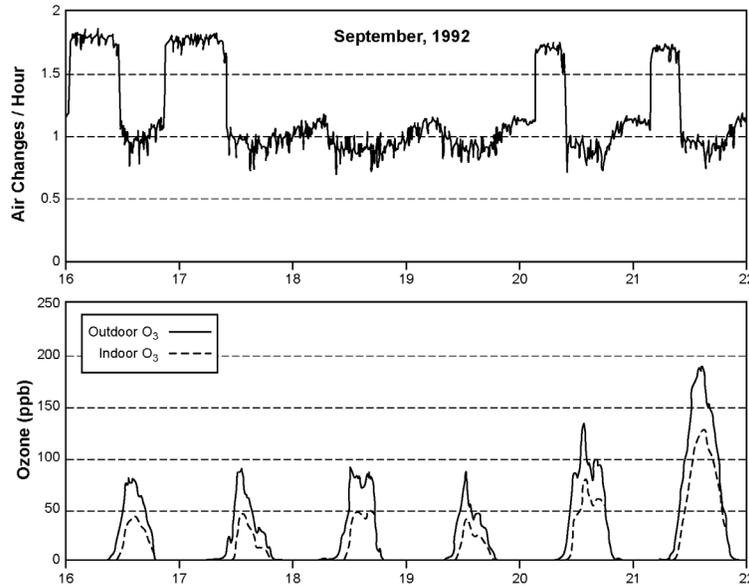


Figure AX3-90. Air exchange rates and outdoor and indoor O₃ concentrations during the fall at a telephone switching station in Burbank, CA.

Source: Weschler et al. (1994).

Matejko Museum during the summer. The findings are included in Table AX3-24 for those locations with reported AERs.

Figure AX3-91 shows O₃ and PAN concentrations in a private residence in Germany. All measurements were made in naturally ventilated rooms.

Johnson (1997) conducted a scripted study using four trained technicians to measure hourly average O₃ concentrations between 07:00 and 19:00 h in Los Angeles, CA during September and October 1995. The ratio of the microenvironmental concentrations to the fixed site monitor on days when the O₃ levels ≥ 20 ppb were as follows: indoor residence, 0.28; other locations indoors, 0.18; outdoor near roadways, 0.58; other locations outdoors, 0.59; and in-vehicle, 0.21. The concentrations indoors and within vehicles varied depending on whether the windows were opened (higher) or closed (lower) and the use of air conditioning. The lower outdoor concentrations, particularly near roadways, probably reflect the reaction of O₃ with NO emitted by automobiles.

Table AX3-24. Indoor and Outdoor Ozone Concentrations

Location	Duration (hours)	AER	Average O₃ (ppb)
Matejko Museum	26		1988-2000
Outdoors (Town Hall Tower)			20
Indoors (third floor, west)		1.26	8.5
Wawel Castle	43		
Outdoors (Loggia)			14.7
Indoors (Senator's Hall)		0.63	2.5
Wawel Castle, outdoors	31.8		42 ^a
Wawel Castle, Room 15	31		8
Wawel Castle, Senator's Hall	31.8		7
Matejko Museum, outdoors	26.9		21 ^b
Matejko Museum, Indoor Gallery	26.9		9

^aOn Loggia of Piano Nobile Level, high above the street.

^bAt street level.

Adapted from Salmon et al. (2000).

A study of the effect of elevation on O₃ concentrations found that concentrations increased with increasing elevation. The ratio of O₃ concentrations at street level (3 m) compared to the rooftop (25 m) was between 0.12 and 0.16, though the actual concentrations were highly correlated ($r = 0.63$) (Väkevä et al., 1999). Differential O₃ exposures may, therefore, exist in apartments that are on different floors. Differences in elevation between the monitoring sites in Los Angeles and street level samples may have contributed to the lower levels measured by Johnson (1997). Furthermore, since O₃ monitors are frequently located on rooftops in urban settings, the concentrations measured there may overestimate the exposure to individuals outdoors in streets and parks, locations where people exercise and maximum O₃ exposure is likely to occur.

Chang et al. (2000) conducted a scripted exposure study in Baltimore during the summer of 1998 and winter of 1999, during which 1-h O₃ samples were collected by a technician who also changed his or her activity every hour. The activities chosen were selected to simulate older

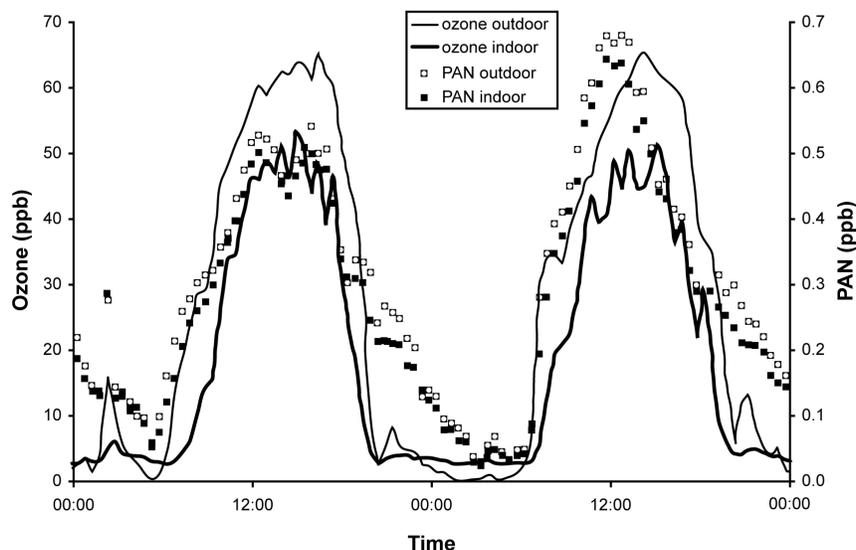


Figure AX3-91. Diurnal variation of indoor and outdoor O₃ and PAN concentrations measured in a private residence, Freising, Germany, August 11-12, 1995.

Source: Jaboki and Fabian (1997).

(> 65 years) adults, based on those activities reported in the National Human Activity Pattern Survey (NHAPS). The scripted activities took place in five different microenvironments: indoor residential (apartment in 24-h air conditioned high rise building), indoor other (restaurant, post office, hospital, shopping mall, and bingo parlor), outdoor near roadway, outdoor away from roadway, and inside motor vehicle. Personal O₃ exposures were significantly lower in indoor than the outdoor microenvironments, because more time was spent indoors. Mean summer concentrations were 15.0 ± 18.3 ppb, with a maximum of 76.3 ppb. Significant correlation was noted for the indoor nonresidential microenvironments and ambient O₃ ($r = 0.34$ in summer, $r = 0.46$ in winter), however, the authors indicated that this finding was unclear due to the low personal/ambient ratios. The personal O₃ exposure levels within the outdoor and in-vehicle microenvironments were significantly correlated with ambient concentration, although the ratio of personal exposure to ambient levels was less than one, with only the top 5% of the ratios exceeding one, indicating that the ambient measurements lead to the maximum concentrations and exposures. The indoor concentrations did not correlate with outdoor

measurements ($r = 0.09$ and $r = 0.05$ for summer and winter, respectively). The correlation for outdoor near roadway and outdoor away from roadway was moderate to high ($0.68 \leq r \leq 0.91$).

The scripted exposure studies show that the O₃ concentrations in the various microenvironments were typically lower than the ambient air concentrations measured at monitoring stations. Exposure models are useful for accounting for the reduced concentrations usually encountered in various microenvironments compared to ambient monitoring station concentrations (see discussion on exposure models earlier in this annex).

Riediker et al. (2003) measured mobile source pollutants inside highway patrol vehicles in Wake County, NC. Measurements were made during the 3 p.m. to midnight shift between August 13 and October 11, 2001 in two patrol cars each day for a total of 50 shifts. All areas of rural and urban Wake County were patrolled. The prominent areas patrolled were major highways and interstates. Ozone concentrations inside the cars were compared with the O₃ measurements at the fixed station in northern Raleigh. The average O₃ concentration inside the cars was 11.7 ppb, approximately one-third of the ambient air concentration. Jakobi and Fabian (1997) found that O₃ concentrations in a moving car were independent of the type of ventilation (windows closed and ventilator operation/ventilator off and windows open). Ozone concentrations inside the car were found to closely follow the outdoor concentrations. When the car was parked, O₃ concentrations outdoors greatly exceeded concentrations inside the car (see Figure AX3-92).

Few studies have been conducted in indoor environments containing O₃ sources. Black et al. (2000) measured O₃ concentrations in a photocopy room at the University of California during one business day. The room volume was 40 m³. Ozone concentrations were generally below 20 ppb, but increased proportionately with increasing photocopier use. Ozone concentrations reached 40 ppb when the hourly average number of copies reached 45. Helaleh et al. (2002) reported daily average O₃ concentrations from 0.8 to 1.3 ppb and 0.9 to 1.0 ppb in a laboratory and photocopy room at a university in Japan. Outdoor O₃ concentrations ranged from 6 to 11 ppb. Because only limited information was available on the sampling system used in the study, the adequacy of the sampling system cannot be determined. Jakobi and Fabian (1997) measured O₃ concentrations in an office associated with the use of a photocopier and a laser printer. They noted a 3.0 ppb increase in O₃ from the use of a 3-year old printer run for 20 min

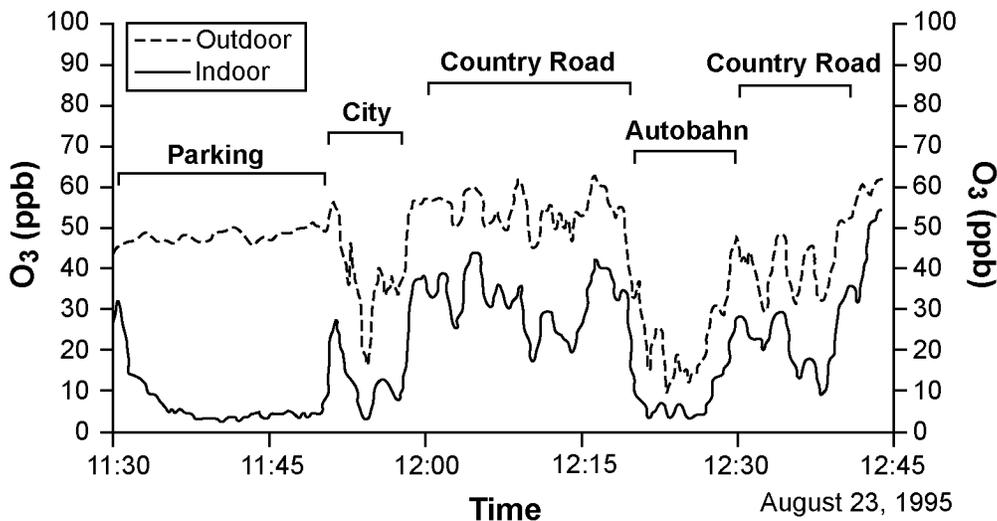


Figure AX3-92. Indoor and outdoor O₃ concentration in moving cars.

Source: Jaboki and Fabian (1997).

at a copy rate of 8 pages/min. There was no detectable change in O₃ concentrations from the use of the laser printer.

The U.S. Environmental Protection Agency (Steiber, 1995) measured O₃ concentrations from the use of three home/office O₃ generators. The O₃ generators were placed in a 27 m³ room with doors and windows closed and the heating, ventilating and air conditioning system off; the AER was 0.3 h⁻¹. The units were operated for 90 min. Ozone concentrations at the low output setting ranged from nondetectable to 14 ppb (averaged output). At the high output setting, averaged output O₃ concentrations exceeded 200 ppb in several cases and had spike concentrations as high as 480 ppb.

Figure AX3-93 includes PAN indoor/outdoor ratios for 10 museums. Four of the museums were equipped with HVAC and chemical infiltration systems.

AX3.10.7.4 Factors Affecting Ozone Concentrations Indoors

In the absence of an indoor source, O₃ concentrations in indoor environments will depend on the outdoor concentration, the air exchange rate (AER) or outdoor infiltration, indoor circulation rate, removal by indoor surfaces, reactions with other indoor pollutants, and

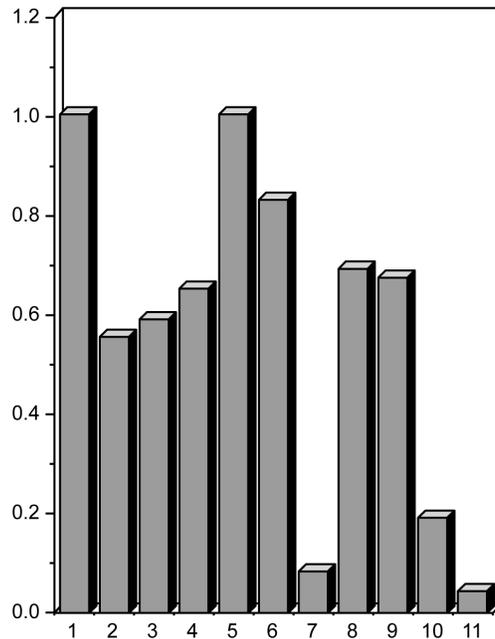


Figure AX3-93. Indoor/outdoor concentration ratios for PAN at 10 southern California museums. Code to locations: 1 El Pueblo Historical Park, Los Angeles; 2 Olivas Adobe House, Ventura; 3 Southwest Museum, Los Angeles; 4 Page Museum, Los Angeles; 5 Museum of Natural History, Los Angeles; 6 Research Library, University of California, Los Angeles; 7 Scott Gallery, Huntington Museum, Pasadena; 8 The J. Paul Getty Museum, Malibu; 9 Los Angeles County Museum of Art, Los Angeles; 10 Gene Autry Western Heritage Museum, Los Angeles (buffer zone); 11 Gene Autry Museum (Conservation Room).

Source: Hisham and Grosjean (1991).

temperature and humidity. Indoor concentrations generally closely track outdoor O₃ concentrations. Limited information on PAN concentrations indoors also indicate that indoor PAN concentrations track outdoor concentrations (Jakobi and Fabian, 1997; Hisham and Grosjean, 1991). Since outdoor concentrations of photochemical oxidants are generally higher during the warmer months, indoor concentrations will also be highest during that time period. (See discussion on ambient concentrations of O₃ earlier in this chapter.)

Air Exchange Rates

Indoor O₃ increases with increasing air exchange rate (Gold et al., 1996; Lee et al., 1999; Jakobi and Fabian, 1997). The AER is the balance of the flow of air in and out of a microenvironment. Infiltration through unintentional openings in the building envelope is the dominant mechanism for residential air exchange. Duct systems account for 30% of the total leakage area of a house. Natural ventilation, airflow through opened windows and doors, also influences air exchange in residential buildings. Forced or mechanical ventilation is the dominant mechanism for air exchange in nonresidential buildings.

Air exchange rates vary depending on the temperature differences, wind effects, geographical region, type of heating/mechanical ventilation system, and building type (U.S. Environmental Protection Agency, 1997; Weschler and Shields, 2000; Colome et al., 1994; Johnson et al., 2004). Air exchange rates are generally higher during the summer and lower during the winter months (Wilson et al., 1996; Murray and Burmaster, 1995; Colome et al., 1994; Research Triangle Institute, 1990). The Gas Research Institute, Pacific Gas and Electric Company, San Diego Gas and Electric Company, and Southern California Gas Company measured the air exchange rates in a subset of 293 randomly selected homes in California as part of an air pollution monitoring study. The average AER varied by type of heating system (wall furnaces > forced-air > electric) and building type (multifamily units > single-family units) (Billick et al., 1984, 1996; Colome et al., 1994).

Howard-Reed et al. (2002) determined that opening a window or exterior door causes the greatest increase in AERs with differences between the indoor and outdoor temperature being important when the windows were closed. Johnson and Long (2004) conducted a pilot study to evaluate the frequency that windows were left open in a community. They found that a visual 2-h survey could be used to estimate the frequency that windows are left open. The occupancy, season, housing density, absence of air conditioning, and wind speed were factors in whether the windows were open.

Johnson et al. (2004) conducted a study using scripted ventilation conditions to identify those factors that affected air exchange inside a test house in Columbus, OH. The test house was a wood-framed, split-level structure with aluminum siding covering the wood outer walls. The house had one exterior door located in the front and another at the rear of the house, single-pane glazed windows, central gas heat, a window air-conditioning unit, and ceiling fans in three

rooms. Eighteen scenarios with unique air flow conditions were evaluated to determine the effect on the AER. The elements of the scenarios included: exteriors doors open/closed, interior doors open/closed, heater on/off, air conditioner on/off, a ceiling fans on/off. The lower level was sealed off during the study. The various scenarios were evaluated during the winter season. The average AER for all scenarios ranged from 0.36 to 15.8 h⁻¹. When all windows and doors were closed, the AER ranged from 0.36 to 2.29 h⁻¹ (0.77 h⁻¹ geometric mean). When at least one exterior door or window was open the AER ranged from 0.5 to 15.8 h⁻¹ (1.98 h⁻¹ geometric mean).

Williams et al. (2003a, 2003b) reported air exchange rates ranging from 0.001 h⁻¹ to 4.87 h⁻¹ (overall arithmetic mean of 0.72 h⁻¹) in houses in the Research Triangle Park area in North Carolina. Air exchange measurements were made in 37 homes as part of a year long study PM panel study.

Air exchange rates for homes in Houston, TX, Los Angeles County, CA, and Elizabeth, NJ were reported by Meng et al. (2005) as part of the Relationship of Indoor, Outdoor and Personal Air (RIOPA) study. The RIOPA study was designed to determine indoor (residual), outdoor, and personal exposure to several classes of pollutants. Approximately 100 homes from each of the areas were sampled across all four seasons. The mean air exchange rate for the Los Angeles County homes was 1.22 h⁻¹, similar to the air exchange rate (1.51 h⁻¹) homes in Los Angeles previously reported by Wilson et al. (1996). The mean air exchange rate for Houston and Elizabeth was 0.71 h⁻¹ and 1.22 h⁻¹, respectively. Air exchange rates for New Jersey were higher than other reported values in the northeast region. The authors attributed these differences to differences in the age of housing stock in the various areas.

Chan et al. (2005) compared air leakage measurements for more than 70,000 houses across the United States, classified as low-income households, energy program houses, and convention houses, to the building size, construction date and various construction characteristics, and geographical location. The construction date and building size were the two most significant predictors of leakage areas. Older and smaller houses had higher normalized leakage areas than the newer and larger houses. Based on their evaluation of new and older residential constructions, Sherman and Matson (1997) found that existing home stock (pre-1980) was quite leaky with an AER of approximately 20.0 h⁻¹. Newer constructions were considerably more airtight.

Murray and Burmaster (1995) conducted an analysis of data compiled by Brookhaven National Laboratories on AERs for 2,844 residential structures in four climatic regions based on heating degree days. (Region 1: IN, MN, MT, NH, NY1, VT, WI; Region 2: CO, CT, IL, NJ, NY2, OH, PA, WA; Region 3: CA3, MD, OR, WA; Region 4: AZ, CA4, FL, TX). Data were also separated by seasons (winter, spring, summer, and fall). The highest overall AERs occurred during the spring and fall season. However, air exchange rates were variable within and between seasons and between regions. Data from the warmest region during the summer months should be reviewed with caution because many of the measurements were made in southern California where windows were more likely to be open than in other areas of the country where air-conditioning is used.

Air exchange rates for 49 nonresidential buildings (14 schools, 22 offices, and 13 retail establishments) in California were reported by Lagus Applied Technology, Inc. (1995). Average mean (median) AERs were 2.45 (2.24), 1.35 (1.09), and 2.22 (1.79) h^{-1} for schools, offices, and retail establishments, respectively. Air infiltration rates for 40 of the 49 buildings were 0.32, 0.31, and 1.12 h^{-1} for schools, offices, and retail establishments, respectively. Air exchange rates for 40 nonresidential buildings in Oregon and Washington (Turk et al., 1989) averaged 1.5 (1.3) h^{-1} (mean median). The geometric mean of the AERs for six garages was 1.6 h^{-1} (Marr et al., 1998). Park et al. (1998) reported AERs for three stationary cars (cars varied by age) under different ventilation conditions. Air exchange rates ranged from 1.0 to 3.0 h^{-1} for windows closed and fan off, 13.3 to 23.5 h^{-1} for windows opened and fan off, 1.8 to 3.7 h^{-1} for windows closed and fan on recirculation (two cars tested), and 36.2 to 47.5 h^{-1} for windows closed and fan on fresh air (one car tested). An average AER of 13.1 h^{-1} was reported by Ott et al. (1992) for a station wagon moving at 20 mph with the windows closed.

Ozone Removal Processes

The most important removal process for O_3 in the indoor environment is deposition on and reaction with indoor surfaces. The rate of deposition is material specific. The removal rate indoors will depend on the indoor dimensions, surface coverings, and furnishings. Smaller rooms generally have larger surface-to-volume ratios (A/V) and remove O_3 faster. Fleecy materials, such as carpets, have larger A/V ratios and remove O_3 faster than smooth surfaces (Weschler, 2000). O_3 can react with carpet, decreasing O_3 concentrations and increasing

emissions of formaldehyde, acetaldehyde, and other C₅–C₁₀ aldehydes. Off-gassing of 4-phenylcyclohexene, 4-vinylcyclohexene, and styrene was reduced (Weschler et al., 1992). The rate of O₃ reaction with carpet diminishes with cumulative O₃ exposure (Morrison and Nazaroff, 2000, 2002). Reiss et al. (1995) reported significant quantities of acetic acid and smaller quantities of formic acid off-gassing from O₃ reactions with latex paint. The emission rate also was relative humidity-dependent, increasing with higher relative humidity. Klenø et al. (2001) evaluated O₃ removal by several aged (1- to 120-month) but not used building materials (nylon carpet, linoleum, painted gypsum board, hand polished stainless steel, oiled beech parquet, melamine-coated particle board, and glass plate). Initially, O₃ removal was high for all specimens tested with the exception of the glass plate. Ozone removal for one carpet specimen and the painted gypsum board remained high throughout the study. For the oiled beech parquet and melamine-coated particle board, O₃ removal leveled off to a moderate rate. Morrison et al. (1998) reported that small amounts of O₃ (~9%) are removed by lined ductwork of ventilation systems. The removal efficiency decreases with continued exposure to O₃. Unlined ductwork is less efficient in removing O₃. Ozone is scavenged by fiberglass insulation (Liu and Nazaroff, 2001). More O₃ was scavenged (60 to 90%) by fiberglass that had not been previously exposed. Table AX3-25 lists the removal rates for O₃ in different indoor environments.

Jaboki and Fabian (1997) found the O₃ decays exponentially. PAN decay is dependent on room temperature and possibly the properties and structure of the materials it comes in contact with. They examined O₃ and PAN decay in several closed rooms and in a car after a period of intensive ventilation. Figure AX3-94 plots the O₃ and PAN decay rates in these environments.

Several studies have examined factors within homes that may scavenge O₃ and lead to decreased O₃ concentrations (Lee et al., 1999; Wainman et al., 2000; Weschler and Shields, 1997). These reactions produce related oxidant species while reducing indoor O₃ levels. Lee et al. (1999) studied 43 homes in Upland, CA in the Los Angeles metropolitan region and reported that O₃ declined faster in homes with more bedrooms, greater amounts of carpeting, and lower ceilings (all of which alter the A/V ratio) and with the use of air conditioning. Homes with air conditioning had indoor/outdoor (I/O) ratios of 0.07, 0.09, and 0.11. Homes without air conditioning had an I/O ratio of 0.68 ± 0.18. Closed windows and doors combined with the use of an air cleaner resulted in an I/O ratio of 0.15. The O₃ I/O ratio was < 0.2 in homes with gas stoves.

Table AX3-25. Rate Constants (h^{-1}) for the Removal of Ozone by Surfaces in Different Indoor Environments

Indoor environment	Surface Removal Rate, k_d (A/V), h^{-1}	Reference
Aluminum Room (11.9 m ³)	3.2	Mueller et al. (1973)
Stainless Steel Room (14.9 m ³)	1.4	
Bedroom (40.8 m ³)	7.2	
Office (55.2 m ³)	4.0	
Home (no forced air)	2.9	Sabersky et al. (1973)
Home (forced air)	5.4	
Department Store	4.3	Thompson et al. (1973)
Office (24.1 m ³)	4.0	Allen et al. (1978)
Office (20.7 m ³)	4.3	
Office/Lab	4.3	Shair and Heitner (1974)
Office/Lab	3.2	Shair (1981)
Office/Lab	3.6	
13 Buildings, 24 ventilation systems	3.6 ^a	Nazaroff and Cass (1986)
Museum	4.3	
Museum	4.3	
Office/Lab	4	Weschler et al. (1989)
Office/Lab	3.2	
Office	2.5	
Lab	2.5	
Cleanroom	7.6	
Telephone Office	0.8 – 1.0 ^b	Weschler et al. (1994) ^b
43 Homes	2.8 ± 1.3	Lee et al. (1999)

^a A/V = assumes surface area to volume ratio = 2.8 m⁻¹

^b Large office, small A/V

Source: Weschler (2000).

Ozone Removal Through Chemical Processes

Ozone chemical reactions in the indoor environment are analogous to those reactions occurring in the ambient air (See Annex AX2). Ozone reactions with unsaturated VOCs in the indoor environment are dependent on the O₃ indoor concentration, the indoor temperature and, in most cases, the air exchange rate/ventilation rate and mixing factor. The air exchange rate

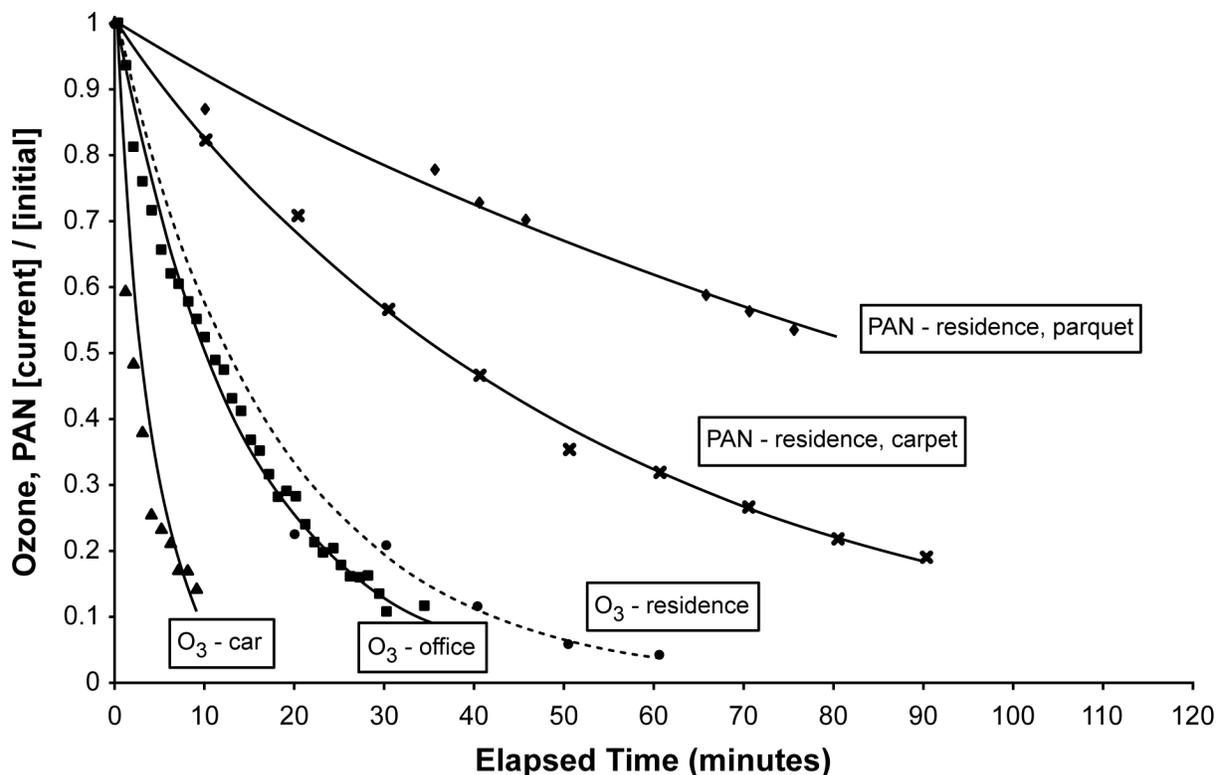


Figure AX3-94. Ozone decay processes versus time measured for several indoor rooms. Room temperature in all cases was ~27 °C and 29 °C in the car.

Adapted from: Jaboki and Fabian (1997).

determines the amount of time available for chemical reactions to take place. At low air exchange rate, the residence time for the pollutants is longer, the reaction time is greater, and the concentration of the products produced by O₃ chemistry is greater (Weschler and Shields, 2000, 2003). Since O₃ is primarily an outdoor pollutant, the air exchange rate will influence the amount of O₃ occurring indoors.

Most unsaturated VOCs in the indoor environment are terpenes or terpene-related compounds from cleaning products, air fresheners, and wood products. Some of the reaction products may more negatively impact human health and artifacts in the indoor environment than their precursors (Wolkoff et al., 1999; Wilkins et al., 2001; Weschler et al., 1992; Weschler and Shields, 1997; Rohr et al., 2002; Nøjgaard et al., 2005). The reactions products of O₃ and terpenes are Criegee biradicals, nitrate radicals, and peroxyacyl radicals. Secondary reaction of

the pollutants may form hydroxy, alkyl, alkylperoxy, hydroperoxy, and alkoxy radicals. The reaction of O₃ with alkenes can produce aldehydes, ketones, and organic acids (Weschler and Shields, 2000; Weschler et al., 1992).

The indoor chemistry of O₃ is described by the following equations. The initial reaction produces an ozonide which rapidly decomposes into one of the two possible combinations.



or



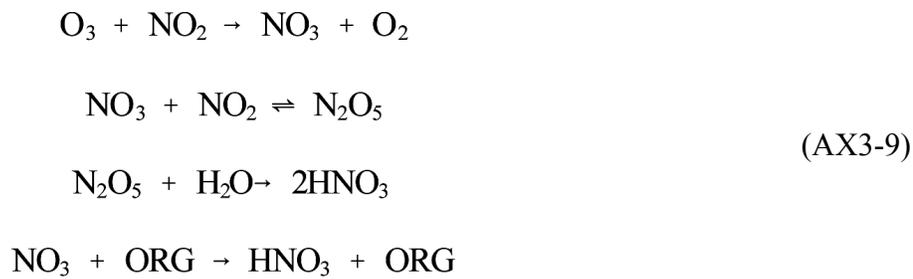
The biradical (*) then rearranges or reacts to produce the highly reactive intermediate products (hydroxy, hydroperoxy, and alkylperoxy radicals) and stable products (aldehydes, ketones and organic acids).

Hydroxy radicals formed from the reaction of O₃ with VOCs are lost to further reaction with VOCs. For each molecule of O₃ consumed, approximately one molecule of the hydroxy radical is produced. The hydroxy radical also is formed through the reaction of nitric oxide and hydroperoxy, and other intermediate products formed from the reaction of O₃ with unsaturated VOCs (Sarwar et al., 2002; Orzechowska and Paulson, 2002). The hydroxy radical can react with various nitrogen compounds, sulfur dioxide, carbon monoxide and other compounds to produce significantly more toxic compounds. In studies by Fick et al. (2003, 2004), the formation of norpinonic and pinonic acid in a ventilation system injected with α-pinene in the presence of O₃ was reported to be almost exclusively the result of oxidation by hydroxy radicals. Fan et al. (2003) attributed the formation of some secondary organic aerosols from the reaction of O₃ with 23 VOCs (as toluene) to reactions with hydroxy radicals. Van den Bergh et al. (2000) found that formaldehyde, acetaldehyde, acetone, campholenealdehyde, and pinonaldehyde are generated from the reaction of α-pinene with hydroxy radicals. A list of the VOCs occurring in

the indoor environment known to react with O₃ and OH radicals is found in Weschler (2000) and Nazaroff and Weschler (2004).

The reaction between O₃ and terpenes has been shown to increase the concentration of indoor particles (Weschler and Shields, 1999, 2003; Weschler, 2004; Clausen et al., 2001; Fan et al., 2003; Wainman et al., 2000). Sarwar et al. (2002) suggested that the hydroxy radical reacts with terpenes to produce products with low vapor pressures that contribute to fine particle growth. The acidity of particles was found to enhance the yield of secondary organic aerosols when α-pinene ozonolysis was carried out in the presence of ammonium sulfate and sulfuric acid. There was almost a 40% increase in organic carbon particles when α-pinene ozonolysis occurred in the presence of sulfuric acid aerosols compared to ammonium sulfate aerosols (Iinuma et al., 2004). Rohr et al. (2002, 2003) measured particle formation in a plexiglas chamber as part of a mouse bioassay study. They found an increase in ultrafine particle numbers as the result of O₃ and α-pinene reactions. When O₃ was introduced into the test chamber, particle concentrations increased to >10⁷ particles/cm³. Clausen found that the reaction of limonene vapor with O₃ increased the particle concentration to 3 × 10⁵ from a background concentration of <10³ particles/cm³. Poupard et al. (2005) and Blondeau et al. (2005) found a negative correlation between O₃ and particle concentration in eight school buildings in France. The researchers assumed that the increased particle concentration and decreased O₃ concentration was likely the result of homogeneous processes involving O₃. However, the assumption could not be verified because the particles were not analyzed for chemical composition.

Weschler et al. (1992) suggested that the reaction between O₃ and NO₂ in the indoor environment may be a significant source of HNO₃. When there are elevated concentrations of both O₃ and NO₂ in the indoor environment, the following reaction sequence may occur:



PAN and PPN are thermally unstable and will decomposed in the indoor environment to peroxyacetyl radicals and NO₂ (See equation AX3-10). Decomposition and formation of PAN in the indoor environment is influenced by NO₂ and NO.



When the concentration ratio of NO/NO₂ is greater than 7, less than 10% of the peroxyacetyl radicals will revert to PAN. Decomposition of PAN is expected to be a relatively fast process when indoor O₃ levels are low and when motor vehicle emissions are large or there is an indoor source of NO_x (Weschler and Shields, 1997).

Sources and Emissions of Indoor Ozone

Ozone enters the indoor environment primarily through infiltration from outdoors through cracks and crevices in the building envelope (unintentional and uncontrolled ventilation) and through building components such as windows and doors and ventilation systems (natural and controlled ventilation). Natural ventilation is driven by the natural forces of wind and temperature. Possible indoor sources of O₃ are office equipment (photocopiers, facsimile machines, and laser printers) and air cleaners (electrostatic air filters and precipitators and O₃ generators). Generally O₃ emissions from photocopiers and laser printers are limited due to installed filtering systems (Black and Worthan, 1999; Leovic et al., 1996; Aldrich et al., 1995). However, emissions increase under improper maintenance conditions (Leovic et al., 1996). Well-maintained photocopiers and laser printers usually emit low levels of O₃ by catalytically reducing the O₃ to oxygen (Aldrich et al., 1995). Leovic et al. (1996, 1998) measured O₃ emissions from four dry-process photocopiers. Ozone emissions ranged from 1300 to 7900 µg/h.

Most electrostatic air filters and precipitators are designed to minimize the production of O₃. However, if excessive arcing occurs, the units can emit a significant amount of O₃ into the indoor environment (Weschler, 2000). Niu et al. (2001) measured O₃ emissions from 27 air cleaners that used ionization processes to remove particulates. The test were conducted in a 2 × 2 × 1.60 m³ stainless steel environmental chamber. The tests were terminated after 1.5 h if no increase in O₃ concentration was noted. If an increase in O₃ was noted, the test was

continued, in some cases, for up to 20 h. Most of the evaluated units emitted no O₃ or only small amounts. Five units were found to emit O₃ ranging from 56 to 2757 µg/h.

There are many brands and models of O₃ generators commercially available. The amount of O₃ emitted by each unit depends on the size of the unit. Ozone emission rates have been reported to range from tens to thousands of micrograms per hour (Weschler, 2000; Steiber, 1995). Ozone emissions supposedly can be regulated using the units control features. However, available information suggests that O₃ output may not be proportional to the control setting. Some units are equipped with a sensor that automatically controls O₃ output by turning the unit on and off. The effectiveness of the sensor is unknown (U.S. Environmental Protection Agency, 2002).

Peroxyacyl nitrates (PAN and PPN) have no known direct emission sources and are formed in the atmosphere from the reaction of NO₂ and hydrocarbons (Grosjean et al., 1996). Peroxyacyl nitrates primarily occur in the indoor environment from infiltration through the building envelop and through openings in the building envelopment. Peroxyacyl nitrates also may be formed in the indoor environment through radical chemistry. PAN may be formed from the reaction of the OH· or NO₃ with acetaldehyde to form the acetyl radical, CH₃CO·. The acetyl radical then reacts with oxygen to form an acetylperoxy radical which reacts with NO₂ to form PAN.



PPN is formed from when the reaction of the OH· with propionaldehyde (Weschler and Shields, 1997).

AX3.10.8 Trends in Concentrations within Microenvironments

There have not been sufficient numbers of measurements of personal exposures or indoor O₃ concentrations to directly document trends over time or location. However, since O₃

concentrations in all microenvironments are primarily derived from ambient sources, trends in ambient air concentrations should reflect trends in personal exposure unless there are differences in activity patterns over time or locations. Overall, a significant downward trend in ambient O₃ concentrations has occurred from 1980 in most locations in the United States, although the trend in the latter part of the 1990s suggests that continued improvements in air quality may have leveled off. Greater declines in ambient O₃ concentrations appear to have occurred in urban centers than in rural regions. The decline in daily and weekly average O₃ concentrations from 1989 to 1995 in rural regions was 5% and 7%, respectively (Wolff et al., 2001; Lin et al., 2001; Holland et al., 1999). A detailed discussion of O₃ trends appears earlier in this annex.

AX3.10.9 Characterization of Exposure

AX3.10.9.1 Use of Ambient Ozone Concentrations

The use of ambient air monitoring stations is still the most common surrogate for assigning exposure in epidemiological studies. Since the primary source of O₃ exposure is the ambient air, monitoring concentration data would provide the exposure outdoors while exercising, a potential important exposure to evaluate in epidemiological studies as well as a relative assignment of exposure with time if the concentration were uniform across the region; the time-activity pattern were the same across the population; and the housing characteristics, such as ventilation rates and the O₃ sinks contributing to its indoor decay rates, were constant for the study area. Since these factors vary by population and location there will be errors in not only the magnitude of the total exposure, but also in the relative total exposure assignment based solely on ambient monitoring data. As discussed earlier in this section, spatial differences in O₃ concentrations within a city and between the height of the monitor and the breath zone (1 to 2 m) exist, increasing uncertainties. The potential exists to obtain more complete exposure assignments for both individuals and populations by modeling O₃ exposure based on ambient air concentration to account for spatial variations outdoors and for time spent indoors, provided housing characteristics and activity patterns can be obtained. For cohort studies, measurement of personal O₃ exposures using passive monitors is also possible.

The potential for error in determining pollutant exposure was expressed by Krzyzanowski (1997), who indicated that while the typical estimate of exposure in epidemiological studies is “an average concentration of the pollutant calculated from the data routinely collected in the area

of residence of the studied population. This method certainly lacks precision and, in most cases, the analyses that use it will underestimate the effect of specific concentrations of a pollutant on health.” It is further stated that when estimating exposure for epidemiological studies it is important to define: (1) representativeness of exposure or environmental data for the population at risk, (2) appropriateness of the averaging time for the health outcome being examined, and (3) the relationship between the exposure surrogate and the true exposure relative to the exposure-response function used in the risk assessment. Zeger et al. (2000) suggested that the largest biases will occur because of errors between ambient and average personal exposure measures. Sheppard et al. (2005a) further indicated that for non-reactive pollutants with non-ambient sources, exposure variability will introduce a large exposure error. However, for acute effects, time series studies using ambient concentration measurements are adequate (Sheppard, 2005b).

Numerous air pollutants can have common ambient air sources resulting in strong correlations among pollutant ambient air concentrations. As a result, some observed associations between an air pollutant and health effects may be due to confounding by other air pollutants. Sarnat et al. (2001) found that while ambient air concentrations of some air pollutants were correlated, personal $PM_{2.5}$ and several gaseous air pollutant (O_3 , SO_2 , NO_2 , CO , and exhaust-related VOCs) exposures were not generally correlated. The findings were based on the results of a multipollutant exposure study of 56 children and elderly adults in Baltimore, MD conducted during both the summer and winter months. Ambient pollutant concentrations were not associated with corresponding personal exposures, except for $PM_{2.5}$. The gaseous pollutants were found to be surrogates of $PM_{2.5}$ and were generally not correlated. The authors concluded that multipollutant models in epidemiologic studies of $PM_{2.5}$ may not be suitable, and health effects attributed to the gaseous pollutants may be the result of $PM_{2.5}$ exposure. It should be noted that the 95th percentile O_3 concentrations in the study was lower than 60 ppb, an O_3 concentration at which respiratory effects are noted. It would be important to examine whether O_3 is a surrogate for personal $PM_{2.5}$ at high O_3 levels when attributing adverse health effects to O_3 or $PM_{2.5}$.

Künzli et al. (1996) assessed potential lifetime exposure to O_3 based on the responses to a standardized questionnaire completed by 175 college freshmen in California. Questions addressed lifetime residential history, schools attended, general and outdoor activity patterns,

driving habits and job history. The purpose was to determine what O₃ monitoring data to use for each time period of their lives, the potential correction factor for indoor levels and periods of high activity to account for differential doses to the lung due to physical activity. The reliability of the responses was checked by having each respondent complete the questionnaire twice, on different days, and the results compared. A lifetime O₃ exposure history was generated for each participant and a sensitivity analysis performed to evaluate which uncertainties would cause the greatest potential misclassification of exposure. Assigned lifetime O₃ concentrations from the nearest monitor yielded highly reliable cumulative values, although the reliability of residential location decreased with increasing residential locations. Individuals involved in moderate and heavy exercise could be reliably identified. Such an approach can be used to evaluate health outcomes associated with chronic exposures to O₃.

AX3.10.9.2 Exposure Selection in Controlled Exposure Studies

Ozone exposures in the environment are variable over time due to changes in the ambient concentrations during the day as the photochemical reactions proceed and also because people move between microenvironments that have different concentrations (Johnson, 1997). Exposures are repeated on sequential days since weather conditions that produce O₃ can move slowly through or become stagnant within a region. For simplicity, most controlled-exposure experiments are conducted at a single concentration for a fixed time period, with a limited number of studies being repeated on a single individual. Few studies have been conducted using multipollutants or photochemical agents other than O₃, to better represent “real-world” exposures with the exception of NO₂. Studies by Hazucha et al. (1992), Adams (2003), and Adams and Ollison (1997) examined the effect of varying O₃ exposure concentrations on pulmonary function. A description of, and findings in, the studies appears in Annex AX5 of this document.

AX3.10.9.3 Exposure to Related Photochemical Agents

Exposures to other related photochemical agents have not been measured using personal samplers nor are these agents routinely measured at O₃ monitoring stations. Photochemical agents produced in the ambient air can penetrate indoors and react with other pollutants to produce other potentially irritating compounds. Reiss et al. (1995) reported that organic acids, aldehydes and ketones were produced indoors by reactions of O₃ with VOCs. The produced compounds included oxidants that can be respiratory irritants. The indoor concentrations were

dependent upon the O₃ concentrations indoors and the AER within the building. Weschler and Shields (1997) summarized indoor air chemical reactions that depend directly or indirectly on the presence of O₃. They indicated that O₃ concentrations are lower indoors than outdoors partly because of gas-phase reactions that produce other oxidants in an analogous fashion to photochemical smog in ambient air. The production of these species indoors is a function of the indoor O₃ concentration and the presence of the other necessary precursors, VOCs, and NO₂, along with an optimal AER. A variety of the photochemical oxidants related to O₃ that are produced outdoors, such as PAN and PPN, can penetrate indoors. These oxidants are thermally unstable and can decompose indoors to peroxyacetyl radicals and NO₂ through thermal decay. PAN removal increases with increasing temperature, and at a given temperature, with increasing NO/NO₂ concentration ratio (Grosjean et al., 2001). Other free radicals that can form indoors include HO• and HO₂•. These free radicals can produce compounds that are known or suspected to be irritating. Little is known about exposure to some of these agents, as not all have been identified and collection and analytical methodologies have not been developed for their routine determination. Lee et al. (1999) reported that homogeneous (gas phase) and heterogeneous (gas phase/solid surface) reactions occur between O₃ and common indoor air pollutants such as NO and VOCs to produce secondary products whose production rate depends on the AER and surface area within the home. Wainman et al. (2000) found that O₃ reacts indoors with *d*-limonene, emitted from air fresheners, to form fine particles in the range of 0.1 to 0.2 μm and 0.2 to 0.3 μm. The indoor process also produces compounds that have been identified in the ambient atmosphere. These species, plus others that may form indoors from other terpenes or unsaturated compounds can present an additional exposure to oxidants, other than O₃, at higher concentrations than present in ambient air, even as the O₃ concentration is being reduced indoors.

The announcement of smog alerts or air quality indices may influence individuals to alter behaviors (avoidance behavior). Neidell (2004), in his evaluation of the effect of pollution on childhood asthma, examined the relationship between the issuance of smog alerts or air quality indices for several counties in California and hospital admissions for asthma in children under age 18 years (not including newborns). Smog alerts are issued in California on days when O₃ concentrations exceed 200 ppb. There was a significant reduction in the number of asthma-

related hospital admissions in children ages 1 to 12 years on smog alert days, indicating that avoidance behavior might be present on days of high O₃ concentrations.

Ozone exposure modeling has been conducted for the general population and sensitive subgroups. The pNEM/O₃ model takes into consideration the temporal and spatial distribution of people and O₃ throughout the area of consideration, variations in O₃ concentrations within microenvironments, and the effects of exertion/exercise (increased ventilation) on O₃ uptake. The pNEM/O₃ model consists of two principal parts: the cohort exposure program and the exposure extrapolation program. The methodology incorporated much of the general framework described earlier in this section on assessing O₃ exposure and consists of five steps: (1) define the study area, population of interest, subdivisions of the study area, and exposure period; (2) divide population of interest into a set of cohorts; (3) develop exposure event sequence for each cohort for the exposure period; (4) estimate pollutant concentration and ventilation rate for each exposure event; and (5) extrapolate cohort exposures to population of interest (U.S. Environmental Protection Agency, 1996b).

There are three versions of the pNEM/O₃ model: general population (Johnson et al., 1996a), outdoor workers (Johnson et al., 1996b), and outdoor children (Johnson et al., 1996c, 1997). These three versions of the model have been applied to nine urban areas. The model also has been applied to a single summer camp (Johnson et al., 1996c). The general population version of the model uses activity data from the Cincinnati Activity Diary Study (CADS; Johnson, 1989). Time-activity studies (Wiley et al., 1991a; Johnson, 1984; Linn et al., 1993; Shamoo et al., 1991; Goldstein et al., 1992; Hartwell et al., 1984) were combined with the CADS data for the outdoor worker version of the model. Additional time-activity data (Goldstein et al., 1992; Hartwell et al., 1984; Wiley et al., 1991a,b; Linn et al., 1992; Spier et al., 1992) were also added to CADS for the outdoor children of the model (U.S. Environmental Protection Agency, 1996b). Home-work commuting patterns are based on information gathered by the U.S. Census Bureau. Ozone ambient air concentration data from monitoring stations were used to estimate the outdoor exposure concentrations associated with each exposure event. Indoor O₃ decay rate is assumed to be proportional to the indoor O₃ concentration. An algorithm assigns the equivalent ventilation rate (EVR) associated with each exposure event. The outdoor children model uses an EVR-generator module to generate an EVR value for each exposure event based on data on heart rate by Spier et al. (1992) and Linn et al. (1992). The models produce exposure

estimates for a range of O₃ concentrations at specified exertion levels. The models were used to estimate exposure for nine air quality scenarios (U.S. Environmental Protection Agency, 1996b).

Korc (1996) used the REHEX-II model, a general purpose air pollution exposure model based on a microenvironmental approach modified to account for the influence of physical activity along and spatial and the temporal variability of outdoor air pollution. Ozone exposure was estimated by demographic groups across 126 geographic subregions for 1980 to 1982, and for 142 geographic subregions for 1990 to 1992. Simulation results were determined for population race, ethnicity, and per capita income and included indoor, in-transit, and outdoor microenvironments. Exposure modeling was stratified by age because of differences in time-activity patterns. Exposure distributions by regional activity pattern data were not considered, rather it was assumed that all individuals within a county had the same exposure distribution by race, ethnicity, and socioeconomic status. Model results for southern California indicated that the segment of the population with the highest exposures were children 6 to 11 years old. Individuals living in low income districts may have greater per capita hours of exposure to O₃ above the NAAQS than those living in higher income districts. The author indicated that O₃ exposure differences by race and ethnicity have declined over time. The noninclusion of details on activity patterns for different populations in the model limit the extrapolations that can be made from the model results.

Children appear to have higher exposures than adults and the elderly. Asthmatics appear to ventilate more than healthy individuals, but tend to protect themselves by decreasing their outdoor exercise (Linn et al., 1992). Additional data are still needed to identify and better define exposures to potentially susceptible populations and improve exposure models for the general population and subpopulation of concern.

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ANNEX AX4. DOSIMETRY OF OZONE IN THE RESPIRATORY TRACT

AX4.1 INTRODUCTION

This annex serves to provide supporting material for Chapter 4—Dosimetry, Species, Homology, Sensitivity, and Animal-to-Human Extrapolation. It includes tables that summarize new literature published since the 1996 Ozone Air Quality Criteria Document or O₃ AQCD (U.S. Environmental Protection Agency, 1996). In addition, it provides descriptions of the new findings, in many cases, with more detail than is provided in the chapter.

Dosimetry refers to the measurement or estimation of the quantity of or rate at which a chemical and/or its reaction products are absorbed and retained at target sites within the respiratory tract (RT). The compound most directly responsible for toxic effects may be the inhaled gas, ozone (O₃), or one of its chemical reaction products (e.g., aldehydes or peroxides). Complete identification of the actual toxic agents and their integration into dosimetry is a complex issue that has not been fully resolved. Thus, most dosimetry investigations are concerned with the dose of the primary inhaled chemical. In this context, a further confounding aspect can be the units of dose (e.g., mass retained per breath, mass retained per breath per body weight, mass retained per breath per RT surface area). That is, when comparing dose between species, what is the relevant measure of dose? This question has not been answered; units are often dictated by the type of experiment or by a choice made by the investigators. There is also some lack of agreement as to what constitutes “dose.” Dahl’s seminal paper (1990) classified O₃ as a reactive gas and discussed the characterization of dose measurement by parameters, including: (1) inhaled O₃ concentration; (2) amount of O₃ inhaled as determined by minute volume, vapor concentration, and exposure duration; (3) uptake or the amount of O₃ retained (i.e., not exhaled); (4) O₃ or its active metabolites delivered to target cells or tissues; (5) O₃ or its reactive metabolites delivered to target biomolecules or organelles; and (6) O₃ or its metabolites participating in the ultimate toxic reactions—the effective dose. This characterization goes from

least complex to greatest, culminating in measurement of the fraction of the inhaled O₃ that participates in the effects of cellular perturbation and/or injury.

Understanding dosimetry as it relates to O₃-induced injury is complex due to the fact that O₃ interacts primarily with the epithelial lining fluid (ELF), which contains surfactant and antioxidants. Ozone reacts with molecules in the ELF to create reactive metabolites, which can then diffuse within the lung or be transported out of the lung to generate systemic effects. Antioxidant defenses can vary between species, region of the RT, and animal age. Section 5.3.1 contains further information on the cellular targets of O₃ interactions and antioxidants.

Experimental dosimetry studies in laboratory animals and humans, as well as theoretical (dosimetry modeling) studies, have been used to obtain information on O₃ dose. Since the 1996 O₃ AQCD (U.S. Environmental Protection Agency, 1996), most new experiments have been carried out in humans to obtain direct measurements of absorbed O₃ in the RT, the upper RT (URT) region proximal to the tracheal entrance, and in the tracheobronchial (TB) region. Experimentally obtaining dosimetry data is extremely difficult in smaller RT regions or locations, such as specific airways or the centriacinar region (CAR; junction of conducting airways and gas exchange region), where lesions caused by O₃ occur. Nevertheless, experimentation is important for determining dose, making dose comparisons between subpopulations and between different species, assessing hypotheses and concepts, and validating mathematical models that can be used to predict dose at specific RT sites and under more general conditions.

Theoretical studies are based on the use of mathematical models developed for the purposes of simulating the uptake and distribution of absorbed gases in the tissues and fluids of the RT. Because the factors affecting the transport and absorption of gases are applicable to all mammals, a model that uses appropriate species or disease-specific anatomical and ventilatory parameters can be used to describe absorption in the species and in different-sized, aged, or diseased members of the same species. More importantly, models also may be used to make interspecies and intraspecies dose comparisons, to compare and reconcile data from different experiments, to predict dose in conditions not possible or feasible experimentally, and to better understand the processes involved in toxicity. However, virtually all of these models have assumed that the reaction rate of O₃ in the liquid lining layer and in tissues is quasi first-order

with respect to O₃ concentration. There is considerable discrepancy between rate constants used in models. Both the uptake of O₃ at the gas-liquid interface and the fraction of O₃ (or its reaction products) that reach epithelial cells are sensitive to the value of these reaction rate constants. A large disparity in rate constants between studies illustrates the limitations in our current state of knowledge and can potential lead to erroneous interpretation of O₃ model predictions.

A review (Miller, 1995) of the factors influencing RT uptake of O₃ stated that structure of the RT region, ventilation, and gas transport mechanisms were important. Additionally, local dose is the critical link between exposure and response. A more detailed discussion of experimental and theoretical dosimetry studies is available in the 1996 O₃ AQCD (Volume III, Chapter 8, U.S. Environmental Protection Agency, 1996).

AX4.2 EXPERIMENTAL OZONE DOSIMETRY INVESTIGATIONS

There have been some advances in understanding human O₃ dosimetry that better enable quantitative extrapolation from laboratory animal data. The next two sections review the available new experimental studies on O₃ dosimetry, which involve only human subjects and are all from the same laboratory. Of the studies considered in the following discussion, five involved the use of the bolus response method as a probe to obtain information about the mechanism of O₃ uptake in the URT and TB regions. Of the remaining two investigations, one focused on total uptake by the RT and the other on uptake by the nasal cavities. Table AX4-1 provides a summary of the newer human studies.

AX4.2.1 Bolus-Response Studies

The bolus-response method has been used as a probe to explore the effects of physiological and anatomical differences or changes on the uptake of O₃ by human beings.

Asplund et al. (1996) studied the effects of continuous O₃ inhalation on O₃ bolus uptake, and Rigas et al. (1997) investigated the potential effects of continuous coexposure to O₃, nitrogen dioxide (NO₂), or sulfur dioxide (SO₂) on O₃ absorption. In both of these studies,

Table AX4-1. New Experimental Human Studies on Ozone Dosimetry^a

Purpose/Objective	Subject Characteristics	Region of Interest	Breathing Patterns/Exposure	Results	Reference
Determine the effect of continuous O ₃ inhalation on O ₃ uptake	8 male, 3 female, 22-31 years old, 166-186 cm, 64-93 kg	Central conducting airways (70-120 mL from lips)	2 h of continuous exposure at rest: 0.0, 0.12, and 0.36 ppm O ₃ . Spontaneous breathing. Bolus test breaths every 30 min using 250 mL/sec constant flow rate.	Averaged over all subjects and the four measurement intervals, the absorbed fraction (AF) changed +0.045, -0.005, and -0.03 for the 0, 0.12, and 0.36 ppm continuous exposures, respectively. These changes are approximately +6, -1, and -4 % based on an average AF value of 0.7 in the range of 70 to 120 mL. ^b Both nonzero exposures were significantly different than the air exposure.	Asplund et al. (1996)
Evaluate the influence of V _D on intersubject variation of O ₃ dose.	10 male, 22-30 years old, 163-186 cm, 64-92 kg; 10 female, 22-35 years old, 149-177 cm, 48-81 kg	Conducting airways	Bolus-response test (V _T = 500 mL at 250 mL/sec constant flow rate). Fowler single-breath N ₂ washout method to determine V _D .	On average, for the same V _p , women had a larger AF than men; women had a smaller V _D than men. However, for the same value of V _p /V _D , AF for men and women were indistinguishable. Further analysis indicated “that previously reported gender differences may be due to a failure in properly accounting for tissue surface within the conducting airways.”	Bush et al. (1996a)
Investigate the effect of continuous exposure to O ₃ , nitrogen dioxide and sulfur dioxide on O ₃ absorption.	6 male, 21-29 years old, 165-185 cm, 60-92 kg; 6 female, 19-33 years old, 152-173 cm, 48-61 kg	Lower conducting airways (70-120 mL from lips)	2 h of continuous exposure at rest: O ₃ (0, 0.36 ppm), SO ₂ (0, 0.36 ppm), or NO ₂ (0, 0.36, 0.75 ppm). 5-min Bolus test every 30 min: V _T = 500 mL; 250 mL/sec constant flow rate.	Averaging over all subjects or by gender, all exposures except O ₃ resulted in an increase of AF. Based on an AF reference value ^b , the change in AF ranged from -3 to +7 %. Only the O ₃ and the NO ₂ (0.36 ppm) exposures were significantly different from the air exposures.	Rigas et al. (1997)

Table AX4-1 (cont'd). New Experimental Human Studies on Ozone Dosimetry^a

Purpose/Objective	Subject Characteristics	Region of Interest	Breathing Patterns/Exposure	Results	Reference
Compare the absorption of chlorine and O ₃ . Determine how the physical-chemical properties of these compounds affect their uptake distribution in the RT.	5 male, 21-26 years old, 168-198 cm, 64-95 kg; 5 female, 18-28 years old, 162-178 cm, 55-68 kg ^c	Conducting airways. Nasal and oral routes	Bolus-response technique; V _T = 500 mL; 3 constant flow rates: 150, 250, and 1000 mL/sec.	Ozone dose to the URT was sensitive to the mode of breathing and to the respiratory rate. With increased airflow rate, O ₃ retained by the upper airways decreased from 95 to 50%. TB region dose ranged from 0 to 35%. Mass transfer theory indicated that the diffusion resistance of the tissue phase is important for O ₃ . The gas phase resistances were the same for O ₃ and Cl ₂ .	Nodelman and Ultman (1999a) ^c
To determine O ₃ uptake relative to inhaled O ₃ dose.	5 male, 5 female, 18-35 years old, 175 ± 13 (SD) cm, 72 ± 13 (SD) kg	Respiratory tract; oral breathing	Breath-by-breath calculation of O ₃ retention based on data from fast response analyzers for O ₃ and airflow rates. Oral breathing: 0.2 or 0.4 ppm O ₃ at V _E of approximately 20 L/min for 60 min or 40 L/min for 30 min.	The FA for all breaths was 0.86. Concentration, minute volume, and time have small but statistically significant effects on AF when compared to intersubject variability. The investigators concluded: for a given subject, constant O ₃ exposure, a given exercise level, and time <2 h, inhaled dose is a reasonable surrogate for the actual uptake of O ₃ . However, the actual doses may vary considerably among individuals who are exposed to similar inhaled doses.	Rigas et al. (2000)

Table AX4-1 (cont'd). New Experimental Human Studies on Ozone Dosimetry^a

Purpose/Objective	Subject Characteristics	Region of Interest	Breathing Patterns/Exposure	Results	Reference
Study the effect of gas flow rate and O ₃ concentration on O ₃ uptake in the nose.	7 male, 3 female, 26 ± years, 170 ± 11 (SD) cm, 75 ± 20 (SD) kg	Nasal cavities	For a given flow rate and exposure concentration, the subjects inhaled through one nostril and exhale through the other. For two 1-h sessions, a series of 9-12 measurements of AF were carried out for 10 s each: (1) O ₃ exposure concentration = 0.4 ppm; flow rates = 3, 5, 8, and 15 L/min. (2) O ₃ exposure = 0.1, 0.2, and 0.4 ppm; flow rate = 15 L/min. (3) O ₃ exposure = 0.4 ppm, flow rate = 15 L/min; AF was measured every 5 min for 1 h.	(1) With the exposure concentration at 0.4 ppm O ₃ , AF decreased from 0.80 to 0.33 when the flow rate was increased from 3 to 15 L/min. (2) At a flow rate of 15 L/min, the AF changed from 0.36 to 0.32 when the exposure concentration increased from 0.1 to 0.4 ppm O ₃ . (3) Statistical analysis indicated that the AF was not associated with the time at which the measurement was taken.	Santiago et al. (2001)
Evaluate intersubject variability in O ₃ uptake; correlate differences in breathing pattern and lung anatomy with O ₃ uptake	nonsmokers, 32 male, 22.9 ± 0.8 years old, 178 ± 1 cm, 80.6 ± 2.5 kg; 28 female, 22.4 ± 0.9 years old, 166 ± 1 cm, 62.1 ± 2.2 kg	Respiratory tract; oral breathing	Continuous: 1 h exposure to 0.25 ppm, exercising at 30 L/min. Bolus: breath-by-breath calculation of O ₃ retention. Timing of bolus varied to create penetration volumes of 10 to 250 mL. Peak inhaled bolus of ~1 ppm.	Continuous: Fractional O ₃ uptake efficiency ranged from 0.70 to 0.98 (mean 0.89 ± 0.06). Inverse correlation between uptake and breathing frequency. Direct correlation between uptake and tidal volume. Intersubject differences in forced respiratory responses not due to differences in O ₃ uptake. Bolus: The penetration volume at which 50% of the bolus was taken up was 90.4 mL in females and 107 mL in males. Distribution of O ₃ shifts distally as the size of the airway increases.	Ultman et al. (2004)

^a See Appendix A for abbreviations and acronyms.

^b Fig. 4, Hu et al. (1994), for the 250 mL/s curve and penetration volume range of 70 to 120 mL; the average AF is approximately 0.7.

^c Subject characteristics are from Nodelman and Ultman (1999b).

subjects were exposed “continuously” to a gas for 2 h. Every 30 min, breathing at 250 mL/s, a series of bolus test breaths was performed targeted at the lower conducting airways.

Differences in bolus-response absorbed fraction from an established baseline indicated the degree to which the “continuous” gas exposure affected the absorption of O₃. Depending on the gas and concentration, changes in absorbed fraction ranged from -3 to +7 % (see Table AX4-1). Continuous O₃ exposure lowered the uptake of O₃, whereas NO₂ and SO₂ increased the uptake of O₃. The investigators concluded that in the tested airways, NO₂ and SO₂ increased the capacity to absorb O₃ because more of the compounds oxidized by O₃ were made available. On the other hand, they conjectured that continuous O₃ exposure depleted these compounds, thereby reducing O₃ uptake.

Bush et al. (1996a) investigated the effect of lung anatomy and gender on O₃ absorption in the conducting airways during oral breathing using the bolus-response technique. Absorption was measured using this technique applied to 10 men and 10 women. Anatomy was defined in terms of forced vital capacity (FVC), total lung capacity (TLC), and dead space (V_D). The absorbed fraction data were analyzed in terms of a function of penetration volume, airflow rate, and an “intrinsic mass transfer parameter” called the overall mass transfer coefficient (Ka), which was determined for each subject and found to be highly correlated with V_D, but not with height, weight, age, gender, FVC, or TLC. That is, in all subjects, whether men or women, dosimetry differences could be explained by differences in V_D. Combining their data with those of Hu et al. (1994), where absorbed fraction was determined for several flow rates, Bush et al. (1996a) inferred that Ka was proportional to flow rate/V_D. The investigators point out that the applicability of their results may be limited because of their assumptions that Ka was independent of location in the RT and that there was no mucous resistance. They also suggested that the dependence of Ka on flow rate and V_D be restricted to flow rates ≤1000 mL/s until studies at higher rates have been performed.

With flow rates of 150, 250, and 1000 mL/s, Nodelman and Ultman (1999b) used the bolus-response technique (a) to compare the uptake distributions of O₃ and chlorine gas (Cl₂) and (b) to investigate how their uptakes were affected by their physical and chemical properties. Ozone dose to the URT was found to be sensitive to the mode of breathing and to the airflow rate. With increased rate, O₃ retained by the upper airways decreased from 95 to 50% and TB

region dose increased from 0 to 35%. At the highest flow rate only 10% of the O₃ reached the pulmonary region. Data were analyzed by expressing the overall diffusion resistance between the respired gas and the epithelial cells as the sum of individual gas-phase and liquid-phase resistances. The liquid-phase resistance made an important contribution to the overall resistance, implying that changes in the reaction rate of O₃ in ELF would cause concomitant changes in the O₃ uptake. The gas-phase resistance was inversely related to the volumes of the oral and nasal cavities during oral and nasal breathing, respectively.

Ultman et al. (2004) used separate bolus and continuous exposure sessions to test the hypotheses that differences in O₃ uptake in lungs are responsible for variation in O₃-induced changes in lung function parameters and that differences in O₃ uptake are due to variations in breathing patterns and lung anatomy. Thirty-two males and 28 female nonsmokers were exposed to bolus penetration volumes ranging from 10 to 250 mL, which was determined by the timing of the bolus injection. The subjects controlled their breathing to generate a target respired flow of 1000 mL/sec. At this high minute ventilation, there was very little uptake in the upper airway and most of the O₃ reached areas where gas exchange takes place. To quantify intersubject differences in O₃ bolus uptake, they measured the penetration volume at which 50% of the O₃ was taken up. Values for penetration volume ranged from 69 to 134 mL and were directly correlated with the subjects' values for anatomic dead space volume. A better correlation was seen when the volume of the upper airways was subtracted. The penetration volume at which 50% of the bolus was taken up was 90.4 mL in females and 107 mL in males. This significant difference in uptake suggests to the authors that, in females, the smaller airways and associated larger surface-to-volume ratio enhance local O₃ uptake and cause reduced penetration of O₃ into the distal lung. Data from the continuous exposure sessions indicated that overall O₃ uptake was related to breathing pattern but was not correlated with V_D. Thus, these findings indicate that overall O₃ uptake is not related to airway size, but that the distribution of O₃ shifts distally as the size of the airway is increased.

General comment on estimating mass transfer coefficients: Bush et al. (1996b) and Nodelman and Ultman (1999a) used a simple model to analyze their bolus-response data. This model, presented by Hu et al. (1992, 1994), assumed steady-state mass transfer by convection (but no

dispersion) and the mass transfer of O₃ to the walls of a tube of uniform cross-sectional area. These assumptions led to an analytical solution (for the absorbed fraction) which was a function of an “overall mass transfer coefficient,” penetration volume, and airflow rate. As the investigators have shown, the model is very useful for statistical analysis and hypothesis testing. Given the absorbed fraction data, the model overall mass transfer coefficients were estimated for each flow rate. In those bolus-response studies that used this method to analyze data, there was no discussion of the models’ “accuracy” in representing mass transfer in the human RT with respect to omitting dispersion. In addition, the formulation of the gas phase mass transfer coefficient does not take into account that it has a theoretical lower limit greater than zero as the airflow rate goes to zero (Miller et al., 1985; Bush et al., 2001). As a consequence, there is no way to judge the usefulness of the values of the estimated mass transfer coefficients for dosimetry simulations that are based on convection-dispersion equations, or whether or not the simple model’s mass transfer coefficients, as well as other parameters derived using these coefficients, are the same as actual physiological parameters.

AX4.2.2 General Uptake Studies

Rigas et al. (2000) performed an experiment to determine the ratio of O₃ uptake to the quantity of O₃ inhaled (fractional absorption, FA). Five men and five women were exposed orally to 0.2 or 0.4 ppm O₃ while exercising at a minute volume of approximately 20 L/min for 60 min or 40 L/min for 30 min. Ozone retention was calculated from breath-by-breath data taken from fast response analyzers of O₃ and airflow rates. The FA was statistically analyzed in terms of subject, exposure concentration, minute volume, and exposure time.

Fractional absorption ranged from 0.56 to 0.98, with a mean \pm SD of 0.85 ± 0.06 for all 2000 recorded breaths. Intersubject differences had the largest influence on FA, resulting in a variation of approximately 10%. Statistical analysis indicated that concentration, minute volume, and exposure time had statistically significant effects on FA. However, relatively large changes in these variables were estimated to result in relatively small changes in FA. Note: the quantity of O₃ retained by the RT is equal to FA times the quantity of O₃ inhaled; thus, relatively large changes in concentration, minute volume, or exposure time may result in relatively large

changes in the amount of O₃ retained by the RT or absorbed locally. Also, according to Overton et al. (1996), differences in PAR dose due to anatomical variability may be considerably larger than corresponding small changes in FA would indicate.

Santiago et al. (2001) studied the effects of airflow rate and O₃ concentration on O₃ uptake in the nasal cavities of three women and seven men. Air was supplied at a constant flow rate to one nostril and exited from the other nostril while the subject kept the velopharyngeal aperture closed by raising the soft palate. Thus, a constant unidirectional flow of air plus O₃ was restricted to the nasal cavities. The fraction of O₃ absorbed was calculated using the inlet and outlet concentrations. Inlet concentration and airflow rate were varied in order to determine their effect on O₃ uptake.

The mean FA decreased from 0.80 to 0.33, with an increase in flow rate from 3 to 15 L/min. The effect of both flow rate and subject on FA was statistically significant. Further analysis indicated that the overall mass transfer coefficient was highly correlated with the flow rate and that the gas phase resistance contributed from 6.3% (15 L/min) to 23% (3 L/min) of the total resistance to O₃ transfer to the nasal cavity surface. Concentration had a small, but statistically significant effect on FA, when the inlet concentration was increased from 0.1 to 0.4 ppm O₃, FA decreased from 0.36 to 0.32. The investigators observed that differences in FA among subjects were important; generally, subject variability accounted for approximately half of the total variation in FA.

As mentioned above, Ultman et al. (2004) tested hypotheses that differences in O₃ uptake in lungs are responsible for variation in O₃-induced changes in lung function parameters and that differences in O₃ uptake are due to variations in breathing patterns and lung anatomy. Thirty-two males and 28 female nonsmokers were exposed continuously for 1 h to either clean air or 0.25 ppm O₃ while exercising at a target minute ventilation of 30 L/min. Ultman et al. first determined the forced expiratory response to clean air, then evaluated O₃ uptake measuring dead space volume, cross-sectional area of peripheral lung (A_p) for CO₂ diffusion, FEV₁, FVC, and FEF_{25%-75%}. The fractional O₃ uptake efficiency ranged from 0.70 to 0.98, with a mean of 0.89 ± 0.06. They found an inverse correlation between uptake and breathing frequency and a direct correlation between uptake and tidal volume. There was a small, but statistically significant decrease in uptake efficiency during the four sequential 15 min intervals of the 1 h

exposure (0.906 ± 0.058 vs. 0.873 ± 0.088 , first and last interval, respectively), in part due to the increased breathing frequency and decreasing tidal volume occurring over the same period. Ozone uptake rate correlated with individual %A_p, but did not correlate with individual %FEV₁. Neither of these parameters correlated with the penetration volume determined in the bolus studies mentioned above. The authors concluded that the intersubject differences in forced respiratory responses were not due to differences in O₃ uptake. However, these data did partially support the second hypothesis, i.e., that the differences in cross-sectional area available for gas diffusion induce differences in O₃ uptake.

Plopper et al. (1998) examined the relationship between O₃ dose and epithelial injury in Rhesus monkeys. Using ¹⁸O content in lung tissues, the respiratory bronchioles were confirmed as the site receiving the greatest O₃ dose (mass ¹⁸O per dry lung weight). Furthermore, the greatest cellular injury occurred in the vicinity of the respiratory bronchioles and was dependent on the delivered O₃ dose to these tissues. After a 2 h exposure, the antioxidant glutathione (GSH) was increased in the proximal intrapulmonary bronchus after 0.4 ppm O₃ and decreased in the respiratory bronchiole after 1.0 ppm O₃. Perhaps an adaptive response, chronic O₃ exposure leads to increased GSH levels in distal bronchioles of both rats and monkeys relative to GSH levels in FA-exposed animals (Duan et al., 1996). Differences in the levels of antioxidants between species and regions of the lung do not appear to be the primary factor determining susceptibility to O₃-induced tissue injury (Duan et al., 1993, 1996). Plopper et al. (1998) concluded that, in monkeys, there was a close association between site-specific O₃ dose, the degree of epithelial injury, and reduced-glutathione depletion. Within a species, antioxidant defenses against O₃ can also vary with animal age (Servias et al., 2005) and exposure history (Duan et al., 1996).

AX4.2.3 Dosimetry Modeling

When all of the animal and human in vivo O₃ uptake efficiency data are compared, there is a good degree of consistency across data sets (U.S. Environmental Protection Agency, 1996). This agreement raises the level of confidence with which these data sets can be used to support dosimetric model formulations.

Schelegle et al. (2001) reported that the terminal bronchioles supplied by short and long paths had similar epithelial injury in rats exposed to 1 ppm O₃ for 8 h. Interestingly, in rats with a C-fiber conduction block to prevent O₃-induced rapid shallow breathing, it was the long path terminal bronchioles that received the greatest epithelial injury. Overall, O₃-induced rapid shallow breathing appears to protect the large conducting airways while producing a more even distribution of injury to the terminal bronchioles (Joad et al ., 2000; Schelegle et al ., 2001). Postlethwait et al . (2000) have also identified the conducting airways as a primary site of acute O₃-induced cell injury. Such data must be considered when developing models that attempt to predict site-specific locations of O₃-induced injury. The early models computed relationships between delivered regional dose and response with the assumption that O₃ was the active agent responsible for injury. It is now known that reactive intermediates, e.g., aldehydes and hydrohydroperoxides are important agents mediating the response to O₃ (further discussed in Section 5.3.1). Thus, models must consider O₃ reaction/diffusion in the ELF and ELF-derived reactions products.

Table AX4-2 presents a summary of new theoretical studies on the uptake of O₃ by the RTs (or regions) of humans and laboratory animals that have become available since the 1996 O₃ AQCD review. They are discussed below.

Overton and Graham (1995) described the development and simulation results of a dosimetry model that was applied to a TB region anatomical model that had asymmetrically branching airways, but which had identical single-path pulmonary units distal to each terminal bronchiole. The anatomical model of the TB region was based on Raabe et al. (1976), which reported lung cast data for the TB region of a 330 g rat. In general, the modeled O₃ dose to lung tissues varied among anatomically equivalent ventilatory units as a function of path length from the trachea, with shorter paths showing greater dose. This conflicts with Schelegle et al . (2001), who exposed rats to 1 ppm O₃ for 8 h and found that the terminal bronchioles supplied by short and long paths had similar epithelial injury. In rats with a C-fiber conduction block to prevent O₃-induced rapid shallow breathing, it was the long path terminal bronchioles that received the greatest epithelial injury.

Table AX4-2. New Ozone Dosimetry Model Investigations^a

Purpose/Objective	Type of mass transport model/Anatomical model ^b	Species/RT region of interest/Regional anatomical models	Ventilation and Exposure	Results	Reference
To describe an RT dosimetry model that uses a branching TB region anatomical model and to illustrate the results of its application to a rat exposed to O ₃ .	One-dimensional (along axis of airflow), time-dependent, convection-dispersion equation of mass transport applied to each airway or model segment. URT: single path; TB: asymmetric branching airways. PUL: single path anatomical model distal to each terminal bronchiole.	Rat/RT/URT: Patra et al. (1987). TB: multiple path model of Raabe et al. (1976). PUL: Mercer et al. (1991).	f = 150 bpm; V _T = 1.5, 2.0, 2.5 mL. One constant concentration.	(1) For V _T = 2.0 mL, f = 150 bpm: The general shape of the dose versus generation plot along any path from the trachea to a sac is independent of path: generally the tissue dose decreases with increasing generation index. In the TB region, the coefficient of variation for dose ranges from 0 to 34 %, depending on generation. The maximum ratio of the largest to smallest dose in the same generation is 7; the average ratio being 3. In the first PUL region model segment, the coefficient of variation for the dose is 29 %. (2) The average dose to the first PUL region model segment increases with increasing V _T .	Overton and Graham (1995)
To incorporate into the CFD model of Kimbell et al. (1993) resistance to mass transfer in the nasal lining and to investigate the effects of this lining on O ₃ uptake.	Three dimensional steady-state Navier-Stokes equations for solving air velocity flow field. Three dimensional steady-state convection-diffusion equation for O ₃ transport. Three-dimensional CFD model of the nasal passages of a rat.	Rat/nasal passages Nasal passages: Kimbell et al. (1993).	Steady-state unidirectional ("inhalation") flow rate = 576 mL/min. One constant concentration.	Predictions of overall uptake were within the range of measured uptake. Results suggest that mucus resistance is important for describing O ₃ dosimetry and this thickness may play a role for determining patterns of O ₃ -induced lesions in the rat nasal passage.	Cohen-Hubal et al. (1996)
To determine if the single-path model is able to simulate bolus inhalation data recorded during oral breathing at quiet respiratory flow.	Single-path, one-dimensional (along axis of airflow), time-dependent, convection-dispersion equation of mass transport. Single-path anatomical model.	Human/RT/URT (oral): Olson et al. (1973). LRT: Weibel (1963).	V _T = 500 mL, f = 15 bpm, constant flow rate = 250 mL/s. Bolus-response simulations. (protocol used is described by Hu et al., 1992).	Simulations are sensitive to conducting airway volume but are relative insensitive to characteristics of the respiratory airspace. Although the gas-phase resistance to lateral diffusion limits O ₃ absorption during quiet breathing, diffusion through mucus may become important at the large respiratory flows that are normally associated with exercise. The single-path convection-diffusion model was a reasonable approach /to simulate the bolus-response data.	Bush et al. (1996b)

Table AX4-2 (cont'd). New Ozone Dosimetry Model Investigations ^a

Purpose/Objective	Type of mass transport model/Anatomical model ^b	Species/RT region of interest/Regional anatomical models	Ventilation and Exposure	Results	Reference
To assess age- and gender-specific differences in regional and systemic uptake.	PBPK, at ages 1, 3, 6, months and 1, 5, 10, 15, 25, 50, and 75 years.	Human/ET/TB	Pulmonary ventilation ranged from 34 mL/s (in 1-month-old) to 190 mL/s (in 15-year-old). V_T varied with age.	Regional extraction is insensitive to age. Extraction per unit surface area is 2- to 8-fold higher in infants compared to adults. PU and ET regions have a large increase in unit extraction with increasing age. Early postnatal period is time of largest differences in PK, due to immaturity of metabolic enzymes.	Sarangapani et al. (2003)
To examine the impact on predictions due to the value used for the TB region volume at FRC and due to TB region volume change during respiration.	Single-path, one-dimensional (along axis of airflow), time-dependent, convection-dispersion equation of mass transport. Single-path anatomical model.	Human/RT/URT: Nunn et al. (1959) LRT: Weibel (1963) Rat/RT/URT: Patra et al. (1987) TB: Yeh et al. (1979) PUL: Mercer et al. (1991)	Human: $V_T = 500$, 2250 mL; $f = 15$, 30 bpm. Rat: $V_T = 1.4$, 2.4 mL; $f = 96$, 157 bpm. One constant concentration.	(1) A better understanding and characterization of the role of TB region expansion (mainly the rat) and volume is important for an improved understanding of respiratory-tract dosimetry modeling of reactive gases. (2) Extrapolations based on dose in the PAR can differ significantly from those based on exposure concentration or total uptake. (3) Human subjects who appear similar outwardly may have very different PAR doses and potentially different responses to the same exposure. (Uptake by the URT was not considered.)	Overton et al. (1996)
To make parameter modifications so that a single-path model would simulate AF from bolus-response experiments involving O ₃ (and Cl ₂).	Single-path, one-dimensional (along axis of airflow), time-dependent, convection-dispersion equation of mass transport. Single-path anatomical model.	Human/RT/URT (oral): Olson et al. (1973). URT (nasal): Olson et al. (1973) and Guilmette et al. (1989) LRT: Weibel (1963).	Oral and nasal breathing. Flow rates = 150, 250, 1000 mL/s, $V_T = 500$ mL. Bolus-response simulations.	(Simulation results for O ₃ only) (1) Using parameter values from the literature and assuming that absorption was gas-phase controlled, the simulations of O ₃ data were realistic at flow rate = 250 mL/s, but not realistic at 1000 mL/s. (2) Accurate simulations at 250 mL/s required modification of mass transfer coefficients reported in the literature for the conducting airways. (3) It was necessary to include a diffusion resistance for the ELF based on an assumed O ₃ reaction rate constant that was much greater than in in vitro estimates. (4) Partial validation of the final parameters (determined at 250 mL/s) was obtained by simulations of bolus-response data at flow rates of 150 and 1000 mL/s. Validation was obtained also by simulating internal measurements of O ₃ in subjects exposed during quiet breathing.	Bush et al. (2001)

^aSee Appendix A for abbreviations and acronyms.

^bThe anatomical models used in an investigation generally differ from those described in the references, e.g., dimensions are often scaled to dimensions appropriate to the dosimetry investigation; or the original structure may be simplified, keeping or scaling the original dimensions.

Rat effects data (from the PAR) are available that are identified with the lobe and the generation in the lobe from which tissue samples were obtained (Pinkerton et al., 1995, 1998). Models, like Overton et al. (1996), can be helpful in understanding the distribution of the magnitude of such effects as well as suggesting sampling sites for future experiments.

Using computational fluid dynamics (CFD), Cohen-Hubal et al. (1996) explored the effect of the mucus layer thickness in the nasal passage of a rat. The nasal lining was composed of mucus and tissue layers in which mass transfer was by molecular diffusion with first order chemical reaction. Physicochemical parameters for O_3 were obtained from the literature. Three scenarios were considered: 10 μm thick mucus layer, no mucus layer, and two nasal passage regions each with a different mucus layer thickness. Predictions of overall uptake were within the range of measured uptake. Predicted regional O_3 flux was correlated with measured cell proliferation for the CFD simulation that incorporated two regions, each with a different mucus thickness. The reaction rate constant used by Cohen-Hubal and co-workers may be too low. Using bolus-response data, Hu et al. (1994) and Bush et al. (2001) estimated a reaction rate constant that is more than a 1000 times as large as that used by Cohen-Hubal et al. (1996). A rate constant this large could result in conclusions different than those based on the smaller constant.

With an RT dosimetry model, Overton et al. (1996) investigated the sensitivity of absorbed fraction (AF), proximal alveolar region (PAR) dose, and PAR dose ratio to TB region volume (V_{TB}) and TB region expansion in human beings and rats. The PAR was defined as the first generation distal to terminal bronchioles and the PAR dose ratio was defined as the ratio of a rat's predicted PAR dose to a human's predicted PAR dose. This ratio relates human and rat exposure concentrations so that both species receive the same PAR dose. In rats the PAR is a region of major damage from O_3 . For each species, three literature values of V_{TB} were used: a mean value and the mean \pm twice the SD. The following predictions were obtained:

(1) The sensitivity of AF and PAR dose to V_{TB} depends on species, ventilation, TB region overall mass transfer coefficient (k_{TB}), and expansion. For $k_{\text{TB}} = 0.26 \text{ cm/s}$ and quiet breathing, AF was predicted to vary by less than 3% for the ± 2 SD range of V_{TB} . In contrast, the PAR dose predicted for the smallest V_{TB} is five times larger than the PAR dose predicted with the

largest V_{TB} . The effect of V_{TB} is much less during heavy exercise: the ratio of maximum to minimum PAR dose was approximately 1.5. In any case, the simulations predicted that fractional changes in AF due to different V_{TB} are not, in general, a good predictor of the fractional changes in PAR doses.

(2) Relative to no expansion in the TB region, expansion decreases both AF and PAR dose. The largest effect of including expansion in the human simulations was to decrease the AF by $\approx 8\%$; in rats, the maximum decrease was $\approx 45\%$. The PAR doses decreased relatively more, 25 and 65% in human beings and rat, respectively.

(3) The authors attempted to obtain an understanding as to uncertainty or variability in estimates of exposure concentrations (that give the same PAR dose in both species) if the literature mean value of V_{TB} was used. For various values of f , V_T , k_{TB} , and expansion, the PAR dose ratios at upper and lower values of V_{TB} deviated in absolute values from the PAR dose ratio calculated at the mean values of V_{TB} by as little as 10% to as large as 310%. The smallest deviation occurred at the largest V_T and smallest k_{TB} for both species; whereas, the largest deviation occurred at the smallest V_T and largest k_{TB} for both species.

Bush et al. (2001) modified the single-path model of Bush et al. (1996b) in order to be able to simulate absorbed fraction data for O_3 (and Cl_2 , which is not considered) for three airflow rates and for oral and nasal breathing. By adjusting several parameters, reasonable agreement between predicted and experimental values was obtained. On the other hand, the O_3 plots of the experimental and predicted values of absorbed fraction versus penetration volume (e.g., Figures 4 and 5 of Bush et al., 2001) show sequential groups composed of only positive or only negative residuals, indicating a lack of fit. Possibly adjusting other parameters would eliminate this. To obtain an independent validation of the model, Bush et al. (2001) simulated measurements of O_3 concentrations made by Gerrity et al. (1995) during both inhalation and exhalation at four locations between the mouth and the bronchus intermedius of human subjects. Simulated and experimental values obtained are in close agreement. Note, however, that Bush et al. (2001) made no quantitative assessment of how well their simulations agreed with the experimental data; assessments were made on the basis of visual inspection of experimental and simulated values plotted on the same figure. Thus, that evaluation of the model was subjective.

Recently, Sarangapani et al. (2003) used physiologically based pharmacokinetic (PBPK) modeling to characterize age- and gender-specific differences in both regional and systemic uptake of O₃ in humans. This model indicated that regional extraction of O₃ is relatively insensitive to age, but extraction per unit surface area is 2- to 8-fold higher in infants compared to adults, due to the region-specific mass transfer coefficient not varying with age. The PU and ET regions have a large increase in unit extraction with increasing age because both regions increase in surface area. Males and females in this model have similar trends in regional extraction and regional unit extraction. In early childhood, dose metrics were as much as 12 times higher than adult levels, but these differences leveled out with age, such that inhalation exposures varied little after age 5. These data suggest that the early postnatal period is the time of the largest difference in pharmacokinetics observed, and this difference is primarily due to the immaturity of the metabolic enzymes used to clear O₃ from the RT.

Mudway and Kelly (2004) attempted to model O₃ dose-inflammatory response using a meta-analysis of 23 exposures in published human chamber studies. The O₃ concentrations ranged from 0.08 to 0.6 ppm and the exposure durations ranged from 60 to 396 min. The analysis showed linear relationships between O₃ dose and neutrophilia in bronchoalveolar lavage fluid (BALF). Linear relationships were also observed between O₃ dose and protein leakage into BALF.

AX4.3 SPECIES HOMOLOGY, SENSITIVITY AND ANIMAL-TO-HUMAN EXTRAPOLATION

Biochemical differences among species are becoming increasingly apparent, and these differences may factor into a species' susceptibility to O₃ exposure effects. Lee et al. (1998) compared SD rats and rhesus monkeys to ascertain species differences in the various isoforms of CYP monooxygenases in response to O₃ exposure (discussed in more detail in Section 5.3.1.2). Differences in activities between rat and monkey were 2- to 10-fold, depending on the isoform and the specific lung region assayed. This study supports the view that differential expression of CYPs is a key factor in determining the toxicity of O₃. As further characterization of species- and region-specific CYP enzymes occurs, a greater understanding of the differences

in response may allow more accurate extrapolation from animal exposures to human exposures and toxic effects.

Arsalane et al. (1995) compared guinea pig and human AM recovered in BALF and subsequently exposed in vitro to 0.1 to 1 ppm for 60 min. Measurement of inflammatory cytokines showed a peak at 0.4 ppm in both species. Guinea pig AM had an increase in IL-6 and TNF- α while human AM had increases in TNF- α , IL-1b, IL-6 and IL-8. This exposure also caused an increase in mRNA expression for TNF- α , IL-1b, IL-6 and IL-8 in human cells. At 0.1 ppm exposures, only TNF- α secretion was increased. These data suggest similar cytokine responses in guinea pigs and humans, both qualitatively and quantitatively.

Dormans et al. (1999) continuously exposed rats, mice, and male guinea pigs to filtered air, 0.2, or 0.4 ppm O₃ for 3 to 56 days or for 28 days to follow recovery at 3, 7, and 28 days PE. Depending on the endpoint studied, the species varied in sensitivity. Greater sensitivity was shown in the mouse as determined by biochemical endpoints, persistence of bronchiolar epithelial hypertrophy, and recovery time. Guinea pigs were more sensitive in terms of the inflammatory response, though all three species had increases in the inflammatory response after three days that did not decrease with exposure. In all species the longest exposure to the highest dose caused increased collagen in ductal septa and large lamellar bodies in Type II cells, but that response also occurred in rats and guinea pigs at 0.2 ppm. No fibrosis was seen at the shorter exposure times and the authors question whether fibrosis occurs in healthy humans after continuous exposure. The authors do not rule out the possibility that some of these differences may be attributable to differences in total inhaled dose or dose actually reaching a target site. Overall, the authors rated mice as most susceptible, followed by guinea pigs and rats.

Comparisons of airway effects in rats, monkeys and ferrets resulting from exposures of 1.0 ppm O₃ for 8 h (Sterner-Kock et al. 2000) demonstrated that monkeys and ferrets had a similar inflammatory responses and epithelial necrosis. The response of these two species was more severe than that seen in rats. These data suggest that ferrets are a good animal model for O₃-induced airway effects due to the similarities in pulmonary structure between primates and ferrets.

The rat is a key species used in O₃ toxicological studies, but Watkinson and Gordon, (1993) suggest that, because the rat has both behavioral and physiological mechanisms that can lower core temperature in response to acute exposures, extrapolation of these exposure data to humans may be limited. Another laboratory (Iwasaki et al., 1998) has demonstrated both cardiovascular and thermoregulatory responses to O₃ at exposure to 0.1, 0.3, and 0.5 ppm O₃ 8 h/day for 4 consecutive days. A dose-dependent disruption of HR and T_{co} were seen on the first and second days of exposure, which then recovered to control values. Watkinson et al. (2003) exposed rats to 0.5 ppm O₃ and observed this hypothermic response which included lowered HR, lowered T_{co}, and increased inflammatory components in BALF. The authors suggest that the response is an inherent reflexive pattern that can possibly attenuate O₃ toxicity in rodents. They discuss the cascade of effects created by decreases in T_{co}, which include: (1) lowered metabolic rate, (2) altered enzyme kinetics, (3) altered membrane function, (4) decreased oxygen consumption and demand, (5) reductions in minute ventilation, which would act to limit the dose of O₃ delivered to the lungs. These effects are concurrent with changes in HR which lead to: (1) decreased CO, (2) lowered BP, (3) decreased tissue perfusion, all of which may lead to functional deficits. The hypothermic response has not been observed in humans, except at very high O₃ exposures.

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AX5. ANNEX TO CHAPTER 5 OF OZONE AQCD

Table AX5-1. Cellular Targets of Ozone Interaction

Concentration ppm	Duration	Species	Effects	Reference
0.22	4 h with exercise	Rat, male, SD, 90 days old, 300-330 g, n = 6/group	Demonstrated the ozonation of PUFA to form nonanal and hexanal in rat BALF. Increases in nonanal not accompanied by significant changes in lung function, epithelial permeability, or airway inflammation. Hexanal levels did not increase significantly. Levels of both aldehydes returned to baseline by 18 h PE.	Frampton et al. (1999)
0.5-10 both with and without 5% CO ₂	1 h	Rat, male, SD, 90 days old, 300-330 g, n = 6-14/group	O ₃ plus CO ₂ increased the V _T and the yield of aldehydes with a maximal aldehyde yield at 2.5 ppm for 1 h. 0.5 ppm O ₃ with 5% CO ₂ , levels of hexanal and nonanal increased at 30 min, decreased slightly from that level at 60 min, was maximal at 90 min and then dropped to 60 min levels at 120 min. Levels of heptanal did not change appreciably during this time course. Suggests that levels of these aldehydes were dependent on a dynamic relationship between their production and the disappearance from the ELF.	Pryor et al. (1996)
0.25-1.0	30-60 min	Rat, male, SD, 250-275 g, n = 3-5/group 3 model systems: isolated epithelial lining fluid, intact lung, and liposome suspensions	PUFAs directly react with O ₃ . The amount of bioactive lipids produced is inversely related to AA availability.	Postlethwait et al. (1998)
0.3-1.1	Chemical systems: 15-10 min. Cell: 1-2 h	Interfacial films (dipalmitoylglycero-3-phosphocholine (DPPC)); Rat, SD BALF; human lung fibroblast cell line	DPPC films: reduced O ₃ reactive absorption by antioxidants. Human lung fibroblast cell line: AA produced cell injury; high levels of O ₃ and AA were needed to induce cell injury; the DPPC films reduced the amount of cell injury. Suggests that O ₃ reactions with ELF substrates cause cell injury; that films of active, saturated phospholipids reduce the local dose of O ₃ -derived reaction products; and that these interfacial phospholipids modulate the distribution of inhaled O ₃ and the extent of site-specific cell injury.	Connor et al. (2004)
0.4	1 h with exercise	Human AM	Ozone exposure caused apoptosis, an increase in a 32-kDa protein adduct, and an increase in ferritin and a 72-kDa heat shock protein. Exposure of AM to HNE replicated these effects suggesting that creation of protein adducts and apoptotic cell death are cellular toxic effects of acute O ₃ exposure and that they are mediated, at least in part by HNE.	Hamilton et al. (1998)

Table AX5-2. Effects of Ozone on Lung Monooxygenases

Concentration ppm	Duration	Species	Effects	Reference
1.0	8 h	Rat, male, SD, 350-600 g, n = 3-6/group	Increases CYP2E1 activity in lobar-bronchi and major daughter airway with 8 h exposure. Decreased CYP2E1 activities in both major and minor daughter airways with 90-day exposure. O ₃ does not result in consistent dramatic alterations in CYP2E1 activities.	Watt et al. (1998)
0.8	8 h/day for 90 days	Rat, male, SD, 275-300 g	CYP2B activity increased. Linked to Clara cells in distal lung only—not in trachea or proximal airway.	Paige et al. (2000a)
1	2 h	Mice, male, 2-3 months old, Clara Cell Secretory Protein deficient, WT strain 129 n = 3/group	CCSP ^{-/-} mice had increases in IL-6 and MT mRNA that preceded decreases in Clara cell CYP2F2 mRNA. WT mice had levels change, but to a lesser degree.	Mango et al. (1998)
NA		Rat, male, SD, adult monkey, Rhesus, 0.75 to 9.7 years old	Microdissection for regiospecific and species-specific differences in isoforms of CYPs. Rat parenchyma: both CYP1A1 and CYP2B were highest. Rat airways: CYP2E1 was highest. Rat airways and parenchyma: P450 reductase activities were high, and conversely, low in trachea. Monkeys: did not exhibit site-selective differences in CYP2B1, CYP1A1, or P450 reductase; however, they had high CYP2E1 activity in parenchyma and distal bronchioles.	Lee et al. (1998)

CYP = Cytochrome P450
 WT = wild-type
 MT = metallothionein
 CCSP = Clara Cell Secretory Protein

Table AX5-3. Antioxidants, Antioxidant Metabolism, and Mitochondrial Oxygen Consumption

Concentration ppm	Duration	Species	Effects	Reference
1.0	6 h/day, 5 days/week for 2 or 3 months	Rat, male Fischer F344, 30-32 days old, n = 4	Immunohistochemistry and immunogold labeling studies. In epithelial cells in airways and parenchyma: reduced Cu-Zn SOD labeling with O ₃ -exposure. In the CAR regions, in both AMs and Type II epithelial cells: significantly increased levels of Mn SOD. Mn SOD levels were not increased in Type I epithelial cells, fibroblasts, or Clara cells. Suggests that the increased levels of Mn SOD in Type II cells in the proximal alveolar duct confer tolerance and protection from further O ₃ -induced injury.	Weller et al. (1997)
0.2	6 h	Dog, male, mongrel, ~9 kg, n = 6/group	Blocking antioxidant transport with probenecid caused heterogeneously distributed increases in peripheral airway resistance and reactivity. Probenecid inhibited O ₃ -induced neutrophilic inflammation, which is evidence of a dissociation between airway function and inflammation. Probenecid caused a 50-60% decrease in plasma urate, a decrease in ascorbate, and a decrease in BALF protein. Suggests probenecid has either a direct or indirect effect on either cytokine or leukotriene transport.	Freed et al. (1999)
0, 0.1, 0.25, 0.5, 1.0 or 1.5	30-720 min	Model of continually mixed, interfacial exposure	Modeled the interactions of O ₃ with three ELF antioxidants, AA, UA and GSH. Ranking of reactivity with O ₃ was UA > AA > GSH. Antioxidants caused no changes in sample pH and protein carbonyl formations. Consumption of the antioxidants occurred in a linear fashion with time and a positive relationship to O ₃ concentration. Suggests that GSH is not an important substrate for O ₃ ; UA appeared to be the most important substrate.	Mudway and Kelly (1998)

AX5-4

Cu = Copper

Zn = Zinc

Mn = Manganese

SOD = Superoxide Dismutase

AM = Alveolar Macrophage

BALF = Bronchoalveolar Lavage Fluid

AA = Ascorbic Acid

UA = Uric Acid

GSH = Reduced Glutathione

Table AX5-4. Lipid Metabolism and Content of the Lung

Concentration ppm	Duration	Species/Cell Line	Effects	Reference
NA	60 min	Cultured human epithelial cells (BEAS-2B)	Incubation with 10 μ M lipid oxidation products caused significant release of arachidonic acid. Suggests that lipid oxidation products cause activation of specific lipases, which then trigger the activation of second messenger pathways (e.g., phospholipase A ₂ or phospholipase C).	Pryor et al. (1995)
NA		Cultured human bronchial epithelial cells (NHBE) and BEAS-2B cells	Incubation with lipid ozonation product 1-palmitoyl-2-(9-oxononanoyl)-sn-glycero-3-phosphocholine (PC-ALF) and 1-hydroxy-1-hydroperoxynonane (HHP-C9). PC-ALF elicited release of (PAF) and prostaglandin E2, but not IL-6. HHP-C9 caused release of PAF and IL-6 in these cells, but not prostaglandin E2. Suggests that O ₃ -induced production of lipid ozonation products causes release of proinflammatory mediators that then generate an early inflammatory response.	Kafoury et al. (1999)
0.06, 0.125, and 0.25 ppm	2 to 48 h	Lung (calf surfactant)	Dose- and time-dependent increase in the formation of 1-palmitoyl-2-(9'-oxo-nonanoyl)-glycerophosphocholine (16:0a/9-al-GPCho), an oxidized phospholipid, which possessed biological activity in three assays. The 16:0a/9-al-GPCho: (1) decreased macrophage viability by necrosis at 6 μ M, (2) induced apoptosis in pulmonary epithelial-like A549 cells at 100-200 μ M, and (3) elicited release of IL-8 from A549 cells at 50-100 μ M.	Uhlson et al. (2002)
0.8	30 min	Human red blood cell (RBC) model	Human RBCs intermittently covered by an aqueous film consisting of rat BALF or BALF plus added reagents that included AA, UA, GSH, Trolox (a vitamin E analog), SOD, catalase, desferrioxamine, deithylenetriaminepentaacetic acid, mannitol or BSA. Oxidation of lipids in BALF or on membranes was assayed by measuring TBARS accumulation and loss of acetylcholinesterase activity. AA and GSH induced dose-dependent oxidative damage to the cell membrane proteins and lipids via secondary oxidant formation. Conclusion: early in O ₃ exposure, ELF antioxidants are high enough to drive reactive absorption of O ₃ into the ELF and to concurrently quench secondary reaction products, thus limiting cell injury. With continued exposure, O ₃ flux would decrease, cellular injury would increase due to depleted antioxidants levels. They hypothesize that especially in areas where O ₃ deposition is high, unreacted O ₃ and cytotoxic products can diffuse to the cell membranes, causing injury.	Ballinger et al. (2005)

Table AX5-4 (cont'd). Lipid Metabolism and Content of the Lung

Concentration ppm	Duration	Species/Cell Line	Effects	Reference
2.0	4 h	Rat BALF exposed to O ₃ in vitro.	The major reaction products identified were 5-hydroperoxy- <i>B</i> -homo-6-oxa-cholestan-3,7a-diol, 5β,6β-epoxycholesterol, and 3β-hydroxy-5oxo-5,6-seco-cholestan-6-al.	Pulfer and Murphy (2004)
0.2, 0.5, or 1.0	1 h	Cultured human bronchial epithelial cells (16-HBE)	Extracted lipid reaction products either immediately or 24 h PE. Higher levels of 5β,6β-epoxycholesterol were recovered in the extract immediately PE. Both 5β,6β-epoxycholesterol and its most abundant metabolite, cholestan-6-oxo-3β,5α-diol, were cytotoxic to 16-HBE cells at physiologically relevant concentrations. Both reaction products were also shown to be potent inhibitors of cholesterol synthesis.	
0.5, 1.0, 2.0, or 3.0	3 h	Mice, C57BL/6J, 8-12 weeks old female. n = 4	In BALF, lavaged cells, and whole lung homogenate there was a dose-dependent increase in formation cholestan-6-oxo-3β,5α-diol at exposure levels of 0.5, 1.0 and 2.0 ppm O ₃ , respectively. In BALF and lavaged cells O ₃ induced increases in 5β,6β-epoxycholesterol at exposure levels of 0.5 and 1.0, respectively.	Pulfer et al. (2005)

PAF = Platelet-Activating Factor

RBC= Red Blood Cell

AA = Ascorbic Acid

GSH = Reduced Glutathione

IL-6 = Interleukin-6

IL-8 = Interleukin-8

ELF = Epithelial Lining Fluid

BALF = Bronchoalveolar Lavage Fluid

BSA = Bovine Serum Albumin

TBARS = thiobarbituric acid

UA = Uric Acid

Table AX5-5. Effects of Ozone on Protein Synthesis

Concentration ppm	Duration	Species	Effects	Reference
0.4	1,3,7,28, or 56 days	Rat, male, Wistar, 200 g, n = 5/group	Centriacinar thickening of septa after 7 days of exposure, which progressed at 28 and 56 days of exposure. After 28 days of O ₃ , the increase in collagen content in ductular septa was apparent and it increased progressively until the 56-day time point. Collagen content decreased with PE recovery, the structural fibrotic changes in ductular septa did not return to control levels. Respiratory bronchioles were present at an increasing degree, which persisted after an 80-d recovery period. Suggests that subchronic O ₃ exposures in rats creates a progression of structural lung injury that can evolve into a more chronic form, which included fibrosis.	van Bree et al. (2001)

Table AX5-6. Effects of Ozone on Differential Gene Expression

Concentration ppm	Duration	Species	Effects	Reference
1	8 h for three consecutive nights	Mice, C57BL/6, 20-25 g, n = 5-6/group	Ozone exposure induced changes in expression of 260 genes (80% repressed and 20% induced). Cell cycle genes upregulated: S-adenosyl methionine decarboxylase 3, ribonucleotide reductase, and clusterin. NF-κB-induced genes upregulated: serum amyloid protein, topoisomerase IIα, monocyte chemoattractant protein, platelet-derived growth factor, and inhibitor of apoptosis. Downregulation of transcripts for isoforms of myosins and actins. CYP family genes downregulated: 2a4, and 2e1, and 2f2, as were aryl-hydrocarbon receptor and several glutathione transferases. Metallothionein 1 and 2 and lactotransferrin upregulated. Major histocompatibility complex genes and lymphocyte specific proteins downregulated.	Gohil et al. (2003)

Table AX5-7. Effects of Ozone on Lung Host Defenses

Concentration ppm	Duration	Species	Effects	Reference
Microbiologic Endpoints				
0.1, 0.3	4 h/day, 5 days/week, 1 or 3 weeks	Rat, male, Fischer F344, 200-250 g	No effect on cumulative mortality from subsequent lung infection with $4-8 \times 10^6$ <i>Listeria monocytogenes</i> , but concentration-related effects on morbidity onset and persistence. One-week exposed rats: listeric burdens trended higher than in controls; 0.3 ppm rats displayed continual burden increases and no onset of resolution; in situ IL-1 α , TNF- α , and IFN- γ levels 48 and 96 h post-infection (4×10^6 level) higher than controls. Three-week exposed rats: no O ₃ -related change in bacterial clearance; IL-1 α , TNF- α , and IFN- γ levels higher than control only at 48 h post-infection (4×10^6) and only with 0.3 ppm rats.	Cohen et al. (2001, 2002)
0.8	3 h	Rat, male, Fischer F344, 8 weeks old, n = 4-10/group	Single exposure to <i>S. zooepidemicus</i> led to differential clearance patterns in exposed rats maintained on <i>ad libitum</i> or O ₃ -mitigating calorie-restricted diets.	Dong et al. (1998)
Clearance Endpoints (Non-Microbial)				
0.01 -1.0	10 min	Rat, SD	Single 10 min exposure of tracheal explants, followed by 1 h incubation with particles, led to dose-related increases in uptake of amosite asbestos and titanium dioxide particles. Effect inhibited by added catalase or desferoxamine, but not by superoxide dismutase.	Churg et al. (1996)
0.4	6 h	Dog, male, mixed breed, 1-3 years old, n = 7/group	Increased tracheal permeability to ^{99m} Tc-DTPA after direct sublobar exposure to O ₃ . Clearance halftimes remained significantly lower for 1-7 days PE, but recovered by 14 days PE.	Foster and Freed (1999)
Alveolar Macrophage Endpoints (General)				
0.8	3 h	Rat, male, SD, 250-275 g, n = 5-6/group	Increased ex vivo AM adherence to epithelial cultures mitigated by cell pretreatment with anti-CD11b or anti-ICAM-1 antibodies.	Bhalla (1996)
0.8	3 h	Rat, male, SD, 250-300 g, n = 5/group	Increased ex vivo AM adherence to epithelial cell cultures mitigated by cell pretreatment with anti-TNF- α /IL-1 α antibodies.	Pearson and Bhalla (1997)
1.0	4 h	Mice cell line (WEHI-3)	Increased intracellular calcium resting levels in WEHI-3 cells. Decreased rates of calcium influx due to digitonin.	Cohen et al. (1996)

Table AX5-7 (cont'd). Effects of Ozone on Lung Host Defenses

Concentration ppm	Duration	Species	Effects	Reference
Alveolar Macrophage Endpoints (Functional)				
0.1, 0.3	4 h/day, 5 days/week, 1 or 3 weeks	Rat, male, Fischer F344, 200-250 g	Superoxide anion: increased AM production (1 week; 0.1, 0.3 ppm); no intergroup differences noted after IFN- γ stimulation. H ₂ O ₂ : reduced production (1 week; 0.1, 0.3 ppm); further reduced production after treatment with IFN- γ (0.1, 0.3 ppm, 1 and 3 weeks).	Cohen et al. (2001)
0.1, 0.3	4 h/day, 5 days/week, 1 or 3 weeks	Rat, male, Fischer F344, 200-250 g	Increased AM superoxide anion production (1 week; 0.1, 0.3 ppm), Lower H ₂ O ₂ production (1 week; 0.1, 0.3 ppm). Reduced production after treatment with IFN- γ - superoxide (0.3 ppm, 1 week) and H ₂ O ₂ (0.1 ppm, 1 week) - relative to cells without IFN- γ treatment. No effects from 3-week exposures.	Cohen et al. (2002)
0.3	5 h/day, 5 days/week, 4 weeks	Rat, male, Fischer F344, 200-250 g, n = 10/group	No effect on AM endotoxin-stimulated IL-1 α , IL-6, or TNF- α production. Decrease in stimulated, but not spontaneous, superoxide formation; variable effects on H ₂ O ₂ formation. No effect on AM spontaneous, endotoxin-, or IFN- γ -stimulated, NO formation.	Cohen et al. (1998)
0.8	3 h	Rat, male, SD, 250- 275 g, n = 5-6/group	Increased AM motility in response to chemotaxin; effect mitigated by cell pretreatment with anti-CD11b or anti-ICAM-1 antibodies.	Bhalla (1996)
0.8	3 h	Rat, male, Fischer F344, 8 weeks old, n = 4-10/group	Decrease in AM phagocytic activity.	Dong et al. (1998)
0.8	3 h	Mice, female, (B6J129SV) (C57BL/6X 129 NOS ^{-/-}), 8-16 weeks old, n = 3-12/group	Increased AM spontaneous and IFN- γ + LPS-induced NOS expression and NO production and PGE ₂ release. Initial decrease in ROI production, with eventual rebound. Knockout (NOS ^{-/-}) mice AM incapable of similar response to O ₃ – no inducible NO or PGE ₂ above control levels and consistent decreased ROI production.	Fakhrzadeh et al. (2002)
1.0	24 h/day, 3 days	Rat, male, Wistar, 8-12 weeks,	BALF from exposed rats subsequently inhibited IFN- γ -induced AM NO production.	Koike et al. (1998, 1999)

Table AX5-7 (cont'd). Effects of Ozone on Lung Host Defenses

Concentration ppm	Duration	Species	Effects	Reference
Cytokines, Chemokines: Production, Binding, and Inducible Endpoints				
0.1, 0.3	4 h/day, 5 days/week, 1 or 3 weeks	Rat, male, Fischer F344, 200-250 g,	Superoxide anion: no intergroup differences noted after IFN- γ stimulation. H ₂ O ₂ : reduced production after treatment with IFN- γ .	Cohen et al. (2001)
0.1, 0.3	4 h/day, 5 days/week, 1 or 3 weeks	Rat, male, Fischer F344, 200-250 g, n = 3-5/group	Decreased expression of CD3 among lung lymphocytes (0.1 ppm only; 3 weeks); effect exacerbated by stimulation with IFN- α (but not with IL-1 α). Decreased expression of CD25 (IL-2R) on CD3 ⁺ lymphocytes (0.3 ppm only; 3 weeks); effect worsened by treatment with IL-1 α (0.1, 0.3 ppm; 3 weeks). No effects on IL-2-inducible lympho-proliferation. Reduced AM production of ROIs after treatment with IFN- γ ; superoxide anion (0.3 ppm, 1 week) and H ₂ O ₂ (0.1 ppm, 1 week) - relative to untreated cells.	Cohen et al. (2002)
0.3	5 h/day, 5 days/week, 4 weeks	Rat, male, Fischer F344, 200-250 g, n = 10/group	No effect on AM endotoxin-stimulated IL-1 α , IL-6, or TNF- α production.	Cohen et al. (1998)
0.3 1.0 2.5	24 or 96 h 1, 2, or 4 h, or 24 h	Mice, male, C57BL/6J, adult, n = 3/group	0.3 ppm: Increased lung: MIP-2, MCP-1, and eotaxin mRNA expression. 1.0 ppm: After 4 h, increased lung: MIP-2, MCP-1, eotaxin, and IL-6 mRNA expression. 2.5 ppm: After 2 h, increased lung: MIP-2, MCP-1, eotaxin, and IL-6 mRNA expression. No exposure-related increases in lung IL-1 α , IL-1 β , IL-1R α , IL-10, IL-12, or IFN- γ mRNA expression.	Johnston et al. (1999a)
1.0	4 h	Mice cell line (WEHI-3)	Decreased binding of IFN- γ by WEHI-3 cells. Decreased superoxide anion production by IFN- γ -treated cells; no similar effect on H ₂ O ₂ production. Decreased IFN- γ -stimulated phagocytic activity. No effect on IFN- γ -inducible Ia (MHC Class II) antigen expression.	Cohen et al. (1996)
1.0	6 h	Rat, male, SD, 200-250 g, n = 3-6/group	Increased AM MIP-1 α , CINC, TNF- α , and IL-1 β mRNA expression. Induced increase in MIP-1 α and CINC mRNA temporally inhibited by cell treatment with anti-TNF- α /IL-1 β antibodies.	Ishii et al. (1997)

AX5-10

Table AX5-7 (cont'd). Effects of Ozone on Lung Host Defenses

Concentration ppm	Duration	Species	Effects	Reference
Cytokines, Chemokines: Production, Binding, and Inducible Endpoints (cont'd)				
1.0	24 h/day, 3 days	Rat, male, Wistar, 8-12 weeks old	BALF from exposed rats subsequently inhibited: ConA-stimulated lymphocyte IFN- γ production, but had no effect on IL-2 production; IL-2-induced lymphoproliferation; and, IFN- γ -induced AM NO production.	Koike et al. (1998, 1999)
1.0	24 h	Mice, male, C57BL/6J, 8 weeks old, n = 3/group	Increased lung: MIP-2 (4 h PE) and MCP-1 (4 and 24 h PE) mRNA expression.	Johnston et al. (2001)
1.0	24 h	Mice, male, C57BL/6J, 8 weeks old, n = 3/group	Increased lung MIP-2 and MCP-1 mRNA expression (4 and 24 h PE); no effects on mRNA levels of IL-1 α , IL-1 β , IL-1R α , IL-6, MIF, MIP-1 α , MIP-1 β , eotaxin, or RANTES at either time point in recovery period. Enhanced expressions of some cytokines/chemokines were maintained longer than normal by coexposure to endotoxin.	Johnston et al. (2002)
1.0	8 h/day, 3 days	Mice (C57BL/6) (C57BL/6Ai NOS ^{-/-}) n = 3-10/group	Knockout (NOS ^{-/-}) mice have more lavageable MIP-2 after exposure than wild-type; both greater than control.	Kenyon et al. (2002)
1.0, 2.5	4 or 24 h	Mice, male, C57BL/6J, adult, n = 3/group	Dose-related increases in cytokine/chemokine induction. Increased lung MIP-1 α , MIP-2, eotaxin (4 and 24 h), IL-6 (4 h only), and iNOS mRNA expression.	Johnston et al. (2000a)
0.6, 2.0	3 h	Mice, C57BL/6, Rat, Wistar, 14-16 weeks old, n = 4-6/group	Increased lung MIP-2 (4 h PE) and MCP-1 mRNA expression (24 h PE); PMN and monocyte increased accumulation in lungs consistent with sequential expression of the chemokines. NF-kB activation also increased 20-24 h PE.	Zhao et al. (1998)
0.8	3 h	Rat, male, SD, 250-300 g, n = 5/group	Increased ex vivo AM adherence to epithelial cells mitigated by cell treatment with anti-TNF- α or IL-1 α antibodies.	Pearson and Bhalla (1997)
0.8	3 h	Mice, female, B6J129SV, C57BL/6X 129 NOS ^{-/-} , 8-16 weeks, n = 3-12/group	Increased AM IFN- γ + LPS-induced NOS expression and NO production, as well as induced PGE ₂ release. Knockout (NOS ^{-/-}) mice AM incapable of similar response to O ₃ - no inducible NO or PGE ₂ above control levels.	Fakhrzadeh et al. (2002)

Table AX5-7 (cont'd). Effects of Ozone on Lung Host Defenses

Concentration ppm	Duration	Species	Effects	Reference
Cytokines, Chemokines: Production, Binding, and Inducible Endpoints (cont'd)				
0.8	3 h	Mice, female, B6J129SV, C57BL/6X 129 NOS ^{-/-} , 8-16 weeks, n = 3-4/group	Increased AM IFN- γ + LPS-induced NOS expression and NO production.	Laskin et al. (2002)
2.0	3 h	Rat, female, SD, 200-225 g, n = 4-6/group	Increased AM spontaneous and IFN- γ + LPS-induced NOS expression and NO production. AM from exposed rats showed rapid onset/prolonged activation of NF- κ B.	Laskin et al. (1998a)
0.08-0.25 and 1% OVA	4 h, 3 times/week, 4 weeks	Mice, female, BALB/c, C57BL/6, 6-8 weeks old, n = 4-12/group	O ₃ - dose-dependent increases in IgE, IL-4, IL-5; recruitment of eosinophils and lymphocytes in BALB/c; O ₃ + OVA - increased IgG, antibody titers, leukotrienes, airway responsiveness, immediate cutaneous hypersensitivity reactions in BALB/c. In C57BL/6 only O ₃ + OVA caused cutaneous hypersensitivity and altered IgG responses.	Neuhaus-Steinmetz et al. (2000)
Alveolar Macrophage/Lung NO- and iNOS-Related Endpoints				
0.3	5 h/day, 5days/week, 4 weeks	Rat, male, Fischer F344, 200-250 g, n = 10/group	No effect on AM spontaneous, endotoxin-, or IFN- γ -stimulated, NO formation.	Cohen et al. (1998)
0.8	3 h	Mice, female, B6J129SV, C57BL/6X 129 NOS ^{-/-} , 8-16 weeks, n = 3-12/group	Increased AM IFN- γ + LPS-induced NOS expression and NO production and PGE ₂ release. Knockout (NOS ^{-/-}) mice AM incapable of similar response to O ₃ - no inducible NO or PGE ₂ above control levels.	Fakhrzadeh et al. (2002)
0.8	3 h	Mice, female, B6J129SV, C57BL/6X 129 NOS ^{-/-} , 8-16 weeks, n = 3-4/group	Increased AM spontaneous and IFN- γ + LPS-induced NOS expression and NO production. AM from exposed mice showed rapid and prolonged activation of NF- κ B, STAT-1 (expression, activity), phosphoinositide 3-kinase, and protein kinase B.	Laskin et al. (2002)

Table AX5-7 (cont'd). Effects of Ozone on Lung Host Defenses

Concentration ppm	Duration	Species	Effects	Reference
Alveolar Macrophage/Lung NO- and iNOS-Related Endpoints (cont'd)				
1.0	8 h/day, 3 days	Mice, C57BL/6, C57BL/6Ai ⁻ NOS ^{-/-} , n = 3-10/group	Knockout (NOS ^{-/-}) mice have more lavageable PMN, MIP-2, and protein in lungs after exposure than wild-type.	Kenyon et al. (2002)
1.0	24 h/day, 3 days	Rat, male, Wistar, 8-12 weeks, n = 2/group	BALF from exposed rats subsequently inhibited IFN- γ -induced AM NO production.	Koike et al. (1998, 1999)
1.0, 2.5	4 or 24 h	Mice, male, C57BL/6J, adult, n = 3/group	Dose-related increase in lung iNOS mRNA expression.	Johnston et al. (2000a)
2.0	3 h	Rat, female, SD, 200-250 g, n = 1-3/group	Increased AM spontaneous, IFN- γ , and LPS-induced NO production, as well as spontaneous and LPS-induced NOS expression. Effect somewhat ameliorated by pretreatment with bacterial endotoxin.	Pendino et al. (1996)
2.0	3 h	Rat, female, SD, 200-225 g, n = 3-6/group	Increased AM spontaneous and IFN- γ + LPS-induced NOS expression and NO production. AM from exposed rats showed rapid onset/prolonged activation of NF- κ B.	Laskin et al. (1998b)
3.0	6 h	Rat, female, Brown Norway, 250-300 g, n = 4-8/group	Increased lung iNOS mRNA expression. Effect blocked by pretreatment with dexamethasone.	Haddad et al. (1995)
0.12, 0.5, or 2	3 h	Mice, female, BALB/c, 5-6 weeks	Dose-dependent increases in nitrate and P _{enh} ; increases in nNOS, but not iNOS or eNOS.	Jang et al. (2002)
Surface Marker-Related Endpoints				
0.8	3 h	Rat, male, SD, 250-275 g, n = 5-6/group	Increased expression of AM CD11b, but no effect on ICAM-1.	Bhalla (1996)
1.0	4 h	Mice cell line (WEHI-3)	No effect on IFN- γ -inducible Ia (MHC Class II) antigen expression on WEHI-3 cells.	Cohen et al. (1996)
1.0	2 h	Rat, female, SD, 170-210 g, n = 8-12/group	Decreased expression of integrins CD18 on AM and CD11b on PMN. No effect on PMN CD62L selection.	Hoffer et al. (1999)

Table AX5-7 (cont'd). Effects of Ozone on Lung Host Defenses

Concentration ppm	Duration	Species	Effects	Reference
Surface Marker-Related Endpoints (cont'd)				
1.0	3 days	Rat, male, Wistar and Fischer F344, 8-10 weeks, n = 3/group	Increased expression of surface markers associated with antigen presentation: Ia (MHC Class II) antigen, B7.1, B7.2, and CD11b/c on BAL cells. Effect attributed to influx of monocytes.	Koike et al. (2001)
0.1, 0.3	4 h/day, 5 days/week, 1 or 3 weeks	Rat, male, Fischer F344, 200-250 g	Decreased expression of CD3 among lung lymphocytes (0.1 ppm only; 3 weeks); effect exacerbated by stimulation of cells with IFN- α (but not with IL-1 α). Decreased expression of CD25 (IL-2R) on CD3 ⁺ lymphocytes (0.3 ppm only; 3 weeks); effect worsened by treatment of cells with IL-1 α (0.1 and 0.3 ppm; 3 weeks).	Cohen et al. (2002)
NK- and Lymphocyte-Related Endpoints				
0.1, 0.3	4 h/day, 5 days/week, 1 or 3 weeks	Rat, male, Fischer F344, 200-250 g	Decreased expression of CD3 among lung lymphocytes (0.1 ppm only; 3 weeks); effect exacerbated by stimulation of cells with IFN- α (but not with IL-1 α). Decreased expression of CD25 (IL-2R) on CD3 ⁺ lymphocytes (0.3 ppm only; 3 weeks); effect worsened by treatment of cells with IL-1 α (0.1 and 0.3 ppm; 3 weeks). Lymphoproliferation: no effect on spontaneous or IL-2-inducible forms; 0.1 ppm increased response to ConA mitogen (1 week only); 0.3 ppm - decreased response to ConA (1 week only).	Cohen et al. (2002)
0.4, 0.8, 1.6	12 h	Mice, male, BALB/c, 6-8 weeks old, n = 5-8/group	Decreased pulmonary delayed-type hypersensitivity reactions to low MW agents, likely via activation of T _H 2-dependent pathways.	Garssen et al. (1997)
1.0	24 h/day, 3 days	Rat, male, Wistar, 8-12 weeks old	Lavage fluid from exposed rats subsequently inhibited ConA-stimulated lymphocyte IFN- γ production, but had no effect on IL-2 production; material also inhibited IL-2-induced lymphoproliferation.	Koike et al. (1999)

Table AX5-7 (cont'd). Effects of Ozone on Lung Host Defenses

Concentration ppm	Duration	Species	Effects	Reference
Susceptibility Factors				
0.3	24 to 72 h	Mice C57BL/6J C3H/HeJ C3H/HeOuJ, 6-8 weeks old, n = 4-8/group	Lavageable protein concentration lowered by inhibition of iNOS and by targeted disruption of <i>Nos2</i> ; reduced <i>Nos2</i> and <i>Tlr4</i> mRNA levels in the O ₃ -resistant C3H/HeJ mice.	Kleeberger et al. (2001b)
1	4 h	CHO-K1 cell line SP-A	Differences exist biochemically and functionally in SP-A variants. O ₃ exposure affects the ability of variants to stimulate TNF- α and IL-8.	Wang et al. (2002)
0.3	24-72 h	Mice, male, C57BL/6J, C3H/HeJ, C3H/HeOuJ, 6-8 weeks old, n = 5-16/group	Identified a candidate gene on chromosome 4, Toll-like receptor 4 (<i>Tlr4</i>), a gene implicated in endotoxin susceptibility and innate immunity. O ₃ -resistant strain C3H/HeJ and C3H/HeOuJ (differing from the O ₃ -resistant strain by a polymorphism in the coding region of <i>Tlr4</i>) were exposed, greater protein concentrations were demonstrated in the OuJ strain. Differential expression of <i>Tlr4</i> mRNA with O ₃ exposure. Suggests quantitative trait locus on chromosome 4 is responsible for a significant portion of the genetic variance in O ₃ -induced lung hyperpermeability; potential interaction between the innate and acquired immune system.	Kleeberger et al. (2000)
0.1	2 h	Mice, male, C57BL/6, 6-8 weeks old	Sensitized the mice to OVA by intratracheal instillation of OVA-pulsed dendritic cells (the principal antigen-presenting cells in airways). Created Th2 lymphocyte-dependent eosinophilic airway inflammation. Groups of mice exposed to O ₃ during sensitization by OVA-pulsed dendritic cells showed no modification of the allergic sensitization process, whereas, previously sensitized mice exposed to O ₃ , demonstrated increases in allergen-induced airway inflammation. Suggests that dendritic cells are an important component of O ₃ -induced eosinophilic airway inflammation.	Depuydt et al. (2002)

Table AX5-7 (cont'd). Effects of Ozone on Lung Host Defenses

Concentration ppm	Duration	Species	Effects	Reference
Susceptibility Factors (cont'd)				
0.1, 0.5, and 1.0	2 h	Human lymphocytes	Subsequent to O ₃ exposure, when lymphocytes were stimulated with pokeweed mitogen (PWM, a T-cell-dependent stimulus) or <i>Staphylococcus aureus</i> Cowan 1 strain (SAC, a T-cell-independent stimulus), both B and T cells were found to be affected by O ₃ preexposure. T cells also demonstrated an increase in IL-6 and a decrease in IL-2, suggesting that O ₃ may have direct effects on IgG-producing cells and concurrently an effect that is mediated by altered production of T cell immunoregulatory molecules.	Becker et al. (1991)
NA		Rat BALF; Murine macrophage cell line (RAW 264.7)	Both SP-A and SP-D directly protected surfactant phospholipids and macrophages from oxidative damage. Both proteins blocked accumulation of TBARS and conjugated dienes generated during oxidation of surfactant lipids or low density lipoprotein particles by a mechanism that does not involve metal chelation or oxidative modification of the proteins.	Bridges et al. (2000)

AM = Alveolar macrophage; PE = Postexposure (i.e., time after O₃ exposure ceased); MIP = macrophage inflammatory protein; PMN = Polymorphonuclear leukocyte; MLN = Mediastinal lymph node; CINC = cytokine-induced neutrophil chemoattractant; BAL = Bronchoalveolar lavage; DTPA = diethylenetriaminepentaacetic acid; ROI = reactive oxygen intermediate/superoxide anion; IFN = Interferon; BALT = Bronchus-associated lymphoid tissue; MCP = monocyte chemoattractant protein; CON A = Concanavalin A; OVA = Ovalbumin; SP-A = Surfactant Protein A; SP-D = Surfactant Protein D

Table AX5-8. Effects of Ozone on Lung Permeability and Inflammation

Concentration ppm	Duration	Species	Effects	Reference
0.1 0.2 0.5	0.5 h, in vitro	Rat, SD, primary alveolar Type II cells	Decreased transepithelial resistance (R_t) after 0.5 ppm from 2 to 24 h PE and at 48 h in monolayers subjected to PMNs. Significantly lower R_t after PMN treatment at 0.2 and 0.5 ppm.	Cheek et al. (1995)
0.1 0.2 0.4 1.0	1 h, in vitro	Guinea pig, male and female, Hartley, and human alveolar macrophages	Exposure of guinea pig alveolar macrophages to 0.4 ppm for 60 min produced a significant increase in IL-6 and TNF- α , and an exposure of human alveolar macrophages to identical O ₃ concentration increased TNF- α , IL-1 β , IL-6 and IL-8 protein and mRNA expression.	Arsalane et al. (1995)
0.2 0.4 0.8	23 h/day for 1 week	Guinea pigs, female (Hartley), 260-330 g n = 4-10/group	Increase in BALF protein and albumin immediately after 0.8 ppm exposure, with no effect of ascorbate deficiency in diet. O ₃ -induced increase in BALF PMN number was only slightly augmented by ascorbate deficiency.	Kodavanti et al. (1995)
0.26	8 h/day, 5 days/week for 1-90 days	Mice, male (mast cell-deficient and -sufficient), 6-8 weeks old n = 4-8/group	Greater increases in lavageable macrophages, epithelial cells and PMNs in mast cell -sufficient and mast cell-deficient mice repleted of mast cells than in mast cell-deficient mice. O ₃ -induced permeability increase was not different in genotypic groups.	Kleeberger et al. (2001b)
0.3	48 h and 72 h. Exposures repeated after 14 days	Mice, male, C57BL/6J and C3H/HeJ, 6-8 weeks old	Greater BALF protein, inflammatory cell and LDH response in C57BL/6J than in C3H/HeJ after initial exposure. Repeated exposure caused a smaller increase in BALF protein and number of macrophages, lymphocytes and epithelial cells in both strains, but PMN number was greater in both strains of mice compared to initial exposure.	Paquette et al. (1994)
0.1 0.3 1.0	60 min	Rat basophilic leukemia cell line (RBL-2H3)	O ₃ inhibited IgE- and A23187 - induced degranulation. Spontaneous release of serotonin and modest generation of PGD ₂ occurred only under conditions that caused cytotoxicity.	Peden and Dailey (1995)
0.3 2.0	72 h 3 h	Mice, male and female, C57BL/6J and C3H/HeJ	Greater PMN response in C57BL/6J than in C3H/HeJ after acute and subacute exposures. Responses of recombinant mice were discordant and suggested two distinct genes controlling acute and subacute responses. Genes termed Inf-1 and Inf-2.	Tankersley and Kleeberger, (1994)
0.3	48 h	Mice, C57BL/6J and C3H/HeJ, 6-8 weeks old	Susceptibility to O ₃ is linked to a quantitative trait locus, and TNF- α is identified as a candidate gene.	Kleeberger et al. (1997)

Table AX5-8 (cont'd). Effects of Ozone on Lung Permeability and Inflammation

Concentration ppm	Duration	Species	Effects	Reference
0.3	24 or 48 h	Mice, male, C57BL/6J, 8 weeks old n = 3/group	0.3 ppm for 24 h caused increase in mRNA for eotaxin, MIP-1a and MIP-2.	Johnston et al. (1999a)
1.0	1, 2 or 4 h		1 ppm for 4 h caused increase in mRNA for eotaxin, MIP-1a, MIP-2, and IL-6.	
2.5	2, 4 or 24 h		2.5 ppm for 2 and 4 h caused increase in mRNA for MIP-1a, MIP-2 and IL-6 and metallothionein. Greater increases and lethality after 24 h.	
0.3	72 h	Mice, male {HeJ, OuJ, Nos2 (+/+) [C57BL/6J-Nos2 (+/+)], and Nos2 (-/-) [C57BL/6J-Nos2 (-/-)]}, 6-8 weeks old	O ₃ induced permeability was decreased by pretreatment with a nitric oxide synthase inhibitor and in animals with iNOS gene knocked out.	Kleeberger et al. (2001a)
0.4	5 weeks	Guinea pigs, male, (Hartley), 5 weeks old (350-450 g) n = 7-8/group	Ovalbumin instillation in the nose caused an increase in O ₃ -induced infiltration of eosinophils in nasal epithelium.	Iijima et al. (2001)
0.15, 0.3, or 0.5	3 h	Rat, male, SD 6-8 weeks old, n = 2-6/group	Time-related increase in permeability and inflammation, with a peak at 8 h PE, after 0.5 ppm. No change following exposure to 0.15 or 3 ppm.	Bhalla and Hoffman (1997)
0.5	4 h, 12-4 PM for daytime and 7-11 PM for nighttime exposures. Exposures repeated 16 h later.	Rat, male, Wistar, 60-90 days old n = 5-15/group	Significantly greater increase in IL-6, but not inflammation, following a nighttime exposure compared to daytime exposure. An initial nighttime exposure resulted in lesser inflammation following a subsequent exposure. Pretreatment with IL-6 receptor antibody abolished cellular adaptive response without affecting inflammatory response induced by initial nighttime exposure.	McKinney et al. (1998)
0.5 1.0 2.0		Rat, male, Fisher, 90 days old n = 6-12/group	Increase in BALF protein and albumin occurred immediately after 2 ppm exposure, and at 18 h after 1 ppm. No increase after 0.5 ppm. The movement of water and protein into airspace were not coupled.	Cheng et al. (1995)

Table AX5-8 (cont'd). Effects of Ozone on Lung Permeability and Inflammation

Concentration ppm	Duration	Species	Effects	Reference
1.0-2.0	3 h	Mice, C57BL/6, 6-8 weeks old and rats, Wistar, 14-16 weeks old n = 4-6/group	Steady state MCP-1 mRNA increase after 0.6 ppm, with maximal increase after 2 ppm. After 2 ppm, MIP-2 mRNA peaked at 4 h PE and MCP-1 mRNA peaked at 24 h PE. BALF neutrophils and monocytes peaked at 24 and 72 h PE, respectively. BALF MCP-1 activity induced by O ₃ was inhibited by an anti-MCP-1 antibody.	Zhao et al. (1998)
0.5	24 h following a 3-d (6 h/day) exposure to cigarette smoke	Mice, male, B6C3F1, 25 ± 2 g, 10 weeks old, n = 6/group	BALF protein, neutrophils and lymphocytes were increased in animals exposed to smoke and then to O ₃ . Macrophages from this group also responded with greater release of TNF-α upon LPS stimulation.	Yu et al. (2002)
0.5	8 h during nighttime	Rat, male, Wistar, SD and Fischer F344, 90 days old n = 3-8/group	Exposure resulted in a significantly greater injury, inflammation and BALF levels of IL-6 in Wistar than in SD or F344 rats.	Dye et al. (1999)
0.8	2h and 6 h	Rats, male, Fisher F344, Juvenile (2 months; 180-250 g), Adult (9 months; 370-420 g), Old (18 months; 375-425 g), Senescent (24 months; 400-450 g) n = 2/group	Comparable effect on the leakage of alveolar protein in rats of different age groups, but a greater increase occurred in interleukin-6 and N-acetyl-beta-D-glucosaminidase in senescent animals than in juvenile and adult rats.	Vincent et al. (1996).
0.8	3 h	Rat, male, SD, 6-8 weeks old, n = 5/group	Increased adhesion of macrophages from exposed animals to rat alveolar type II epithelial cells in culture. Treatment with anti-TNF-α + anti-IL-1α antibody decreased adhesion in vitro, but not permeability in vivo.	Pearson and Bhalla (1997)
0.8	3 h	Rat, male, SD 6-8 weeks old, n = 5/group	Increase in fibronectin protein in BALF and lung tissue, and fibronectin mRNA in lung tissue. The increase produced by O ₃ was amplified in animals pre-treated intra-tracheally with rabbit serum to induce inflammation.	Gupta et al. (1998)
0.8	3 h	Rat, male, SD, 200-225 g, n = 2-9/group	Treatment of animals with IL-10 prior to O ₃ exposure caused a reduction in O ₃ induced BALF protein, albumin and fibronectin and tissue fibronectin mRNA.	Reinhart et al. (1999)

Table AX5-8 (cont'd). Effects of Ozone on Lung Permeability and Inflammation

Concentration ppm	Duration	Species	Effects	Reference
0.8	8 h	Monkey, male, Rhesus, 3 years 8 months-3 years 10 months old n = 2-6/group	Pretreatment of monkeys with a monoclonal anti-CD18 antibody resulted in a significant inhibition of O ₃ -induced neutrophil emigration and accumulation of necrotic airway epithelial cells.	Hyde et al. (1999)
0.8	48 h	Rat, male, SD, 6-8 weeks old,	Cyclophosphamide treatment ameliorated O ₃ -induced BALF neutrophils and albumin after short term and 1-day exposure. Anti-neutrophil serum reduced lavageable neutrophils but did not affect permeability.	Bassett et al. (2001)
1.0-2.0	3 h	200-225 g, n = 3-8/group		
0.8	8 h	Monkeys, male, Rhesus, 3 years 8 months-3 years 10 months old (5.1-7.6 kg) n = 2-6/group	Tracheal epithelium of exposed animals expressed b6 integrin. The integrin expression was reduced or undetectable in animals treated with CD-18 antibody.	Miller et al. (2001)
0.8	3 h	Mice, female, C57BL/6X 129 NOS ^{-/-} knockout and wild-type B6J129SV F2, 8-16 weeks old, n = 3-12/group	Alveolar macrophages from O ₃ exposed wild-type mice produced increased amounts of NO, peroxynitrite, superoxide anion, and PGE2. Nitrogen intermediates were not produced and PGE2 was at control level in exposed NOSII knockout mice. These mice were also protected from O ₃ -induced inflammation and injury.	Fakhrzadeh et al. (2002)
1.0	5 min exposure of airway segments following bronchoscopy	Dogs, male, Mongrel, Adult, n = 1-4/group	Mast cells from O ₃ -exposed airways of ascaris sensitive dogs released significantly less histamine and PGD2 following in vitro challenge with ascaris antigen or calcium ionophore.	Spannhake (1996)
1.0	8 h, assayed 1 and 2 h PE	Monkeys (Rhesus)	Increase in steady state IL-8 mRNA in airway epithelium. Increase in IL-8 protein staining declined at 24 h after exposure.	Chang et al. (1998)
0.2 0.5 1.0	In vitro at liquid/air interface	Primary TBE, BEAS-2b S and HBE1	Dose related increase in IL-8 release in the conditioned media. Ozone produced greater toxicity in cell lines than in primary cultures.	
1.0	3 h	Rat, male, SD, 6-8 weeks old, n = 4-5/group	Time-related increase in BALF protein, fibronectin (Fn), and alkaline phosphatase (AP) activity. Fn mRNA detected in macrophages, and AP in Type II cells and in BALF PMNs from exposed animals only.	Bhalla et al. (1999)

Table AX5-8 (cont'd). Effects of Ozone on Lung Permeability and Inflammation

Concentration ppm	Duration	Species	Effects	Reference
1	2 h	Rats, female, SD, 170-210 g n = 8-12/group	The expression of CD18 on alveolar macrophages and CD11b on blood PMNs was lowered by exposure, but CD62L expression on blood PMNs was not affected.	Hoffer et al. (1999)
1	3 h	Rat, male, SD, 6-8 weeks old, n = 5/group	Time-related increase in BALF albumin, PMNs, MIP-2 and ICAM-1, and increase in MIP-2 mRNA only at early time point in BALF macrophages. MIP-2 mRNA not detected in lung tissue.	Bhalla and Gupta (2000)
1	3 h	Rat, male, SD, 250-275 g, n = 6/group	Ozone induced increase in BALF albumin, fibronectin and PMN number was associated with an increase in expression of TNF- α , IL-1 α , IL-6 and IL-10 mRNA. Pretreatment with anti-TNF- α antibody caused downregulation of gene expression and reduction of BALF albumin and PMN number, but not fibronectin.	Bhalla et al. (2002)
1	6 h	Rat, male, SD, 200-250 g, n = 3-6/group	Increase in number of macrophages with mRNA transcripts and immunocytochemical staining of IL-1, TNF- α , MIP-2 and cytokine-induced neutrophil chemoattractant (CINC). Chemokine activities were reduced by treatment of macrophages with anti-IL-1 β and anti-TNF- α antibodies.	Ishii et al. (1997)
0.5 1.0 2.5	4 h	Mice, male (129 wild-type or Clara Cell Secretory Protein ^{-/-}), 2-5 months old, n = 3/group	Increases in IL-6 and metallothionein mRNA by 2 h after exposure to 1 ppm. mRNA increases were further enhanced in CCSP ^{-/-} mice.	Mango et al. (1998)
1.0	8 h/night for three nights	Mice, (C57BL/6 wild-type and iNOS knockout) n = 3-10/group	O ₃ exposure produced greater injury, as determined by measurement of MIP-2, matrix metalloproteinases, total protein, cell content and tyrosine nitration of whole lung protein, in iNOS knockout mice than in wild-type mice.	Kenyon et al. (2002)
1.0	4 h	Mice, male (129 strain, wild-type and Clara Cell Secretory Protein-deficient), 2-3 months old, n = 3/group	Increases in abundance of mRNAs encoding eotaxin, MIP-1a and MIP-2 in CCSP ^{-/-} , but no change in wild-type mice.	Johnston et al. (1999b)

Table AX5-8 (cont'd). Effects of Ozone on Lung Permeability and Inflammation

Concentration ppm	Duration	Species	Effects	Reference
1.2	6 h	Rat, male, Brown Norway, 200-250 g, n = 4/group	Eotaxin mRNA expression in the lungs increased 1.6-fold immediately after and 4-fold at 20 h. Number of lavageable eosinophils increased 3- and 15-fold respectively at these time points. Alveolar macrophages and bronchial epithelial cells stained positively for eotaxin.	Ishii et al. (1998)
2.0	3 h	Mice, male, C57BL/6J, 6-8 weeks old, n = 5-10/group	O ₃ -induced increase in protein and PMNs in BALF, and pulmonary epithelial cell proliferation were significantly reduced in animals pretreated with UK-74505, a platelet activating factor-receptor antagonist.	Longphre et al. (1999)
2.0	3 h	Rat, female, SD, 6-8 weeks old	BALF cells from exposed animals released 2 to 3 times greater IL-1 and TNF- α , and greater fibronectin. Immunocytochemistry showed greater staining of these mediators in lung tissue from exposed rats.	Pendino et al. (1994)
1.1	8 h	Rat, Wistar, -depleted of neutrophils, 43 days old, n = 9-10/group	Epithelial necrosis in the nasal cavity, bronchi, and distal airways. Proliferation of terminal bronchiolar epithelial cells also decreased by O ₃ exposure, suggesting a role for neutrophils in the repair process.	Vesely et al. (1999)
0.32	48 h (subacute) 3 h (acute)	Mice, male, C57BL/6J, WT TNRF1KO TNRF2KO 6-8 weeks old, n = 3-12/group	TNFR1 and TNFR2 KOs less sensitive to subacute O ₃ exposure than WT. With acute exposures, airway hyperreactivity was diminished in KO mice compared to WT mice, but lung inflammation and permeability were increased.	Cho et al. (2001)
0.3	24 to 72 h	Mice C57BL/6J C3H/HeJ C3H/HeOuJ 6-8 weeks old, n = 5-16/group	Differential expression of <i>Tlr4</i> mRNA.	Kleeberger et al. (2000)
2.0	3 h	Mice C3H/HeJ, A/J, C57BL/6J, 129/SvIm, CAST/Ei, BTBR, DBA/2J, FVB/NJ, BALB/cJ, n = 6-24/group	Two strains consistently O ₃ -resistant: C3H/HeJ and A/J. Two strains consistently O ₃ -vulnerable: C57BL/6J and 129/SvIm. Five strains with inconsistent phenotypes with intermediate responses: CAST/Ei, BTBR, DBA/2J, FVB/NJ, and BALB/cJ.	Savov et al. (2004)

Table AX5-8 (cont'd). Effects of Ozone on Lung Permeability and Inflammation

Concentration ppm	Duration	Species	Effects	Reference
1	3 h- examined at 3 h PE	Guinea pigs, male, Dunkin-Hartley, OVA-sensitized	PMN levels significantly increased, without any change in BAL protein levels, suggesting a lack of correlation between the two endpoints. Increased AHR.	Sun et al. (1997)
1	1 h examined 24 h PE		Increase in PMN, no increase in BAL protein levels. No increased AHR, suggesting a dissociation between PMN levels and AHR.	
0.4	1 or 5 days/ 12 h/day, recovery period in fresh air of 5, 10, 15, or 20 days after the 5-d preexposure	Rat, Wistar, male, 7 weeks old, n = 5/group	Exposure for 5 days caused lower BALF proteins, fibronectin, IL-6, and inflammatory cells than animals exposed for 1 day. Postexposure challenge with single O ₃ exposures at different time points showed that a recovery of susceptibility to O ₃ (as measured by BALF levels of albumin, IL-6, and the number of macrophages and neutrophils) occurred at ~15-20 days, but total protein and fibronectin levels remained attenuated even at 20 days post-5-day exposure. The recovery with regards to BrdU labeling occurred in 5-10 days after the 5-day exposure.	Van Bree et al. (2002)
2	2 h, examined 2, 12, and 48 h PE	Rat, female, SD, 200-250 g n = 4-7/group	Adherence of neutrophils to pulmonary vascular endothelium was maximal within 2 h after exposure and returned to control levels by 12 h PE.	Lavnikova et al. (1998)
1.0 or 2.5	4, 20, or 24 h, examined immediately PE 10 min	Mice, C57BL/6J, 36 h and 8 weeks old Endotoxin (10 ng) n = 3/group	RPA for IL-12, IL-10, IL-1 α , IL-1 β , IL-1Ra, MIF, IFN- γ , MIP-1 α , MIP-2, IL-6, and Mt. Newborn mice: increased Mt mRNA only. 8-week-old mice: increased MIP-1 α , MIP-2, IL-6, and Mt mRNA. Both age groups had similar cytokine/chemokine profiles with endotoxin exposure, suggesting that the responses to endotoxin, which does not cause epithelial injury, and the responses to O ₃ , which does, demonstrate that differences in inflammatory control between newborn and adult mice is secondary to epithelial injury.	Johnston et al. (2000b)
0.8	3 days, continuous	Rat, male, SD, 30 days old, n = 6/group	General dietary restriction to 20% of the freely-fed diet for 60 days caused an extreme reduction in body weight and higher survivability. Levels of antioxidants and detoxifying enzymes increased less than in freely fed animals.	Elsayed (2001)

Table AX5-8 (cont'd). Effects of Ozone on Lung Permeability and Inflammation

Concentration ppm	Duration	Species	Effects	Reference
1.8	3 h	Mice, female, C57BL/6J CBA C3H/HeJ AKR/J SJL/J, 6-8 weeks old, n = 4-7/group	Both exposure levels caused a transient increase in CC16 in serum that correlated with BALF changes in protein, LDH, and inflammatory cells. Inverse relationship between preexposure levels of CC16 in BALF and epithelial damage based on serum CC16 levels and BALF markers of inflammation. Inverse relationship between preexposure levels of albumin in BALF and lung epithelium damage. Suggests that a major determinant of susceptibility to O ₃ is basal lung epithelial permeability. C57BL/6J mice had lower levels of CC16a (the more acidic form) than C3H/HeJ. Both the strains had similar levels of CC16b. Suggests that basal lung epithelial permeability is a major determinant of susceptibility; greater epithelial permeability observed in C57BL/6J may be due to difference in the expression of CC16a and possibly other antioxidant/inflammatory proteins.	Broeckeaert et al. (2003)
0.11	24 h/day for up to 3 days, assays immediately or at 16 h PE			
1 or 3	2-6 h, assayed at 2, 8 and 24 h PE	Rat, female, Brown Norway, 250-300 g, n = 4-8/group	MIP-2 peaked at 2 h and rapidly declined. PMNs in BALF increased at 2, 8 and 24 h. No significant increase in AMs, eosinophils, lymphocytes or epithelial cells. MIP expression preceded increase in PMN. Both responses suppressed by dexamethasone, which suggests a mechanism of glucocorticoid regulation of inflammation.	Haddad et al. (1995)
1 or 3	3 h	Rat, male, Brown Norway, 200-250 g, n = 3/group	Increase in lung CINC mRNA within 2 h PE exposure. Significant increase in PMNs in BALF 24 h PE. Anti-CINC antibody (1 mg, i.v.) suppressed neutrophilia but not the increase in AHR to acetylcholine. Anti-CINC antibody inhibited BALF neutrophilia induced at 3 ppm AHR. Results suggest that CINC causes O ₃ -induced neutrophil chemoattraction, but is not involved in the induction of ozone-induced AHR.	Koto et al. (1997)
0.1-2	3 h, assayed 6 h PE (exposure-response)	Mice, C57BL/6, n = 2-4/group	O ₃ ≥ 1 ppm increased MIP-2 mRNA and recruitment of neutrophils. MIP-2 increase was immediate and decreased to control by 24 h PE.	Driscoll et al. (1993)
2	3 h, assayed 0, 2, 6, or 24 h PE (time-course)			

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Table AX5-8 (cont'd). Effects of Ozone on Lung Permeability and Inflammation

Concentration ppm	Duration	Species	Effects	Reference
0.12, 0.24, 0.5	3 h, NF-κB assayed 0 h PE, TNF-α assayed 0, 1, 2, 4, 16, 20 or 22 h PE	Cultures of human nasal epithelial (HNE) cells	Electron spin resonance signal suggested free radical production. Small dose-response activation of NF-κB coincided with O ₃ -induced free radical production. TNF-α increased with exposures to 0.24 and 0.5 ppm at 16 h PE. Results suggest that the human airway epithelium plays a role in directing the inflammatory response to inhaled O ₃ via free radical-mediated NF-κB.	Nichols et al. (2001)
0.8	3 h	Rats, SD, 200-250 g, n = 5-6/group	AMs from O ₃ -exposed rats exhibited greater motility and greater adhesion in cultures of epithelial cells (ARL-14). O ₃ -induced motility and adhesion were attenuated with AMs incubated in the presence of Mabs to leukocyte adhesion molecules, CD11b, or epithelial cell adhesion molecules, ICAM-1. Increased surface expression of CD11b but no change in ICAM-1 expression in AMs from O ₃ -exposed rats. Demonstration of alteration of AM functions following O ₃ exposure. Possible dependence of these functions on the biologic characteristics, rather than the absolute expression, of cell adhesion molecules.	Bhalla (1996)
2	3 h	Mice, male and female, C57BL/6J, assayed immediately or 3, 6, 9, or 21 h PE	Increase in tissue expression of ICAM-1 3 -9 h PE, remaining until 21 h PE. Bronchioles and terminal bronchiole/alveolar duct regions: Enhanced ICAM-1-IR 0 - 3 h PE, returning to baseline by 21 and 9 h, respectively. Lung parenchyma: maximal ICAM-1 expression and PMN influx concurrent 3 h, followed by transepithelial migration of PMNs to the airway lumen. Suggests regional variations in airway inflammatory activity; upregulation of ICAM-1 may play a role in local regulation of PMN influx to the airways after acute exposure.	Takahashi et al. (1995a)
2	4 h	Rat, SD, male, 225-250 g, treated with 10 mg/kg ebselen every 12 h from 1 h before O ₃ exposure, n = 4/group	Ebselen significantly decreased pulmonary inflammation (albumin and PMN in BALF) 18 h PE without altering AM expression of iNOS. Ebselen inhibited the nitration reaction of tyrosine residues and enhanced expression of Cu-, Zn-, and Mn SOD. Suggests that ebselen scavenges peroxynitrite during O ₃ -induced inflammation and may protect against acute lung injuries by modulating the oxidant-related inflammatory process.	Ishii et al. (2000a)

Table AX5-8 (cont'd). Effects of Ozone on Lung Permeability and Inflammation

Concentration ppm	Duration	Species	Effects	Reference
3	2 h	Human transformed bronchial epithelial cells (16-HBE) Guinea pigs, Hartley, male, 450-550 g, n = 3-5/group	NO donors increased IL-8 production dose-dependently. TNF- α plus IL-1 β plus INF γ increased IL-8 in culture supernatant of epithelial cells. NOS inhibitors (aminoguanidine plus NG-nitro-L-arginine methyl ester) attenuated the cytokine-induced IL-8 production. O ₃ induced AHR to acetylcholine and increased PMN in BALF. Persisting for 5 h. Pretreatment with NOS inhibitors did not affect AHR or PMN accumulation 0 h PE, but, inhibited at 5 h PE. Suggests that endogenous NO, through upregulation of IL-8, modulates O ₃ -induced airway inflammation and AHR.	Inoue et al. (2000)
0.12, 0.5, 1, or 2	3 h	Mice, female, BALB/c, 5-6 weeks old	O ₃ exposure caused dose-dependent increases in nitrate (indicative of in vivo NO generation). Increases in enhanced pause (P _{enh}) were also dose-dependent. Increases in NOS-1, but not in NOS-3 or iNOS isoforms. Suggest that NOS-1 may induce airway responsiveness by neutrophilic airway inflammation.	Jang et al. (2002)

PMN = Polymorphonuclear leukocyte

PE = Postexposure (time after O₃ exposure ceased)

BAL = Bronchoalveolar lavage

BALF = Bronchoalveolar lavage fluid

Table AX5-9. Effects of Ozone on Lung Structure: Acute and Subchronic Exposures

Concentration ppm	Duration	Species	Effects	Reference
0.1 0.5 1.0	8 h/day × 1 day 8 h/day × 1 day 8 h/day × 1, 10, 75, and 90 days	Rat; male, SD, 350-600 g, n = 3-6/group	No dose-related response on CYP2E1, one of six P450 enzymes identified in respiratory tissue. CYP2E1 activity was elevated (250% and 280%) in the lobar bronchi/major daughters airways immediately after 1.0 ppm O ₃ exposure for 1 day and 10 days, respectively, but not in the trachea or distal bronchioles; CYPE1 activity was unchanged and decreased after 1.0 ppm O ₃ exposure for 75 and 90 days, respectively.	Watt et al. (1998)
0.2 0.4	3, 7, 28, and 56 days; 3-, 7-, and 28-day recovery from 28 days of exposure	Mice, male, NIH, Rat, male, Wistar RIV:Tox Guinea pig, male, Hartley CrI:(HA)BR, 7 weeks old, n = 3-9/group	Concentration-related centriacinar inflammation, with a maximum after 3 days of exposure; number of alveolar macrophages and pulmonary cell density increased progressively until 56 days of exposure, with the guinea pig the most sensitive species. Concentration and exposure-time dependent hypertrophy of bronchiolar epithelium in mouse only. Exposure to 0.2 ppm for 3 and 7 days caused significant histological and morphometric changes in all 3 species; exposure for 56 days caused alveolar duct fibrosis in rat and guinea pigs. Total recovery in rats after 28-d exposure, but not in guinea pigs or mice.	Dormans et al. (1999)
0.2 0.4 0.8	23 h/day for 7 days	Guinea pig, female, Hartley; ±AH ₂ diet	Treatment-related lesions were observed after exposure to 0.4 and 0.8 ppm O ₃ ; lesions were primarily seen in the terminal bronchioles and consisted of mononuclear cell and neutrophilic infiltrate and thickening of the peribronchiolar interstitium. Effects were only marginally exacerbated by the AH ₂ (ascorbic acid) deficient diet and lesions were resolved after 1 week in FA.	Kodavanti et al. (1995)
0.4	12 h/day; 1- or 7-day exposure	Rat, Wistar RiV:TOX, male and female, 1, 3, 9, and 18 months of age, n = 5-6/group	Centriacinar inflammation (increased alveolar macrophages and PMNs; increased proximal and ductular septal density) was greatest in young rats (1 month and 3 months for 1-and 7-day exposures, respectively) and decreased with age. No major gender differences were noted.	Dormans et al. (1996)

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Table AX5-9 (cont'd). Effects of Ozone on Lung Structure: Acute and Subchronic Exposures

Concentration ppm	Duration	Species	Effects	Reference
0.4 1.0	2 h	Monkey; adult male Rhesus	Reduced glutathione (GSH) increased in the proximal intrapulmonary bronchus after 0.4 ppm O ₃ and decreased in the respiratory bronchiole after 1.0 ppm O ₃ . Local O ₃ dose (measured as excess ¹⁸ O) varied by as much as a factor of three in different airways of monkeys exposed to 1.0 ppm, with respiratory bronchioles having the highest concentration and the parenchyma the lowest concentration. After exposure to 0.4 ppm, the O ₃ dose was 60% to 70% less and epithelial injury was minimal, except in the respiratory bronchiole, where cell loss and necrosis occurred, but was 50% less than found at 1.0 ppm.	Plopper et al. (1998)
0.5	8 h + BrdU to label epithelial cells	Rat, male, Fischer F344, 13 weeks old, n = 6/group	O ₃ exposure induced a transient influx of neutrophils and a significant (17%) loss of NTE cells 2-4 h after exposure. Increased epithelial DNA synthesis was first detected 12 h PE. LI and ULLI indices of epithelial cell DNA synthesis were greatest 20-24 h and still elevated 36 h PE; numeric density of NTE cells returned to control levels 20-24 h PE.	Hotchkiss et al. (1997)
0.5	8 h/day, 3 or 5 days; + fluticasone propionate (FP) intranasally	Rat, male, Fischer F344, 203-232 g, n = 6/group	No significant difference of fluticasone propionate on morphometry of the maxilloturbinates; O ₃ exposure caused neutrophilic rhinitis with 3.3- and 1.6-fold more intraepithelial neutrophils (3-day and 5-day exposure, respectively) and marked mucous cell metaplasia (5-day exposure only) with numerous mucous cells and approximately 60 times more intraepithelial mucosubstances in the nasal transitional epithelium; FP-treated rats exposed to O ₃ had minimal nasal inflammation and mucous cell metaplasia.	Hotchkiss et al. (1998)
0.5	8 h/day, 3 days + endotoxin (100 µg/mL) intranasally	Rat, male, Fischer F344/N Hsd, 12 weeks old, n = 6/group	Endotoxin-induced neutrophilia in nasal mucosa with NTE; mucous cell metaplasia was not detected in air/endotoxin-exposed rats, was observed in O ₃ /saline-exposed rats, and was most severe in O ₃ /endotoxin-exposed rats.	Fanucchi et al. (1998)

Table AX5-9 (cont'd). Effects of Ozone on Lung Structure: Acute and Subchronic Exposures

Concentration ppm	Duration	Species	Effects	Reference
0.5	8 h/day, 1, 2, or 3 days + BrdU to label epithelial cells + antirat neutrophil antiserum	Rat, male, Fischer F344/N, 10-12 weeks old, n = 6-8/group	Acute O ₃ exposure induced a rapid increase in rMuc-5AC mRNA levels prior to the onset of mucous cell metaplasia; neutrophilic inflammation coincided with epithelial DNA synthesis and upregulation, but was resolved when mucous cell metaplasia first appeared in the NTE. Maxilloturbinates lined with NTE determined the epithelial labeling index, numeric densities of neutrophils, total epithelial and mucous secretory cells, amount of stored intraepithelial mucosubstances, and steady-state rMUC-5AC mRNA levels. Four days after a 3-d exposure, antiserum-treated, O ₃ -exposed rats had 66% less stored intraepithelial mucosubstances and 58% fewer mucous cells in their NTE than did controls. Antiserum treatment had no effects on O ₃ -induced epithelial cell proliferation or mucin mRNA upregulation.	Cho et al. (1999a, 2000)
0.5	8 h/day, 3 days + endotoxin	Rat, male, Fischer F-344, 10-12 weeks old, n = 6/group	Enhanced epithelial lesions in the NTE and respiratory epithelium of the nose and conducting airways by endotoxin and O ₃ exposures, respectively; synergistic effects of coexposure mediated by neutrophils. Endotoxin increased rMuc-5AC mRNA levels in the NTE of O ₃ -exposed rats; neutrophil depletion, however, had no effect on endotoxin-induced upregulation of mucin gene mRNA levels. Endotoxin enhanced the O ₃ -induced increase in stored mucosubstances (4-fold increase), but only in neutrophil-sufficient rats.	Wagner et al. (2001a,b)
0.5	8 h/day, 1 and 3 days + OVA (1%, 50 µL/nasal passage)	Rat, male, Brown Norway, 10-12 weeks old, n = 6/group	O ₃ enhanced the appearance of eosinophils in the maxilloturbinates of OVA-challenged rats but did not increase inflammation in other nasal tissues; O ₃ /OVA coexposures for 3 days increased the number of epithelial cells as well as the appearance of mucus-containing cells in the NTE lining the maxilloturbinates.	Wagner et al. (2002)
1	8 h	Rat, male, SD, 10 weeks old, Ferret, male, 18 months old, Monkey, male, Rhesus, 4 years old, n = 4-8/group	Severe, acute infiltration of neutrophils along with necrotic bronchiolar epithelium in all lung regions, especially in the centriacinar region; necrosis and inflammation was more severe in ferrets and monkeys than in rats.	Sterner-Kock et al. (2000)

Table AX5-9 (cont'd). Effects of Ozone on Lung Structure: Acute and Subchronic Exposures

Concentration ppm	Duration	Species	Effects	Reference
0.5	8 h/day for 3 days, assayed 2 h or 4 days PE	Rat, male, Fischer F344/N, with or without prior exposure to 100 µg/day endotoxin, 10-12 weeks old, n = 8/group	<p>2 h PE: Endotoxin/O₃ rats had 48 and 3 times more PMNs in the NTE than did saline/air- and saline/O₃-exposed rats, respectively at 2 h PE. O₃-only rats had 35% more NTE cells and 2-fold more mucin mRNA than did saline/air-exposed rats.</p> <p>4 days PE: Endotoxin/O₃ rats had 5 and 2 times more IM and mucous cells, respectively, than did saline/air- and saline/O₃- rats.</p> <p>No mucous cell metaplasia was present in those rats killed at 4 days postexposure. Suggests that pre-existing rhinitis augments O₃-induced mucous cell metaplasia.</p>	Cho et al. (1999b)
0.8	8 h/day for 90 days	Rats, SD, male, 275-300 g, treated i.p. with 1-nitronaphthalene (0, 50, or 100 mg/kg)	1-nitronaphthalene (a pulmonary toxicant requiring metabolic activation)-treated rats exposed to O ₃ showed greater histopathologic and morphometric effects in the centriacinar region of the lung. Caused denudation of the basement membrane and necrosis of remaining epithelial cells. Increased severity of ciliated cell toxicity in O ₃ -exposed rats. No differences in the intrapulmonary airways or trachea in sensitivity to 1-nitronaphthalene, suggesting a site-selective synergy between O ₃ and 1-nitronaphthalene.	Paige et al. (2000b)

AM = Alveolar macrophage
 PE = Postexposure (i.e., time after O₃ exposure ceased)
 LM = Light microscopy
 EM = Electron microscopy

RB = Respiratory bronchiole
 TB = Terminal bronchiole
 IAS = Inter-alveolar septum
 PMN = Polymorphonuclear leukocyte

Table AX5-10. Effects of Ozone on Lung Structure: Subchronic and Chronic Exposures

Concentration ppm	Duration	Species	Effects	Reference
Mexico City <u>Ambient</u> : 0.018 (≥0.12 for 18 1-h intervals)	23 h/day for 7 weeks	Rat, male and female, Fischer F344, 8 weeks old	No inflammatory or epithelial lesions in nasal airways or respiratory tract.	Moss et al. (2001)
0.12 0.5 1.0	6 h/day, 5 days/week for 20 months	Rat, male, Fischer F344, 6-8 weeks old	LM morphometry of CAR remodeling. Thickened tips of alveolar septa lining ADs (alveolar entrance rings) 0.2 mm from TB in rats exposed to 0.12 ppm and to 0.6 mm in rats exposed to 1.0 ppm. At 0.5 and 1.0 ppm, atrophy of nasal turbinates, mucous cell metaplasia in NTE, increased volume of interstitium and epithelium along ADs due to epithelial metaplasia, and bronchiolar epithelial hyperplasia. At 1.0 ppm, increased AMs and mild fibrotic response (increase in interstitial matrix and cellular interstitium; the latter due to increase in volume in interstitial fibroblasts). More effects in PAR than in terminal bronchioles. Effects not influenced by gender or by aging. Effects similar to, or model of, early fibrotic human disease (e.g., idiopathic pulmonary fibrosis).	Catalano et al. (1995a,b); Chang et al. (1995); Harkema et al. (1994, 1997a,b) Pinkerton et al. (1995); Plopper et al. (1994); Stockstill et al. (1995)
0.12 0.50 1.0	6 h/day, 5 days/week for 24 and 30 months	Mice, male and female, B6C3F1, 6-7 weeks old, n = 50/group	Effects in the nose and centriacinar region of the lung at 0.5 and 1.0 ppm. Nasal lesions were mild: hyaline degeneration, hyperplasia, squamous metaplasia, fibrosis, suppurative inflammation of transitional and respiratory epithelium; and atrophy of olfactory epithelium. Lung lesions: alveolar/bronchiolar epithelial metaplasia and histiocytosis in terminal bronchioles, alveolar ducts, and proximal alveoli. Severity was greatest in mice exposed to 1.0 ppm O ₃ , but there was minimal interstitial fibrosis.	Herbert et al. (1996)
0.12 1.0	6 h/day, 5 days/week, for 2 or 3 months	Rat, male, Fischer F344/N, 4-5 weeks old, n = 4/group	Morphometric changes (epithelial thickening, bronchiolarization) occurred after 2 or 3 months exposure to 1.0 ppm O ₃ ; effects were similar to those found with 20 months exposure (<i>see Pinkerton et al., 1995</i>)	Pinkerton et al. (1998)

Table AX5-10 (cont'd). Effects of Ozone on Lung Structure: Subchronic and Chronic Exposures

Concentration ppm	Duration	Species	Effects	Reference
0.011	6 months	Rat, male, Wistar, 2 months	CO = 1.25 ppm; PM = 35.18 µg/m ³ ; SO ₂ = 29.05 µg/m ³ . Induction of secretory hypertrophy, acidic mucous secretion, and ciliary damage.	Lemos et al. (1994)
0.25 0.5	8 h/day, 7 days/week for 13 weeks	Rat, male, Fischer F344/N HSD, 10-14 weeks old n = 5-6/group	Mucous cell hyperplasia in nasal epithelium after exposure to 0.25 and 0.5 ppm O ₃ ; still evident after 13 weeks recovery from 0.5 ppm O ₃ exposure. Mucous cell metaplasia found only after 0.5 ppm O ₃ , but still detectable 13 weeks PE.	Harkema et al. (1999)
0.4	23.5 h/day for 1, 3, 7, 28, or 56 days	Rat, Wistar, 7 weeks old, n = 5/group	Acute inflammatory response (increased PMNs and plasma protein in BALF) reached a maximum at day 1 and resolved within 6 days during exposure; AMs in BALF increased progressively up to day 56, and slowly returned to near control levels with PE recovery. Histological examination and morphometry of the lungs revealed CAR inflammatory responses throughout O ₃ exposure; thickening of septa was observed at day 7. Ductular septa thickened progressively at day 7, 28, and 56 of exposure; showed increased collagen at day 28, which was further enhanced at day 56. Increased RBs with continuous exposure. Collagen and bronchiolization remained present after a recovery period.	Van Bree et al. (2002)
0.5	8 h/day for 1, 3, and 6 months	Rat, male, Fischer F344/N	Increased Bcl-2, a regulator of apoptosis, after 1 month, decreasing somewhat thereafter, returning to baseline by 13 weeks PE; increased number of metaplastic mucous cells in NTE after 3 and 6 months.	Tesfaigzi et al. (1998)
0.5	8 h/day for 5 days, every 5 days for a total of 11 episodes	Monkey; Rhesus, 30-day-olds, n = 6/group	Increased density and distribution of goblet cells in RB whole mounts stained with AB/PAS; extensive remodeling of distal airway with O ₃ and O ₃ + HDMA challenge; increased airways resistance and reactivity, and respiratory motor adaptation also occurred. Authors conclude that periodic cycles of acute injury and repair associated with the episodic nature of environmental patterns of O ₃ exposure alters postnatal morphogenesis and epithelial differentiation in the distal lung of infant primates.	Schelegle et al. (2003); Chen et al. (2003); Plopper and Fanucchi (2000)

Table AX5-10 (cont'd). Effects of Ozone on Lung Structure: Subchronic and Chronic Exposures

Concentration ppm	Duration	Species	Effects	Reference
0.8	8 h/day for 90 days + 1-NN (100 mg/kg)	Rat, male, SD, 275-301 g	Increased O ₃ -induced centriacinar toxicity (histopathology, TEM, morphometry) of 1-Nitronaphthalene (1-NN), a pulmonary cytotoxicant requiring metabolic activation, especially to ciliated cells.	Paige et al. (2000b)
0.5	11 episodes of 5 days each, 8 h/day followed by 9 days of recovery	Monkey, <i>Macaca mulatta</i> , 30 days old	In small conducting airways O ₃ caused decrements in density of airway epithelial nerves. Reduction greater with HDMA + O ₃ . O ₃ or HDMA + O ₃ caused increase in number of PGP 9.5 (pan-neuronal marker) in airway. CGRP-IR nerves were in close contact with the PGP9.5 positive cells. Appearance of clusters of PGP9.5 ⁺ /CGRP ⁻ cells. Suggests episodic O ₃ alters developmental pattern of neural innervation of epithelial compartment.	Larson et al. (2004)
0.5	11 episodes of 5 days each, 8 h/day followed by 9 days of recovery	Monkey, Rhesus, 30 days old, n = 6/group	Abnormalities in the BMZ included: (1) irregular and thin collagen throughout the BMZ; (2) perlecan depleted or severely reduced; (3) FGFR-1 immunoreactivity was reduced; (4) FGF-2 immunoreactivity was absent in perlecan-deficient BMZ, but was present in the lateral intercellular space (LIS), in basal cells, and in attenuated fibroblasts; (5) syndecan-4 immunoreactivity was increased in basal cells.	Evans et al. (2003)

TB = Terminal bronchiole
 PE = Postexposure (i.e., time after O₃ exposure ceased)
 AM = Alveolar macrophage
 LM = Light microscopy
 TEM = Transmission Electron Microscopy

BMZ = Basement Membrane Zone
 EM = Electron microscopy
 RB = Respiratory bronchiole
 IAS = Interalveolar septum
 C × T = Product of concentration and time

Table AX5-11. Effects of Ozone on Pulmonary Function

Concentration ppm	Duration	Species	Effects	Reference
0.5	6 or 23 h/day over 5 days	Rats, male, Fischer 344, 90 days old, n = 28-36/group, ambient temperature 10, 22, or 34 °C	Toxicity increased with decreases in temperature. At 10 °C: decreased body weight, total lung capacity, BALF protein, alkaline phosphatase activity, % PMN, and lysozyme. Ozone-induced changes in lung volume were attenuated during the 5 exposure days and returned to control levels after 7 days recovery. The responses to repeated O ₃ exposure in rats were exacerbated by reduced ambient temperature, presumably as a result of increased metabolic activity.	Wiester et al. (1996)
2	3 h, assayed 1 and 24 h PE	Mice, male, C57BL/6J C3H/HeJ, 53 days old, n = 5-7/group challenged by CO ₂ (5 or 8%)	C57BL/6J mice: CO ₂ -induced changes in V _E were attenuated 1 h after O ₃ exposure; V _T was reduced 1 h after O ₃ exposure; the diminished V _T 1 h after O ₃ was coincident with reduced <i>f</i> , mean inspiratory flow, and slope of V _E -to-%CO ₂ relationship compared with FA.; V _E partially reversed 24 h after O ₃ relative to FA. C3H/HeJ: V _T was reduced 1 h after O ₃ exposure; increased <i>f</i> to sustain the hypercapnic VE response similar to air exposure. Suggests that control of ventilation during response to CO ₂ is governed, in part, by genetic factors in these two strains of mice, implying differential O ₃ susceptibility.	Tankersley et al. (1993)
0.3	48 and 72 h, with re-exposure after 14 days of recovery	Mice, C57BL/6J, C3H/HeJ, 6-8 weeks old	V _E and <i>f</i> were measured before and immediately after exposure. Normocapnic V _E was greater following subacute O ₃ exposure in C57BL/6J mice than in C3H/HeJ mice, due to increased <i>f</i> and reduced V _T , respectively. Ventilatory responses to both normocapnia and hypercapnia were similar after O ₃ reexposure in both strains. Suggests that: increased V _T in C57BL/6J mice may contribute to the increased susceptibility to lung injury due to a greater dose of O ₃ reaching the lower lung; mechanistic separation of airway inflammation and ventilation.	Paquette et al. (1994)
2	2-3 h, assayed 0 h PE	Mice, male, C57BL/6J, C3H/HeJ, 4 or 11-12 weeks old, n = 4-6/group	Using ¹⁸ O-labeled O ₃ . C3H/HeJ mice had 46% less ¹⁸ O in lungs and 61% less in trachea, than C57BL/6J. C3H/HeJ mice had a greater body temperature decrease following O ₃ exposure than C57BL/6J mice. Suggests that the differences in susceptibility to O ₃ are due to differences the ability to decrease body temperature and, consequently decrease the dose of O ₃ to the lung.	Slade et al. (1997)

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Table AX5-11 (cont'd). Effects of Ozone on Pulmonary Function

Concentration ppm	Duration	Species	Effects	Reference
2	3 h, assayed 6 h after exposure	Mice, male and female, AKR/J, C3H/HeJ, CBA/J, 129/J, NJ, C57BL/6J, C3HeB/FeJ, SJL/J	<p>Measured tracheal transepithelial potential in the six strains and in progeny of B6 and C3 strain mice. F1 mice and second generation backcrosses with the resistant parent were O₃ resistant. Ratios of 1:1 (resistant:susceptible) were obtained with second generation backcrosses with the susceptible parent, suggesting simple autosomal recessive inheritance of susceptibility.</p> <p>Susceptible phenotype: 129/J, A/J, B6, C3HeB/FeJ, and SJL/J.</p> <p>Resistant phenotype: AKR/J, C3, and CBA/J.</p> <p>Different pattern of susceptibility than with inflammation, suggesting that the responses are controlled by disparate genetic factors.</p>	Takahashi et al. (1995b)
2	3 h	Mice, C3H/HeJ, A/J, C57BL/6J, 129/SvIm, CAST/Ei, BTBR, DBA/2J, FVB/NJ, BALB/cJ, n = 6-24/group	<p>Used whole body plethysmography and enhanced pause index (P_{enh}) evaluations.</p> <p>C57BL/6J, BALB/cJ, 129/SvIm, BTBR: were highly sensitive to O₃; exhibited significant increases in P_{enh} to MCh at 6 and 24 h after exposure to O₃.</p> <p>DBA/2J, A/J, FVB/NJ, CAST/Ei, C3H/HeJ: increases in sensitivity to MCh at 6 h after exposure, return to near baseline by 24 h after exposure to O₃.</p>	Savov et al. (2004)

V_E = Minute ventilation
V_T = Tidal volume
f = Frequency of breathing
FA = Filtered air
MCh = Methacholine

Table AX5-12. Effects of Ozone on Airway Responsiveness

Concentration ppm	Exposure Duration	Species, Sex, Strain, and Age	Observed Effect(s)	Reference
0.1 0.3	4 h/day, 4 days/week for 24 weeks	Guinea pig, male and female, Hartley, 200-250 g, n = 10-20/group	O ₃ exposure did not produce airway hyperresponsiveness to ACh in nonsensitized animals; in OVA-sensitized animals, there was increased responsiveness to both nonspecific (ACh) and specific (OVA) airway challenge that persisted for 4 weeks after exposure 0.1 and 0.3 ppm O ₃ . Effects were not gender specific and were not associated with BALF inflammatory indicators, but were associated with antigen-specific antibodies in blood.	Schlesinger et al. (2002a,b)
0.15 0.30 0.60 1.2	4 h	Guinea pig, male Hartley, 500-600 g, n = 5-8/group	Increased airway responsiveness to Hist, but not ACh, 16-18 h after 1.2 ppm O ₃ exposure only. Increased responsiveness to SP occurred after exposure to ≥0.3 ppm O ₃ .	Segura et al. (1997)
0.3	4 h/day for 1, 3, 6, 12, 24, or 38 days	Guinea pig, male Hartley, 500-600 g, n = 6-7/group	Increased airway responsiveness to SP occurred 16-18 h after exposure to 0.3 ppm O ₃ for 1, 3, 6, 12, and 24 days; but not after 48 days. Highly significant correlation between airway responsiveness and BALF total cells, AMs, neutrophils, and eosinophils, suggesting that airway inflammation is involved.	Vargas et al. (1998)
0.5	8 h/day for 5 days, repeated every 14 days for 6 months	Rhesus monkey, male, 30 days old, n = 6/group	Increased airway responsiveness to Hist after 10 episodes of exposure to O ₃ + HDMA in sensitized infant monkeys.	Schelegle et al. (2003)
1	1 h	Guinea pig, male, Dunkin-Hartley, 250-300 g, n = 6-7/group	Increased bronchial responsiveness at 3 h, but not 24 h after O ₃ ; OVA had no effect on baseline, but enhanced airway responsiveness 24 h after O ₃ .	Sun et al. (1997)
1	1 h	Mice, male, C57BL/6, 6 weeks old, n = 10-31/group	Ozone caused increased C _{dyn} and V _E , and decreased P _a O ₂ in OVA-sensitized mice.	Yamauchi et al. (2002)
2	2 h	Rat, male, Fischer F344, 14 months old, n = 6/group	Increased airway responsiveness to MCh 2 h PE.	Dye et al. (1999)

Table AX5-12 (cont'd). Effects of Ozone on Airway Responsiveness

Concentration ppm	Exposure Duration	Species, Sex, Strain, and Age	Observed Effect(s)	Reference
0.3-3.0	3 h	Mice, AJ, male and female, aged 2, 4, 8, or 12 weeks, n = 42-50/group	Nose-only exposure plethysmographs. V_E decreased with increasing age. O_3 caused concentration-related decrease in V_E at all ages, but with less response in the 2-weeks old. Younger mice with less decrease in O_3 -induced VE demonstrated 3- to 4-times greater inhaled dose when normalized for body weight. The 2- to 4-weeks mice showed no AHR at any dose, while the 8- and 12-week old mice demonstrated dose-related increases in AHR. Older mice demonstrated increased levels of IL-6 and MIP-2. Suggests that young mice are less sensitive to O_3 for the endpoints of two cytokine and AHR.	Shore et al. (2002)
0.3	5 h	Mice, BALB/c, 3 weeks old, n = 5/group	Mice OVA-sensitized day 7-14; exposed day 21-23, assayed day 24 or 25 Decrease in P_{enh} in rats exposed to O_3 , as a function of MCh concentration.	Goldsmith et al. (2002)
2	3 h	Mice, C57BL/6J, and ob/ob, 8-12 weeks old, n = 6-7/group	Compared C57BL/6J and ob/ob mice (strain obese due to defect in gene coding for satiety hormone leptin). Intravenous MCh challenge induced AHR and inflammation in both groups, but was greater in obese mice. Dose per gram of lung tissue was greater in obese mice. Suggests obese mice get greater dose of O_3 .	Shore et al. (2003)
2		Rats, male and female, SD, 2, 4, 6, 8, or 12 weeks, n = 4-19/group	Nose-only-exposure plethysmographs exposure. 8,12 week rats: O_3 -induced 40-50% decreases in V_E (primarily due to decrease in V_T). 6 week rats: O_3 -induced changes in V_E were significantly less. 2, 4 week rats: no O_3 -induced changes in V_E . BALF protein and PGE2 were greater than in older rats. Suggests higher delivered dose to younger rats, decreased ventilatory response, and greater lung injury.	Shore et al. (2000)
2	2 h	Guinea pigs, male, Hartley, 400-600 g, n = 6/group	AHR to MCh peaked 2 h PE; PMN in BALF increased until 6 h PE. Tazanolast (a mast cell stabilizing drug, doses 30, 100, or 300 mg/kg) administered before O_3 exposure inhibited O_3 -induced AHR dose-dependently. Suggests that mast cells may play in role in the development of AHR.	Igarashi et al. (1998)

Table AX5-12 (cont'd). Effects of Ozone on Airway Responsiveness

Concentration ppm	Exposure Duration	Species, Sex, Strain, and Age	Observed Effect(s)	Reference
1 or 3	4 h, assayed 4 to 72 PE	Mice, normal WBB6F1 (1/1) and mast cell-deficient WBB6F1-kit W /kit W-v (kit W /kit W-v) 8-12 weeks old, n = 3-11/group	Demonstrated O ₃ -induced cutaneous, as well as bronchial, mast cell degranulation. PMN influx observed at 1 ppm only in normal mice. AHR in response to MCh with 1 ppm observed in both. Suggests that mast cells are involved in O ₃ -induced PMN influx but not AHR.	Noviski et al. (1999)
2	2 h	Cat, 2-3 kg, n = 5/group	Cats anesthetized and mechanically ventilated, challenged with ACh. Pretreated with polyethylene glycol-superoxide dismutase (PEG-SOD) or PEG-catalase (PEG-CAT) 5 min before O ₃ exposure. PEG-SOD partially prevented O ₃ -induced AHR, PEG-CAT did not. Suggests superoxide involvement in O ₃ -induced AHR.	Takahashi et al. (1993)
0.75	4 h, MCh challenge 6 h PE	Mice FVB/N, and FVB/N with β_2 -AR transgene, 10-14 weeks old, n = 10/group	Targeted expression (using CCSP promoter) of β_2 -adrenergic receptors (β_2 -AR) to airway epithelium to mimic agonist activation. Heterozygous mice from generations 2 to 4 used. MCh challenge dose needed to increase P _{enh} was greater in CCSP- β_2 -AR mice. CCSP- β_2 -AR mice less responsive to O ₃ . Suggests that β_2 -ARs regulate airway responsiveness and that β -agonists induce bronchodilation through activation of receptors on smooth muscle cells and epithelial cells.	McGraw et al. (2000)
2	2 h, assayed 2 h PE	Rat, male, SD, 2.5-3.5 months old, n = 5/group	Neonatal rats treated with capsaicin. Challenged with MCh following O ₃ . Capsaicin-treated rats: O ₃ had no effect on pulmonary conductance; decreased dynamic compliance; increase in AHR. During O ₃ exposure: 50% decrease in HR and 2.5 °C decrease in core temperature in both controls and capsaicin rats. Suggests that C-fibers inhibit O ₃ -induced AHR but do not modulate HR or core temperature.	Jimba et al. (1995)

Table AX5-12 (cont'd). Effects of Ozone on Airway Responsiveness

Concentration ppm	Exposure Duration	Species, Sex, Strain, and Age	Observed Effect(s)	Reference
1	3 h, assayed 4 h PE	Rat, SD, treated with capsaicin or tachykinin antagonists, n = 6/group	<p>Rats treated with CP-99994 (neurokinin-1 receptor antagonist) and SR-48968 (neurokinin-2-receptor antagonist). O₃ induced greater numbers of PMN in BALF of treated rats. The antagonists has no effects on pulmonary mechanics or airway responsiveness.</p> <p>Suggests that tachykinins are involved in the protective effects of C-fibers against O₃-induced inflammation.</p> <p>Capsaicin treatment induced increased PMN in BALF. O₃ exposure reduced V_E in both vehicle and capsaicin-treated rats, but the capsaicin treatment caused a greater, more immediate reduction.</p> <p>Suggests that the increase in BALF PMN is not due to a greater inhaled dose of O₃ reaching the lung.</p>	Takebayashi et al. (1998)
2	3 h, ACh challenge 0 and 24 h PE	Mice, 8 weeks old, 15-25 g. DBA/2J, AKR/J, A/J, C3H/HeJ, C57BL/6J, SJL/H, 129/J, n = 6-8/group	<p>Differing susceptibility to O₃: Hyperreactive-DBA/2J, AKR/J, A/J; Hyporeactive-C3H/HeJ, C57BL/6J, SJL/H; Intermediate 129/J. ACh challenge 25 or 50 µg/kg.</p> <p>ACh 24 h PE: Airway responses increased in A/J strain at 25 µg/kg and in C57BL/6J and SJL/J strains at 50 µg/kg.</p> <p>Ozone did not alter reactivity in other strains. MCh or carbachol challenge not affected by O₃, suggesting that cholinesterase function is affected by O₃. C57BL/6J and A/J mice treated with cyclophosphamide (an immunosuppressant) or anti-PMN caused decreased O₃-induced PMN levels but did not alter AHR, suggesting that O₃-induced ACh hyperreactivity correlates with susceptibility and that PMN influx is independent of AHR.</p>	Zhang et al. (1995)

Table AX5-12 (cont'd). Effects of Ozone on Airway Responsiveness

Concentration ppm	Exposure Duration	Species, Sex, Strain, and Age	Observed Effect(s)	Reference
0.05	4 h, challenged with iv 5-HT	Rats, male, Long-Evans, SD, Fisher 344, Brown-Norway, BDII, BDE, DA, Lewis and Wistar, 6-8 weeks old, n = 10/group	<p>AHR: developed in Lewis, BDII and Long-Evans rats 90 min after O₃. Baseline AHR differed among strains; did not correlate with O₃-induced AHR.</p> <p>PMN influx: did not occur in any strain.</p> <p>LE rats: AHR lasted ≥ 12 h PE with no change in BALF PMN, LDH, alkaline phosphatase, or protein.</p> <p>Suggests that O₃-induced AHR occurs without airway inflammation and that genetic factors may alter the sensitivity to O₃.</p>	Depuydt et al. (1999)
0.2	7 h, assayed 3 h PE	Rabbits, New Zealand white, 5 kg, n = 5-7/group	<p>O₃-induced decrease in tracheal transepithelial potential difference, but no change in lung resistance.</p> <p>ACh challenge: no change in compartmentalized lung resistance; 140% increase in O₃-induced lung resistance.</p> <p>Bilateral vagotomy: no change in compartmentalized lung resistance; enhancement of O₃-induced peripheral lung reactivity.</p> <p>Suggests that O₃ exposure may affect tracheal epithelial function and increase central airway reactivity, possibly through vagally-mediated mechanisms.</p>	Freed et al. (1996)
0.4	4 h, assayed by ACh, SP, or histamine challenge 0 or 48 h PE	Rabbits, New Zealand white, male and female, 2.5-3 kg, n = 4-6/group	<p>Used isolated perfused lung model allowing partitioning of the total pressure gradient into arterial, pre- and postcapillary, and venous components. O₃-induced inhibition of pulmonary mechanical reactivity to ACh, SP, and histamine. No change in baseline pulmonary resistance or dynamic compliance. At 48 h PE O₃ altered vasoreactivity of the vascular bed. Ozone-induced modification of the vasoreactivity of the vascular bed at 48 h PE and elevation of arterial segmental pressure. Suggests that O₃ can directly induce vascular constriction both immediately and 2 days following exposure and can inhibit ACh-, SP-, and histamine-induced changes in lung mechanics.</p>	Delaunois et al. (1998)

Table AX5-12 (cont'd). Effects of Ozone on Airway Responsiveness

Concentration ppm	Exposure Duration	Species, Sex, Strain, and Age	Observed Effect(s)	Reference
0, 0.12, 0.5, or 1.0	6 h/day, 5 days/week for 20 months	Rat, male and female, Fischer 344, 6-7 weeks old	Isolated eighth generation airways following O ₃ exposure. Circumferential tension development was measured in response to bethanechol, acetylcholine, and electrical field stimulation and normalized to smooth muscle area. 0.5 ppm caused an increase in smooth muscle area. Maximum responses of the small bronchi of male rats were significantly reduced after exposure to 0.12 and 0.5 ppm O ₃ . Suggests that O ₃ -induced increases in airway responsiveness do not persist with near-lifetime exposure and that chronic exposure alters smooth muscle cell function.	Szarek et al. (1995)
0.5	8 h/day for 7 days	Guinea pig, male, Hartley, 5 weeks old	Repeated exposure increased rapidly adapting receptor activity to substance P, methacholine, and hyperinflation; no significant effects on baseline or substance P- and methacholine-induced changes in lung compliance and resistance. Suggest that because agonist-induced changes in receptor activity precede lung function changes, the responsiveness of rapidly adapting receptors was enhanced.	Joad et al. (1998)
0.5	8 h/day for 5 days followed by 9 days of FA; for 11 episodes	Monkey, Rhesus, 30-d old, n = 6/group	Half of the monkeys were sensitized to house dust mite allergen (HDMA) at 14 and 28 days of age before exposure. HDMA and histamine aerosol challenges administered until R _{aw} doubled. Baseline R _{aw} elevated after 10 exposure episodes in the HDMA + O ₃ group compared to the FA, HDMA, and O ₃ exposure groups. Aerosol challenge with HDMA at the end of the 10th episode did not significantly affect R _{aw} , V _T , f, or S _a O ₂ . AHR appeared to develop following episode 6. Aerosol challenge with HDMA at the end of the 10th episode did not significantly affect R _{aw} , V _T , f, or S _a O ₂ . HDMA + O ₃ group: had increases in serum IgG, histamine and eosinophils; greater alteration in airway structure and content suggesting that O ₃ can enhance the structural remodeling and allergic effects of HDMA sensitization exposure groups.	Schelegle et al. (2003)

Table AX5-12 (cont'd). Effects of Ozone on Airway Responsiveness

Concentration ppm	Exposure Duration	Species, Sex, Strain, and Age	Observed Effect(s)	Reference
1	8 h	Rat, Wistar, some treated with capsaicin, n = 6-8/group	<p>Vehicle-treated: O₃-induced rapid shallow breathing pattern; BrdU label started at the bifurcation of the main stem bronchi and increased distally.</p> <p>Capsaicin treated: no O₃-induced changes in respiratory frequency; reduced BrdU labeling density in the terminal bronchioles supplied by short airway paths. Suggests that O₃-induced rapid shallow breathing is protective of conducting airways and allows distribution of injury to more distal regions.</p>	Schelegle et al. (2001)
1	2 h	Rat, male, Wistar, 100-120 days old, n = 7-10/group	<p>Examined the site-specific deposition of ¹⁸O at breathing frequencies of 80, 120, 16, or 200 bpm at a V_T to produce a constant minute ventilation of 72.8 ml/min/100 g body weight.</p> <p>All frequencies: parenchymal areas had a lower content of ¹⁸O than trachea and bronchi; right caudal parenchymal levels did not change.</p> <p>80 to 160 bpm: deposition reduced in midlevel trachea and increased in both mainstream bronchi; increased deposition in parenchyma supplied by short (cranial) airway paths.</p> <p>200 bpm: increased deposition in trachea increased; increased deposition in right cranial and caudal bronchi regions: decreased content in right cranial parenchymal.</p> <p>Suggests that the effect of rapid, shallow breathing is to create a more evenly distributed injury pattern with less deposition of O₃) in the trachea and a small effect on deposition in the parenchyma.</p>	Alfaro et al. (2004)

MCh = Methylcholine, ACh = Acetylcholine, Hist = Histamine, 5-HT = 5-Hydroxytryptamine, SP = Substance P, FS = Field Stimulation, CCh = Carbachol, TX = Thromboxane, KCl = Potassium Chloride, Pt = Platinum; Route: iv = intravenous, inh = inhalation., sc = subcutaneous, ip = intraperitoneal, OVA = Ovalbumin, BALF = bronchoalveolar lavage fluid, HDMA = House Dust Mite Allergen, C_{dyn} = Dynamic Lung Compliance, V_E = Minute Ventilation, P_aO₂ = partial pressure of arterial oxygen, AHR = airway hyperreactivity, V_T = Tidal Volume, R_{aw} = airway resistance, f = frequency of breathing, S_aO₂ = oxygen saturation of arterial blood.

Table AX5-13. Effects of Ozone on Genotoxicity/Carcinogenicity

Concentration ppm	Exposure Duration	Species, Sex, Strain, and Age	Observed Effect(s)	Reference
1	0, 12, 24, 48, 72, or 96 h	Guinea pigs, Dunkin-Hartley, male, 2 mo-old, n = 4/group	Following O ₃ exposure, two main bronchi were removed and tracheobronchial cells were isolated and assayed for DNA strand breaks using fluorimetric analysis. Ozone induced an increase in BALF protein and in DNA strand breaks, but did not change cell yield or viability. The amount of DNA in alkali lysates was decreased at 72 h, which suggests an increase in strand breaks at that time point.	Ferng et al. (1997)
1 or 2	90 min	Mice, female, BALB/c (20.6 g) or Muta TM (26.0 g) n = 11-21/group	O ₃ -induced increase in strand breaks up to 200 min following exposure. No effects after 200 min. O ₃ did not affect the level of oxidized amino acids in lung or the level of 8-oxo-deoxyguanosine in nuclear DNA. O ₃ -induced induction of IL-6 mRNA following DNA strand breaks, which does not support inflammation causing DNA damage.	Bornholdt et al. (2002)
2	90 min/day for 5 days		Mutagenic mice had no O ₃ -induced mutations in cII transgene.	
0.12, 0.50, and 1.0	6 h/day, 5 days/week for up to 9 months	Mice, female, A/J, n = 29-35/group	At 5 months, no difference in lung tumor multiplicity or incidence. At 9 months, no differences in lung tumor multiplicity between control mice and mice exposed to any concentration of O ₃ . The highest, and only statistically significant lung tumor incidence, was found in the mice exposed to 0.5 ppm O ₃ . In the O ₃ -exposed mice allowed to recover in filtered air, only the mice exposed to 0.12 ppm O ₃ had increases in lung tumor incidence and multiplicity. Authors consider the results to be spurious and of no significance for data interpretation.	Witschi et al. (1999)
0.5	6 h/day, 5 days/week for 12 weeks	Mice, male and female, B6C3F ₁ , 5-6 weeks old, n = 20 M and 20 F	Sporadic differences in mean body weight between O ₃ -exposed mice and air-exposed controls, as well as significant differences in the mean absolute and relative weights of liver, spleen, kidney, testes, and ovary. No O ₃ -related increased incidence of neoplasms in lung tissue. Oviductal carcinomas observed upon histopathologic examination in 30% of O ₃ -exposed female mice.	Kim et al. (2001)
0, 0.12, 0.5, or 1.0	6 hr/day, 5 days/week, to ppm 2-yr and lifetime	Rats, male and female, Fischer F-344/N, n = 5 M + 5 F (acute) n = 50 m + 50 F/group	Cocarcinogenicity study with subcutaneous administration of 0, 0.1, or 1.0 mg/kg body weight of 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) and inhalation of 0 or 0.5 ppm O ₃ to male rats. O ₃ caused dose-related increase in inflammation in CAR; increased fibrosis; extension of the bronchiolar epithelium to the proximal alveoli; but no increase in neoplasms. NNK (1.0 mg/kg) alone causes increased bronchiolar/alveolar neoplasms. NNK + O ₃ : no enhancement of neoplasms. Suggests that O ₃ is not carcinogenic; does not enhance neoplasms growth; and creates mild site-specific lesions which persist with continued exposure.	Boorman et al. (1994)

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Table AX5-14. Systemic Effects of Ozone

Concentration ppm	Duration	Species	Effects	Reference
NEUROBEHAVIORAL EFFECTS				
0.1 0.2 0.5 1.0	4 h	Rat, male, Wistar, 47-50 days old, n = 25/group	Rats exposed for 4 h to 0.2, 0.5, and 1 ppm O ₃ showed long-term memory deterioration and decreased motor activity, which was reversed 24 h later. Brain and pulmonary Cu/Zn SOD levels were increased in animals exposed to 0.1, 0.2, and 0.5 ppm O ₃ , but decreased in animals exposed to 1 ppm O ₃ .	Rivas-Arancibia et al. (1998)
0.1 0.4 0.7 1.1 1.5	4 h	Rat, male, Wistar, 300-350 g, n = 10/group	O ₃ caused memory impairment at ≥0.7 ppm (one trial passive avoidance test), decreased motor activity at ≥1.1 ppm, and increased lipid peroxidation at ≥0.4 ppm. Lipid peroxidation levels from the frontal cortex, hippocampus, striatum and cerebellum increased with increasing O ₃ concentration.	Dorado-Martinez et al. (2001)
0.3 0.6	30 days	Mice, CD-1 M, F, 28-33 g, n = 6-7/group	O ₃ exposure slightly but selectively affected neurobehavioral performance in male mice assessed with a 5-min open-field test on exposure day 4 and 19 and on day 3 after the end of the exposure. O ₃ exposure, however, did not grossly affect neurobehavioral development. Reversal learning in the Morris water maze test was consistently impaired in both prenatally and adult exposed mice. In addition, longer latency to step-through in the first trial of the passive avoidance test and a decrease in wall rearing in the hot-plate test were recorded in O ₃ prenatally exposed mice. Except for the first open-field test, altered responses were observed only in animals exposed to 0.3 ppm O ₃ .	Sorace et al. (2001)
0.35 0.75 1.5	12 h	Rat, male, Wistar, 270 g, n = 10/group	O ₃ exposure decreased paradoxical sleep after 2 h of exposure, and increased slow wave sleep after 12 h of exposure at all O ₃ concentrations; 5-HT concentrations in the pons increased with increasing O ₃ concentration.	Paz and Huitrón-Reséndiz (1996)
0.7	4 h	Rat, male, Wistar, 47-50 days old, n = 6-10/group	Vitamin E administered before or after O ₃ exposure blocked memory deterioration (passive avoidance) and increases in lipid peroxidation levels in the striatum, hippocampus and frontal cortex that were associated with oxidative stress.	Guerrero et al. (1999)
0.7	4 h	Rat, male, Wistar, 27 months old, n = 3-4/group	O ₃ exposure increased ultrastructural alterations in the hippocampus and prefrontal cortex in aged rats compared with controls. These areas are related to learning and memory functions, which are the first degenerative aging changes observed.	Niño-Cabrera et al. (2002)

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Table AX5-14 (cont'd). Systemic Effects of Ozone

Concentration ppm	Duration	Species	Effects	Reference
NEUROBEHAVIORAL EFFECTS (cont'd)				
0.7 0.8	4 h	Rat, male, Wistar, 47, 540, or 900 days old, n = 10-30/group	Taurine (43 mg/kg) given before or after O ₃ exposure improved memory deterioration in an age-specific manner. Old rats showed peroxidation in all control groups and an improvement in memory with taurine. When taurine was applied before O ₃ , peroxidation levels were high in the frontal cortex of old rats and the hippocampus of young rats; in the striatum, peroxidation caused by O ₃ was blocked when taurine was applied either before or after exposure.	Rivas-Arancibia et al. (2000)
1	12 h/day during dark period	Rat, female, adult, n = 6/group	O ₃ exposure during pregnancy affects the neural regulation of paradoxical sleep and circadian rhythm of rat pups 30, 60, and 90 days after birth.	Haro and Paz (1993)
1	4 h	Rat, male, Wistar, n = 24/group	O ₃ caused alterations in long-term memory and a significant reduction of dendritic spines. Results provide evidence that deterioration in memory is probably due to the reduction in spine density in the pyramidal neurons of the hippocampus.	Avila-Costa et al. (1999)
1	3 h	Rat, male, Wistar, 275 g, n = 10/group	O ₃ or its reaction products affect the metabolism of major neurotransmitter systems as rapidly as after 1 h of exposure. There were significant increases in dopamine (DA), and its metabolites noradrenaline (NA) and 3,4 dihydroxyphenylacetic acid (DOPAC), and 5-hydroxyindolacetic acid (5-HIAA) in the midbrain and the striatum.	González-Piña and Paz (1997)
1.5	24 h	Rat, male, Wistar, n = 11/group	Adult rats exposed to O ₃ spend decreased time in wakefulness and paradoxical sleep and a significant increase in time in slow-wave sleep. Neurochemical changes include increased metabolism of serotonin in the medulla oblongata, pons, and midbrain.	Huitrón-Reséndiz et al. (1994)
0.5	20 h/day for 5 days	Rat, SD, 220-240 g, n = 10-20/group	O ₃ produced marked neural disturbances in structures involved in the integration of chemosensory inputs, arousal, and motor control. O ₃ inhibited tyrosine hydroxylase activity in noradrenergic brainstem cell groups, including the locus ceruleus (-62%) and the caudal A2 subset (-57%). Catecholamine turnover was decreased by O ₃ in the cortex (-49%) and striatum (-18%) but not in the hypothalamus.	Cottet-Emard et al. (1997)

Table AX5-14 (cont'd). Systemic Effects of Ozone

Concentration ppm	Duration	Species	Effects	Reference
<u>NEUROBEHAVIORAL</u>				
0.4, 0.8, or 1.2	24 h	Cat, male, adult, n = 5/group	Evaluated EEG of sleep-wake organization in cats. 0.4 O ₃ did not change the amount of sleep parameters, did decrease paradoxical sleep during first 8 h of exposure. At 1.2 ppm paradoxical sleep was reduced during O ₃ exposure, followed by a dose-related increase of slow-wave sleep. Suggests O ₃ -induced changes in sleep patterns.	Paz and Bazan-Perkins (1992)
0.75, 1.5 and 3.0	4 h	Rat, male, Wistar, 250-300 g, n = 15/group	Recorded evoked potential in visual cortex and lateral geniculate nucleus. P1, N1 and P2 components delayed in the visual cortex and lateral geniculate nucleus at 3.0 ppm O ₃ . N1 component in the visual cortex affected at 1.5 ppm O ₃ . Suggest O ₃ -induced alterations in synaptic excitability and conduction mechanisms in the visual pathway.	Custodio-Ramirez and Paz (1997)
1-1.5	4 h	Rat, male, Wistar, ~250 g n = 5/group	O ₃ -induced loss of dendritic spines on primary and secondary dendrites of granule cells; swelling of Golgi apparatus and mitochondrion; dilation cisterns of the rough endoplasmic reticulum; vacuolation of neuronal cytoplasm. Suggests O ₃ -induced oxidative stress creates alterations in the granule layer of the olfactory bulb and possible modifications of function.	Colín-Barenque et al. (1999)
<u>NEUROENDOCRINE EFFECTS</u>				
0.5 to 3.0	3 h	Rat, male, SD, 44-47 days old, n = 4-6/group	Hyperthyroid, T ₄ -treated rats (0.1-1.0 mg/kg/day for 7 days) had increased pulmonary injury (BALF LDH, albumin, PMNs) at 18 h PE compared to control rats.	Huffman et al. (2001)
1.0	24 h	Rat, male, SD, 3-4 months old	Hyperthyroid, T ₃ -treated rats had increased metabolic activity and O ₃ -induced pulmonary injury, but lipid peroxidation, as assessed by alkane generation, was not affected.	Sen et al. (1993)

Table AX5-14 (cont'd). Systemic Effects of Ozone

Concentration ppm	Duration	Species	Effects	Reference
<u>CARDIOVASCULAR EFFECTS</u>				
0.1 0.3 0.5	5 h	Rat, Wistar young (4-6 months) and old (22-24 months) n = 9-14/group	Transient rapid shallow breathing with slightly increased HR appeared 1-2 min after the start of O ₃ exposure, possibly due to olfactory sensation; persistent rapid shallow breathing with a progressive decrease in HR occurred with a latent period of 1-2 h. The last 90-min averaged values for relative minute ventilation tended to decrease with the increase in the level of exposure to O ₃ and these values for young rats were significantly lower than those for old rats. An exposure of young rats to 0.1 ppm O ₃ for shorter than 5 h significantly decreased the tidal volume and HR and increased breathing frequency, but no significant changes were observed in old rats. There were no differences between young and old rats in non-observable-adverse-effect-levels (NOAELs) for the O ₃ -induced persistent ventilatory and HR responses, when the NOAELs were determined by exposure to 0.3 and 0.5 ppm O ₃ .	Arito et al. (1997)
0.1 0.3 0.5	8 h/day for 4 days	Rat, male, Wistar, 10 weeks old, n = 9/group	Circadian rhythms of HR and core body temperature were significantly decreased on the first and second O ₃ exposure days in a concentration dependent manner, and returned to control levels on the third and fourth days.	Iwasaki et al. (1998)
0.25 to 2.0	2 h to 5 days	Rat, Fischer F344, Mice, C57BL/6J, C3H/HeJ, Guinea pig, Hartley, n = 4-10/group	Robust and consistent decreases in HR and core body temperature; smaller decreases in metabolism, minute ventilation, blood pressure, and cardiac output that vary inversely with ambient temperature and body mass.	Watkinson et al. (2001)
0.5	6 h/day 23 h/day for 5 days	Rat, male, Fischer F-344, 100-120 days old, n = 4-6/group	Minimal extrapulmonary effects were observed at a core body temperature of 34 °C; O ₃ exposures at 22 and 10 °C produced significant decreases in heart rate (160 and 210 beats/min, respectively), core body temperature (2.0 and 3.5 °C, respectively), and body weight (15 and 40 g, respectively). Decreases in these functional parameters reached their maxima over the first 2 exposure days and returned to control levels after the 3rd day of exposure.	Watkinson et al. (1995); Highfill and Watkinson (1996)

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Table AX5-14 (cont'd). Systemic Effects of Ozone

Concentration ppm	Duration	Species	Effects	Reference
<u>CARDIOVASCULAR EFFECTS</u> (cont'd)				
0.5	8 h	Rat, male, Fischer F-344, 270-330 g, n = 6/group	O ₃ exposure increased atrial natriuretic peptides in the heart, lung, and circulation, suggesting they mediate the decreased BP and pulmonary edema observed with similar O ₃ exposures.	Vesely et al. (1994a,b,c)
0	24 h/day	Rat, male, Fischer F-344 kept at one of three temperatures: 10 °C, 22 °C, 34 °C at rest, moderate or heavy CO ₂ -stimulated ventilation, 100-120 days old, n = 4-8/group	0.5 ppm O ₃ for both 6 h/day and 23 h/day caused decreases in heart rate and core temperature (termed hypothermic response) and increases in BALF inflammatory markers. Exercise in 0 ppm O ₃ caused increases in heart rate and core temperature, 0.5 ppm O ₃ decreases. CO ₂ and O ₃ induced the greatest deficits. Dose, animal mass, and environmental stress are suggested to modify the hypothermic response.	Watkinson et al. (2003)
0.5	6 h/day			
0.5	23 h/day			
0.5				
<u>REPRODUCTIVE AND DEVELOPMENTAL EFFECTS</u>				
0.2 0.4 0.6	Continuous up to days 17 of pregnancy	Mice, male and female, CD-1, 25-27 g	No significant effects on either reproductive performance, postnatal somatic and neurobehavioral development (as assessed by a Fox test battery) or adult motor activity (including within-session habituation); some subtle or borderline behavioral deficits were noted, however.	Petruzzi et al. (1995)
0.3 0.6 0.9	Continuous up to postnatal day 26	Mice, male and female, CD-1, 27-30 g, n = 11-15/group	O ₃ caused subtle CNS effects but did not affect the animals' capability to learn a reflexive response (limb withdrawal); females exposed to 0.6 ppm O ₃ showed a reduced preference for the right paw than both their same-sex controls and 0.6 ppm males. The effect was more robust in the case of an organized avoidance response (wall-rearing).	Petruzzi et al. (1999)

Table AX5-14 (cont'd). Systemic Effects of Ozone

Concentration ppm	Duration	Species	Effects	Reference
REPRODUCTIVE AND DEVELOPMENTAL EFFECTS (cont'd)				
0.3 0.6	Continuous until gestational day 17	Mice, male and female, CD-1, 28-30 g, n = 6-9/group	Exposure to O ₃ did not grossly affect neurobehavioral development, as assessed by somatic and sensorimotor development (postnatal day (PND) 2-20), homing performance (PND 12), motor activity (PND 21), passive avoidance (PND 22-23), water maze performances (PND 70-74), and response to a nociceptive stimulus (PND 100).	Sorace et al. (2001)
0.4 0.8 1.2	Continuous during gestation day 7-17	Mice, CD-1	No effect of O ₃ on reproductive performance; no significant somatic developmental effects in O ₃ -exposed pups except for a delay in eye opening that was not concentration dependent.	Bignami et al. (1994)
0.6	Continuous from birth to weaning	Mice, male and female, CD-1, 25-27 g, n = 13-16/group	Exposure to O ₃ did not produce any significant impairment of the acquisition phase during swimming navigation, a sensitive indicator for hippocampal damage; however, O ₃ slightly increased the swimming paths during the last day of the reversal phase. Mice exposed to O ₃ showed a slightly but significantly higher swimming speed during all the days, which was unrelated to differences in body weight and to navigational performances. Moreover, mice exposed to O ₃ (with the exception of one animal) had a strong tendency to make turns to the left while the controls, independent of sex, preferred clockwise turns.	Dell'Omo et al. (1995a,b)
1	12 h/day for entire gestation, assayed at postnatal day 0, 12, and 60	Rat, male and female, Wistar, n = 9-10/group	Histological and planimetric analysis using sagittal sections of the anterior cerebellar lobe. PND 0: O ₃ -induced cerebellar necrosis. PND 12: diminished molecular layer; pale nucleoli and perinucleolar bodies in Purkinje cells. PND 60: Purkinje cells with clumps of chromatin around periphery. Suggests that gestational exposure to O ₃ induces permanent cerebellar damage.	Rivas-Manzano and Paz (1999)
EFFECTS ON LIVER, SPLEEN, THYMUS				
1.0 2.0	3 h	Rat, female, SD, 200-225 g	High O ₃ exposure stimulates hepatocytes to produce increased amounts of nitric oxide as well as protein, possibly mediated by cytokines such as TNF- α produced by alveolar macrophages. When macrophage function is blocked, hepatic injury induced by O ₃ is prevented.	Laskin et al. (1994, 1996, 1998b); Laskin and Laskin (2001)

Table AX5-14 (cont'd). Systemic Effects of Ozone

Concentration ppm	Duration	Species	Effects	Reference
<u>EFFECTS ON LIVER, SPLEEN, THYMUS</u> (cont'd)				
2.0	2 h	Rat, male, Fischer F-344, 2, 9, or 24 months old, n = 2/group	Utilizing electron paramagnetic resonance (EPR) spectroscopy of chloroform extracts of liver homogenates, a significant flux of hydrogen peroxide produced from the reaction of O ₃ with lipids of the extracellular lining could be a source of biologically relevant amounts of hydroxyl radical. EPR signals for carbon-centered alkoxy and alkyl adducts were detected with C-phenyl <i>N-tert</i> -butyl nitron (PBN) in the liver of animals exposed to O ₃ .	Vincent et al. (1996)
<u>EFFECTS ON CUTANEOUS TISSUE</u>				
0.5	2 h	Mice, hairless female	α tocopherol levels in the stratum corneum (SC) were not affected by O ₃ exposure (0.5 ppm) alone, but were significantly depleted by combined exposure to UV and O ₃ .	Valacchi et al. (2000)
0.8	6 h	Mice, SKH-1 hairless	Increased lipid peroxidation in the skin epidermis and dermis activated stress proteins HSP27 and HO-1, and activated a proteolytic enzyme system (MMP-9) related to matrix injury and repair processes.	Valacchi et al. (2003)
0.8 1.0 10.0	2 h	Mice, SKH-1 hairless	High O ₃ depletes hydrophilic antioxidants in the SC: vit. C decreased to 80%, GSH decreased to 41%, and uric acid decreased to 44% of control levels after exposure to ≥ 1.0 ppm O ₃ .	Weber et al. (2000)
1.0 5.0 10.0	2 h	Mice	High O ₃ exerts an oxidizing effect on the outermost layer of the skin (SC); depletes low-molecular-weight antioxidants (α tocopherol, vit. C, glutathione, uric acid) in a concentration dependent manner; increases malondialdehyde levels associated with lipid peroxidation.	Weber et al. (2001)
0, 0.8, 1, and 10	2 h	Mice, SKH-1 hairless	1 ppm O ₃ depleted SC levels of vitamin C (80%), GSH (41%), and UA (44%). Suggests that hydrophilic antioxidants in the SC modulate the effects of O ₃ -induced oxidative stress.	Weber et al. (1999)

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RER = Rough endoplasmic reticulum
 PE = Postexposure (i.e., time after O₃ exposure ceased)
 TSH = Thyroid stimulating hormone
 T₃ = Triiodothyronine
 T₄ = Thyroxine
 cyt. = Cytochrome

NADPH = Reduced nicotinamide adenine dinucleotide phosphate
 NADH = Reduced nicotinamide adenine dinucleotide
 B[a]P = Benzo[a]pyrene
 NK = Natural killer
 PHA = Phytohemagglutinin
 ConA = Concanavalin A

LPS = Lipopolysaccharide
 SRBC = Sheep red blood cell
 TBA = Thiobarbituric acid
 IgE = Immunoglobulin E.
 PHA = Phytohemagglutinin

Table AX5-15. Interactions of Ozone With Nitrogen Dioxide

Concentration ppm		Duration	Species	Endpoints	Interaction	Reference
O ₃	NO ₂					
<u>MORPHOLOGY</u>						
0.8	14.4	6 h/day, 7 days/week for 90 days	Rat, male, SD, 10-12 weeks old, n = 4/group	Morphometry of lung parenchyma; DNA probes for procollagen; in situ mRNA hybridization.	Synergistic; more peripheral centriacinar lesion, but same after 7, 78, and 90 days of exposure.	Farman et al. (1999)
0.3	1.2	Continuous for 3 days	Rat, male, SD, 3 months old, n = 4/group	DNA single strand breaks; polyADPR synthetase of AMs; total cells, protein, and LDH in BALF.	None; effect due to O ₃ .	Bermúdez et al. (1999); Bermúdez (2001)
<u>BIOCHEMISTRY</u>						
0.8	14.4	6 h/day, 7 days/week for 9 weeks	Rat, male, SD, 10-12 weeks old n = 4/group	Lung hydroxyproline, hydroxypyridinium, DNA, and protein content of whole lung; morphology and labeling index.	Synergistic; fibrosis after 7-8 weeks of exposure; 50% mortality at ~10 weeks.	Farman et al. (1997)
0.4	7	90 days	Rat, male, SD, 200-225 g	PMN, pulmonary edema, fibrosis, MIP-2.	1-3 days: enhanced MIP-2, IL-1 β , TNF- α , thioredoxin, and IL-6 expression; pulmonary edema and PMN influx, which reversed by day 8; activation of NF- κ B. 15-45 days: no tissue responses observed, suggesting adaptation. 60 and 90 days: increased lung collagen; increased expression of transforming growth factor-13 and TNF- α , activation of NF- κ B. MnSOD and GPX not altered during exposure. Suggests that cytokines play a role in the early responses to combined O ₃ and NO ₂ and that pulmonary fibrosis is more dependent on concentration than on cumulative dose.	Ishii et al. (2000b)

Table AX5-15 (cont'd). Interactions of Ozone With Nitrogen Dioxide

Concentration ppm		Duration	Species	Endpoints	Interaction	Reference
O ₃	NO ₂					
BIOCHEMISTRY (cont'd)						
0.8	14.4	1, 5, and 8 weeks	Rat, male, SD, 10-12 weeks old, n = 4/group	Immunohistochemistry and morphometric analysis of TNF- α and MnSOD levels in alveolar ducts.	Triphasic response. 1-3 weeks: initial inflammation; TNF- α increased in proximal area. 4-5 weeks: partial resolution. 6-8 weeks: rapidly progressive fibrosis; elevated MnSOD; TNF- α increased in proximal area. TNF- α increased in interstitial cells at all time points. Suggests O ₃ -induced increases in MnSOD in areas of injury and in more protected areas; O ₃ -induced increases in TNF- α correlate spatiotemporally with injury.	Weller et al. (2000)

BAL = Bronchoalveolar lavage.

PG = Prostaglandin.

G-6-PD = Glucose-6-phosphate dehydrogenase.

GDT = GSH-disulfide transhydrogenase.

GSHPX = GSH peroxidase.

SOD = Superoxide dismutase.

DR = Disulfide reductase.

NADPH-CR = Reduced nicotinamide adenine dinucleotide phosphate-cytochrome c reductase.

GSH = Glutathione.

6-PG-D = 6-phosphogluconate dehydrogenase.

Table AX5-16. Interactions of Ozone with Formaldehyde

O₃	HCHO	Duration	Species	Endpoints	Interaction	Reference
0.4	3.6	8 h/day for 3 days	Rat, male, Wistar, n = 20/group	<p>O₃ or HCHO: no changes in formaldehyde dehydrogenase, glutathione S-transferase, glutathione reductase, and glucose-6-phosphate dehydrogenase activities.</p> <p>O₃ + HCHO: slightly decreased enzyme activities</p> <p>HCHO alone: rhinitis, necrosis, degeneration, hyperplasia and squamous metaplasia of nasal respiratory epithelium.</p> <p>O₃: PMN influx; disarrangement, flattening and slight basal cell hyperplasia of the nonciliated cuboidal epithelium. Proliferating cell nuclear antigen levels elevated.</p>	Proliferative response: No interactive effects	Cassee and Feron (1994)
0.6	10	3 h, with exercise at 2× resting ventilation	Rat, male, SD, 7 weeks	HCHO did not alter O ₃ -induced changes in breathing pattern. Parenchymal injury attributed to O ₃ alone.	Additive effects in transitional epithelium and trachea	Mautz (2003)
0.2-10	0.4-4	30 min	Mice, BALB/c, n = 4	Continuously measured f , V_T , expiratory flow, T_i , T_e , and respiratory patterns during acute exposures. HCHO: appeared to be a pure sensory irritant at lower concentrations. O ₃ : induced non-dose-dependent transient increase in rapid, shallow breathing. No effect level of HCHO was 0.3 ppm, for O ₃ 1.0 ppm. Suggests that O ₃ and HCHO have the same respiratory effects in BALB/c mice and humans, with similar sensitivities.	Not additive	Nielson et al. (1999)

Table AX5-17. Interactions of Ozone with Tobacco Smoke

O ₃	HCHO	Duration	Species	Endpoints	Interaction	Reference
1.5	7 ml breaths at 33% challenge	1 h	Guinea pig, male, Hartley, 320-460 g, n = 5 to 9	<p>Pulmonary resistance and dynamic lung compliance were compared pre- and post-O₃ exposure.</p> <p>Pre-O₃: cigarette smoke induced bronchoconstriction after 1 min.</p> <p>Post-O₃: cigarette smoke induced bronchoconstriction more quickly and for a longer period.</p> <p>Selective antagonism of neurokinin 1 and 2 receptors blocked then enhanced O₃-induced bronchoconstriction, suggesting that endogenous tachykinins modulate O₃-induced bronchoconstriction.</p>	Synergistic	Wu et al. (1997)
0.5	ADSS 30 mg/m ³	6 h/day for 3 days 24 h	Mice, male, B6C3F1, 10 weeks old, n = 11	<p>Aged and diluted side stream cigarette smoke (ADSS) exposure followed by O₃.</p> <p>ADSS + O₃: greater increase in BALF cells, %PMN, and proteins compared to alone; 402% increase in proliferating cells in CAR; LPS-stimulated release of IL-6 decreased; LPS-stimulated release of TNF-α increased.</p> <p>ADSS alone: no change in number of proliferating cells in CAR; LPS-stimulated release of TNF-α increased.</p> <p>O₃ alone: 280% increase in proliferating cells in CAR; LPS-stimulated release of IL-6 decreased.</p> <p>Suggests that O₃-induced lung injury is enhanced by prior ADSS exposure.</p>	Synergism	Yu et al. (2002)

Table AX5-18. Interactions Of Ozone With Particles

Concentration		Duration	Species	Endpoints	Interaction	Reference
O₃ (ppm)	PM (mg/m³)					
<u>SULFURIC ACID</u>						
0.1 0.2	0.02-0.15 (0.4-0.8 µm)	23.5 h/day or intermittent 12 h/day for up to 90 days	Rat, male, SD, 250-275 g, n = 6/group	Morphology Biochemistry	No interaction	Last and Pinkerton (1997)
0.1 0.3 0.6	0.50 (0.3 µm) 0.125 (0.3 µm)	3 h	Rabbit NZW male, 3.5-4.5 kg, n = 5/group	AM intracellular pH homeostasis and H ⁺ extrusion	Antagonism	Chen et al. (1995)
0.1 0.3 0.6	0.50 (0.3 µm) 0.125 (0.3 µm)	3 h	Rabbit NZW male, 3.5-4.5 kg, n = 5/group	Airway responsiveness (in vitro bronchial rings + ACh)	Antagonism	El-Fawal et al. (1995)
0.6	0.5 (0.06 and 0.3 µm MMD)	4 h/day for 2 days	Rat, male, SD, 250-300 g, n = 10/group	Morphology: volume percentage of total parenchyma containing injured alveolar septae; bromodeoxyuridine cell labeling index in the periacinar region	Synergism: ultrafine + O ₃ , but not fine Synergism: fine + O ₃	Kimmel et al. (1997)
<u>PARTICLE MIXTURES</u>						
0.1	Diesel PM (NIST #2975) reacted with O ₃ for 48 h	24 h (IT)	Rat, male, SD, 250-300 g, n = 4-13	Inflammation	Synergism	Madden et al. (2000)
0.16 0.30 0.59	0.05-0.22 mg/m ³ ammonium bisulfate 0.03-0.10 mg/m ³ C 0.11-0.39 pm NO ₂ 0.02-0.11 mg/m ³ HNO ₃ , (0.3 µm MMAD)	4 h/day, 3 days/week for 4 weeks	Rat, male, Fischer F344N, 11 weeks old, n = 8-30	breathing pattern, morphology, lavagable protein, and clearance	Complex interactions, but possible loss of typical attenuation seen with O ₃ only exposure, reflecting persistence of inflammation.	Mautz et al. (2001)

Table AX5-18 (cont'd). Interactions Of Ozone With Particles

Concentration		Duration	Species	Endpoints	Interaction	Reference
O ₃ (ppm)	PM (mg/m ³)					
PARTICLE MIXTURES (cont'd)						
0.2	0.07 and 0.14 mg/m ³ ammonium bisulfate (0.45 µm MMMD); 0.05 and 0.10 mg/m ³ carbon	4 h/day, 3 days/week for 4 weeks	Rat, male, Fischer F344, 22-24 months old, n = 5-10	BAL protein and albumin; plasma hydroxylase and fibronectin	Questionable interaction. No changes in BALF protein or prolyl 4-hydroxylase in blood. Small decrease in plasma fibronectin with combined exposure.	Bolarin et al. (1997)
0.2	0.50 mg/m ³ ammonium bisulfate (0.45 µm MMMD) and elemental carbon	4 h/day, 3 days/week for 4 weeks; nose only	Rat, Fischer F344N-NIA, 22-24 months old	DNA labeling of dividing lung epithelial and interstitial cells by 5-bromo-2-deoxyuridine	Synergism. Increased AM phagocytosis and respiratory burst. Decreased lung collagen.	Kleinman et al. (2000)
0.3	0.063 to 1.57 mg/m ³ CAPs (Boston) + ip OVA sensitization	Sensitized at day 7 and 14. Challenged at day 21, 22, and 23. 5 h O ₃ exposure	Mice, BALB/c, n = 5-6/group	Airway function	Interaction: increased R _L and airway responsiveness in normal and OVA-sensitized mice.	Kobzik et al. (2001)
0.4	0.20 and 0.50 mg/m ³ fine, H ₂ O ₂ -coated carbon (0.26 µm MMMD)	4 h/day for 1 or 5 days	Rat, SD, 300 g, n = 10	Inflammation	Synergism for effect on day 5. Greater response at high dose, contrasts with O ₃ along where inflammation was greatest at 0.4 ppm on day 1.	Kleinman et al. (1999)
0.5	Endotoxin (IN) 100 µg 24 h and 48 h after the 3rd O ₃ exposure	8 h/day for 3 days	Rat, Fischer F344, 10-12 weeks old, n = 6/group	Nasal morphology	Synergism: increased intraepithelial mucosubstances and mucous cell metaplasia	Fanucchi et al. (1998) Wagner et al. (2001a,b)
0.5	OVA (IN) 50 µl (1%)	8 h/day for 1 day or 3 consecutive days	Rat, Brown, Norway, 10-12 weeks old, n = 6/group	Nasal morphology	Synergism: increased intraepithelial mucosubstances and mucous all metaplasia.	Wagner et al. (2002)

Table AX5-18 (cont'd). Interactions Of Ozone With Particles

Concentration		Duration	Species	Endpoints	Interaction	Reference
O ₃ (ppm)	PM (mg/m ³)\					
<u>PARTICLE MIXTURES</u> (cont'd)						
0.8	0.5 mg, 1.5 mg, or 5 mg of PM from Ottawa Canada (EHC-93)	2, 4, and 7 days after IT instillation	Rat, male, Wistar, 200-250 g, n = 5/group	Inflammation	Interaction: increased TNF- α in BALF.	Ulrich et al. (2002)
1	0.11 mg/m ³ ultra fine carbon (25 nm CMD) + endotoxin (IH)	6 h	Rat, male, Fischer F344, 10 weeks and 22 months old, n = 3/group Mice, male, TSK, 14-17 months old, n = 6-7/group	Inflammation	Interaction: increased PMNs and ROS release from BALF cells for old rats and mice primed with endotoxin; depressed in young rats.	Elder et al. (2000a,b)
1	Endotoxin (37.5 EU) for 10 min	4, 20, or 24 h	Mice, C57BL/6J, 36 h old, 8 weeks old, n = 12/group	Inflammation	Synergism: increased BALF protein and PMNs.	Johnston et al. (2000b, 2002)
1	Endotoxin (IN) 0, 2, or 20 μ g in 120 μ L	8 h, repeated after 24 h	Rat, male, Fischer F344, 10-12 weeks old, n = 6/group	Lung morphometric analysis and inflammation	Synergism: increased BALF PMNs and mucin glycoprotein; increased intraepithelial mucosubstances and mucingene mRNA.	Wagner et al. (2003)

Table AX5-18 (cont'd). Interactions Of Ozone With Particles

Concentration		Duration	Species	Endpoints	Interaction	Reference
O ₃ (ppm)	PM (mg/m ³)					
<u>PARTICLE MIXTURES</u> (cont'd)						
0.8	EHC-93, 5 mg/m ³ or 50 mg/m ³	4 h exposure, clean air for 32 h, ³ H injection followed by assay at 90 min	Rat, male, Fischer F344, 200-250 g, n = 6/group	Control rats: ³ H labeling (indicative of proliferation) low in bronchioles and parenchyma. EHC-93 alone: no induction of proliferation. O ₃ alone: increased cell labeling in bronchioles and parenchyma, suggestive of reparative cell proliferation. EHC-93 + O ₃ : both doses of EHC-93 potentiated proliferation, especially in epithelia of terminal bronchioles and alveolar ducts, but not distal parenchyma. Suggests that ambient PM can enhance O ₃ -induced proliferations and exacerbate injury.	Synergism of proliferation	Vincent et al. (1997)
0.8	(EHC93) at 50 mg/m ³	4 h, exposure, clean air for 32 h, ³ H injection followed by assay at 90 min	Rat, male, Fischer F344, 200-250 g, n = 4/group	O ₃ + EHC-93: epithelial cell injury and proliferation (³ H-labeling) higher than single exposures; higher in periductal region than in whole lung counts; greater numbers of AMs and PMNs in lung tissue compartment than in single exposures. Suggests that exposures to urban PM have few effects alone, but can potentiate O ₃ -induced injury.	Synergism	Adamson et al. (1999)

Table AX5-18 (cont'd). Interactions Of Ozone With Particles

Concentration		Duration	Species	Endpoints	Interaction	Reference
O ₃ (ppm)	PM (mg/m ³)					
PARTICLE MIXTURES (cont'd)						
0.15	HNO ₃ 50 µg/m ³	4 h/day, 3 days/week for 40 weeks, nose-only exposure	Rat, male, Fischer F344/N, 8 weeks old, n = 4-5/group	<p>O₃ alone: 28% increase in lung putrescine.</p> <p>HNO₃ alone: 21% decrease in lung putrescine</p> <p>O₃ and O₃ + HNO₃: 56% increase in lung putrescine</p> <p>Pulmonary spermidine and spermine did not change with any exposure.</p> <p>Suggests role of putrescine in regulation of inflammation.</p>	Synergism	Sindhu et al. (1998)
0.5	Carbon Black (CB), 0.5 or 1.5 mg/rat	Intratracheal CB followed by 7 days or 2 months of O ₃	Rat, male, Wistar, 7 weeks old, n = 7-8/group	<p>Phagocytotic capacity: decreased in CB-exposed group, unchanged in O₃ group. Formation of superoxide anion radicals and numbers of ingested particles increased at 2 months in O₃ group.</p> <p>Chemotactic migration: decreased in CB-treated group.</p> <p>Suggests that CB impairs phagocytosis and chemotactic migration in AMs, whereas O₃ stimulates these functions.</p>	Synergism	Creutzenberg et al. (1995)

Table AX5-18 (cont'd). Interactions Of Ozone With Particles

Concentration			Duration	Species	Endpoints	Interaction	Reference
O ₃ (ppm)	PM (mg/m ³)						
PARTICLE MIXTURES (cont'd)							
0.018	CH ₂ O TSP PM ₁₀ PM _{2.5}	3.3 ppb 0.068 mg/m ³ 0.032 mg/m ³ 0.016 mg/m ³	23 h/day for 7 weeks	Rat, male and female, Fischer F344, 9 weeks old, n = 5/group	Exposure to filtered and unfiltered Mexico City air. Histopathology revealed no nasal lesions in exposed or control rats; tracheal and lung tissue from both groups showed similar levels of minor abnormalities.		Moss et al. (2001)

VMD = Volume median diameter
 σg = Geometric standard deviation
 MMAD = Mass median aerodynamic diameter
 CMD = Count median diameter
 PM = Particulate Matter
 OVA= Ovalbumin
 R_L = Total Pulmonary Resistance

AED = Aerodynamic diameter
 BAL = Bronchoalveolar lavage
 AM = Alveolar macrophage
 IN = Intranasal
 IT = Intratracheal
 Unless indicated otherwise, whole-body exposures used

Table AX5-19. Effects of Other Photochemical Oxidants

Concentration ppm	Duration	Species	Effects	Reference
H ₂ O ₂ (10, 20, or 100 ppb) and/or (NH ₄) ₂ S ₂ O ₈ (429 or 215 Ág/m ³ ; 0.3-0.4 gm mass median diameter)	2 h, assayed 0 or 24 h PE	Rat, female, SD, n = 4-18/group	Exposures alone or in combination. H ₂ O ₂ + (NH ₄) ₂ S ₂ O ₈ : no effect on BALF cell number, viability, protein or LDH at either time point; increased PMNs adhered to vascular epithelium; increased TNF- α by AMs at both time points; at 0 h PE, transient increase in superoxide anion by AMs; decreased NO production; nitrotyrosine detected; heme oxygenase-1 expression upregulated in AMs; H ₂ O ₂ only: decreased NO production which persisted for 24 h. Suggests that PM-induced effects are augmented by H ₂ O ₂ and that PM-induced tissue injury may be modulated by cytotoxic mediators produced by AMs.	Morio et al. (2001)
PAN 0.13,0.66,1.31	3 h	PBL from mice, male, CD-1, 5 weeks old, n = 25	In vitro: Exposed peripheral blood lymphocytes (PBL) to PAN; assayed for chromosome aberrations, sister chromatid exchanges and DNA damage. DNA damage was observed at cytotoxic concentrations of PAN. No effects at noncytotoxic exposures.	Kligerman et al. (1995)
0.077,0.192,0.384	1 h	Mice, male, B6C3F1, 6 weeks old, n = 4	In vivo: Nose-only exposures. No dose-related effects at any exposure level in any assay. Suggests that PAN, both in vitro and in vivo, is not a DNA damaging agent or clastogen.	
0, 15, 39, or 78 ppm	1 h	Hamster, Chinese, n = 4	Measured frequency of thioguanine-resistant lung fibroblasts and frequency of micronuclei in either the bone marrow or the lungs. Mutation frequencies not altered from control levels. No chromosome breakage was observed in bone marrow or lung. Suggests no mutagenicity in vivo.	Heddle et al. (1993)
3 ppm PAN	1 month	Salmonella TA100	Gas phase exposure PAN-induced mutants: 59% GC \rightarrow TA; 29% GC \rightarrow AT; 2% GC \rightarrow CG; 10% multiple mutations — primarily GG \rightarrow TT tandem-base substitutions.	DeMarini et al. (2000)
~300 ppb	4, 7, 10, or 12 h	Mice, Big Blue [®] , male, 4 weeks old, n = 15	Nose-only exposure. Mutagenic at the lacI gene in the lung; no tandem-base mutations.	
78 ppm	24 h	Nasal tissue: 3.9% of the radiolabel. Lung: 0.3 % of radiolabel.	Suggests that PAN is weakly mutagenic in Salmonella (with a signature GG \rightarrow TT transversion) and in mouse lung.	
~80 ppm ³ H-PAN	1 h			

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ANNEX AX6. CONTROLLED HUMAN EXPOSURE STUDIES OF OZONE AND RELATED PHOTOCHEMICAL OXIDANTS

AX6.1 INTRODUCTION

Results of ozone (O₃) studies in laboratory animals and in vitro test systems were presented in Chapter 5 and Annex 5. The extrapolation of results from animal studies is one mechanism by which information on potential adverse human health effects from exposure to O₃ is obtained. More direct evidence of human health effects due to O₃ exposure can be obtained through controlled human exposure studies of volunteer subjects or through field and epidemiologic studies of populations exposed to ambient O₃. Controlled human exposure studies, discussed in this chapter, typically use fixed concentrations of O₃ under carefully regulated environmental conditions and subject activity levels.

Most of the scientific information selected for review and evaluation in this chapter comes from the literature published since 1996 which, in addition to further study of physiological pulmonary responses and respiratory symptoms, has focused on mechanisms of inflammation and cellular responses to injury induced by O₃ inhalation. Older studies are discussed where only limited new data are available and where new and old data are conflicting. The reader is referred to both the 1986 and 1996 Air Quality Criteria documents (U.S. Environmental Protection Agency, 1986, 1996) for a more extensive discussion of older studies. Summary tables of the relevant O₃ literature are included for each of the major subsections. In summarizing the human health effects literature, changes from control are described if statistically significant at a probability (p) value less than 0.05, otherwise trends are noted as such.

AX6.2 PULMONARY FUNCTION EFFECTS OF OZONE EXPOSURE IN HEALTHY SUBJECTS

AX6.2.1 Introduction

The responses observed in young healthy nonsmoking human adults exposed to ambient O₃ concentrations include decreased inspiratory capacity; mild bronchoconstriction; rapid, shallow breathing pattern during exercise; and symptoms of cough and pain on deep inspiration. In addition, O₃ has been shown to result in airway hyperresponsiveness as demonstrated by an increased physiological response to a nonspecific bronchoconstrictor, as well as airway injury and inflammation assessed via bronchoalveolar lavage and biopsy. Reflex inhibition of inspiration and consequent decrease in inspiratory capacity results in a decrease in forced vital capacity (FVC) and total lung capacity (TLC) and, in combination with mild bronchoconstriction, contributes to a decrease in the forced expiratory volume in 1 s (FEV₁). Given that both FEV₁ and FVC are subject to decrease with O₃ exposures, changes in the ratio (FEV₁/FVC) become difficult to interpret and so are not discussed.

The majority of controlled human studies have investigated the effects of exposure to variable O₃ concentrations in healthy subjects performing continuous exercise (CE) or intermittent exercise (IE) for variable periods of time. These studies have several important limitations: (1) the ability to study only short-term, acute effects; (2) the inability to link short-term effects with long-term consequences; (3) the use of a small number of volunteers that may not be representative of the general population; and (4) the statistical limitations associated with the small sample size. Nonetheless, studies reviewed in the 1996 EPA criteria document (U.S. Environmental Protection Agency, 1996) provided a large body of data describing the effects and dose-response characteristics of O₃ as function of O₃ concentration (C), minute ventilation (\dot{V}_E), and duration or time (T) of exposure. In most of these studies, subjects were exposed to O₃ and to filtered air (FA [reported as 0 ppm O₃]) as a control. The most salient observations from these studies were: (1) healthy subjects exposed to O₃ concentrations ≥ 0.08 ppm develop significant reversible, transient decrements in pulmonary function if \dot{V}_E or T are increased sufficiently, (2) there is a large degree of intersubject variability in physiologic and symptomatic responses to O₃ and these responses tend to be reproducible within a given individual over a several months period, and (3) subjects exposed repeatedly to O₃ over several

days develop a tolerance to successive exposures, as demonstrated by an attenuation of responses, which is lost after about a week without exposure.

In this section, the effects of single O₃ exposures of 1- to 8-h in duration on pulmonary function in healthy nonsmoking subjects are examined by reviewing studies that investigate: (1) the O₃ exposure-response relationship; (2) intersubject variability, individual sensitivity, and the association between responses; and (3) mechanisms of pulmonary function responses and the relationship between tissue-level events and functional responses. Discussion will largely be limited to studies published subsequent to the 1996 EPA criteria document (U.S. Environmental Protection Agency, 1996)

AX6.2.2 Acute Ozone Exposures for Up to 2 Hours

At-Rest Exposures. Exposure studies investigating the effects of O₃ exposures on sedentary subjects were discussed in the 1986 EPA criteria document (U.S. Environmental Protection Agency, 1986). The lowest O₃ concentration at which significant reductions in FVC and FEV₁ were reported was 0.5 ppm (Folinsbee et al., 1978; Horvath et al., 1979). Based on the average O₃ responses in these two studies (corrected for FA responses), resting young adults (n = 23, age = 22) exposed to 0.5 ppm O₃ have a ~4% reduction in FVC and a ~7% reduction FEV₁. At lower O₃ concentrations of 0.25 to 0.3 ppm, resting exposures did not significantly affect lung function.

Exposures with Exercise. Collectively, the studies reviewed in the 1996 EPA criteria document (U.S. Environmental Protection Agency, 1996) demonstrated that healthy young adults performing moderate to heavy IE or CE of 1 to 2.5 h duration, exposed to 0.12 to 0.18 ppm O₃ experienced statistically significant decrements in pulmonary function and respiratory symptoms. As an example, 2 hr exposures to 0.12 and 0.18 ppm O₃ during heavy IE (exercise $\dot{V}_E = 65$ L/min) have resulted in FEV₁ decrements of $2.0 \pm 0.8\%$ (mean \pm SE; n = 40) and $9.5 \pm 1.1\%$ (n = 89), respectively (McDonnell and Smith, 1994). Significant decrements in pulmonary function have been reported in heavily exercising healthy adults exposed for 1 h with CE at O₃ concentrations of 0.12 ppm (Gong et al., 1986), 0.16 ppm (Avol et al., 1984), and 0.2 ppm (Adams and Schelegle, 1983; Folinsbee et al., 1984).

In an attempt to describe O₃ dose-response characteristics, many investigators modeled acute responses as a function of total inhaled O₃ dose ($C \times T \times \dot{V}_E$), which was found to be a

better predictor of response than O_3 concentration, \dot{V}_E , or T of exposure, alone. In an analysis of 6 studies with 1 to 2 h exposures to between 0.12 and 0.18 ppm O_3 with exercise, Folinsbee et al. (1988) reported a good correlation ($r = 0.81$) between total inhaled O_3 dose and FEV_1 decrements. For a given exposure duration, total inhaled O_3 dose can be increased by increases in C and/or \dot{V}_E . In exposures of fixed duration, results of several studies suggested that O_3 concentration was a more important predictor of response or explained more of the variability in response than \dot{V}_E (Adams et al., 1981; Folinsbee et al, 1978; Hazucha, 1987). Based on a review of previously published studies, Hazucha (1987) noted that relative to the FEV_1 decrement occurring at a given C and \dot{V}_E , doubling C (e.g., from 0.1 to 0.2 ppm) would increase the FEV_1 decrement by 400%, whereas doubling the \dot{V}_E (e.g., from an exercise \dot{V}_E of 20 to 40 L/min) which would only increase the FEV_1 decrement by 190%. Thus, C appears to have a greater affect than \dot{V}_E on FEV_1 responses even when total inhaled O_3 doses are equivalent.

New studies (i.e., not reviewed in the 1996 EPA criteria document) that provide spirometric responses for up to 2 h exposures are summarized in Table AX6-1. Most of these newer studies have investigated mechanisms affecting responses, inflammation, and/or effects in diseased groups versus healthy adults, accordingly their findings may be summarized differently in several sections of this chapter. Rather than being interested in responses due to O_3 versus FA exposures, many of the newer studies have tested the effects of a placebo versus treatment in modulating responses to O_3 exposure. Studies appearing in Table 1, but not discussed in this section, are discussed in other sections of this chapter as indicated within the table.

McDonnell et al. (1997) pooled the results of eight studies entailing 485 healthy male subjects exposed for 2 h on one occasion to one of six O_3 concentrations (0.0, 0.12, 0.18, 0.24, 0.30, or 0.40 ppm) at rest or one of two levels of IE (\dot{V}_E of 25 and 35 L/min/m² BSA). FEV_1 was measured preexposure, after 1 h of exposure, and immediately postexposure. Decrements in FEV_1 were modeled by sigmoid-shaped curve as a function of subject age, O_3 concentration, \dot{V}_E , and T. The modeled decrements reach a plateau with increasing T and dose rate ($C \times \dot{V}_E$). That is, for a given O_3 concentration, exercise \dot{V}_E level, and after a certain length of exposure, the FEV_1 response tends not to increase further with increasing duration of exposure. The modeled FEV_1 responses increased with $C \times \dot{V}_E$ and T, decreased with subject age, but were only

Table AX6-1. Controlled Exposure of Healthy Humans to Ozone for 1 to 2 Hours During Exercise^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.0 0.4	0 784	2 h IE 4 × 15 min on bicycle, V _E = 30 L/min	NA	5 M, 4 F 6 M, 7 F	Healthy adults 25 ± 2 years old Mild atopic asthmatics 22 ± 0.7 years old	O ₃ -induced reductions in FVC (12%, 10%) and FEV ₁ (13%, 11%) for asthmatic and healthy subjects. Significant reductions in mid-flows in both asthmatics and healthy subjects. Indomethacin pretreatment significantly decreased FVC and FEV ₁ responses to O ₃ in healthy but not asthmatic subjects. <i>See Section AX6.3.2 and Tables AX6-3 and AX6-13.</i>	Alexis et al. (2000)
0.0 0.2	0 392	2 h IE 4 × 15 min at V _E = 20 L/min/m ² BSA	20 °C 50% RH	8 M, 5 F	Healthy NS median age 23 years	Median O ₃ -induced decrements of 70 mL, 190 mL, and 400 mL/s in FVC, FEV ₁ , and FEF ₂₅₋₇₅ , respectively. Spirometric responses not predicted of inflammatory responses. <i>See Sections AX6.2.5.2, AX6.5.6, and AX6.9.3 and Table AX6-12.</i>	Blomberg et al. (1999)
0.0 0.2	0 392	2 h IE 4 × 15 min at V _E = 20 L/min/m ² BSA	20 °C 50% RH	10 M, 12 F	Healthy NS mean age 24 years	Significant O ₃ -induced decrement in FEV ₁ immediately postexposure but not significantly different from baseline 2 h later. No correlation between Clara cell protein (CC16) and FEV ₁ decrement. CC16 levels, elevated by O ₃ exposure, remained high at 6 h postexposure, but returned to baseline by 18 h postexposure. <i>See Table AX6-13.</i>	Blomberg et al. (2003)
0.0 0.33	0 647	2 h IE 4 × 15 min on bicycle ergometer (600 kpm/min)	NA	9 M	Healthy NS 26.7 ± 7 years old	O ₃ -induced reductions in FVC (7%). FRC not altered by O ₃ exposure. Post FA, normal gradient in ventilation which increased from apex to the base of the lung. Post O ₃ , ventilation shifted away from the lower-lung into middle and upper-lung regions. The post O ₃ increase in ventilation to mid-lung region was correlated with decrease in midmaximal expiratory flow (r = 0.76, p < 0.05).	Foster et al. (1993)
0.0 0.35	0 690	2.2 h IE 2 × 30 min on treadmill (V _E ≈ 50 L/min) Final 10 min rest	19-23 °C 48-55% RH	15 M	Healthy NS 25.4 ± 2 years old	Pre- to post-O ₃ , mean FVC and FEV ₁ decreased by 12 and 14%, respectively. Following O ₃ exposure, there was a pronounced slow phase evident in multibreath nitrogen washouts which, on average, represented a 24% decrease in the washout rate relative to pre-O ₃ .	Foster et al. (1997)

AX6-5

Table AX6-1 (cont'd). Controlled Exposure of Healthy Humans to Ozone for 1 to 2 Hours during Exercise^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions ^c	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.0	0	2 h rest or IE (4 × 15 min at $\dot{V}_E = 25$ or 35 L/min/m ² BSA)	22 °C 40% RH	485 M (each subject exposed at one activity level to one O ₃ concentration)	Healthy NS 18 to 36 years old mean age 24 years	Statistical analysis of 8 experimental chamber studies conducted between 1980 and 1993 by the U.S. EPA in Chapel Hill, NC. Decrement in FEV ₁ described by sigmoid-shaped curve as a function of subject age, O ₃ concentration, \dot{V}_E , and time. Response decreased with age, was minimally affected by body size corrections, and was not more sensitive to O ₃ concentration than \dot{V}_E . <i>Also see Section AX6.5.</i>	McDonnell et al. (1997)
0.12	235						
0.18	353						
0.24	471						
0.30	589						
0.40	784						
0.4	784	2 h IE 20 min mild-mod. exercise, 10 min rest	NA	4 M, 5 F	Healthy NS 30 ± 3 years old	Subjects previously in Nightingale et al. (2000) study. Placebo-control: Immediately postexposure decrements in FVC (9%) and FEV ₁ (14%) relative to pre-exposure values. FEV ₁ decrement only 9% at 1 hr postexposure. By 3 h postexposure, recovery in FVC to 97% and FEV ₁ to 98% of preexposure values. Significant increases in 8-isoprostane at 4 h postexposure. Budesonide for 2 wk prior to exposure did not affect responses.	Montuschi et al. (2002)
0.0	392	2 h IE 4 × 15 min at $\dot{V}_E = 20$ L/min/m ² BSA	20 °C 50% RH	6 M, 9 F	Healthy adults 24 years old	O ₃ -induced FEV ₁ decrement (8%, healthy adults; 3% asthmatics) and PMN increase (20.6%, healthy adults; 15.2% asthmatics). Primary goal was to investigate relationship between antioxidant defenses and O ₃ responses in asthmatics and healthy adults. <i>See Tables AX6-3 and AX6-13.</i>	Mudway et al. (2001) Stenfors et al. (2002)
0.2				9 M, 6 F	Mild asthmatics 29 years old		
0.4	784	2 h IE 20 min mild-mod. exercise, 10 min rest	NA	6 M, 9 F	Healthy NS mean age ~31 years	Placebo-control: O ₃ caused significant decrements in FEV ₁ (13.5%) and FVC (10%) immediately following exposure, a small increase in MCh-reactivity, and increased PMNs and myeloperoxidase in induced sputum at 4 h postexposure. FEV ₁ at 96% and FVC at 97% preexposure values at 3 h postexposure. Budesonide for 2 wk prior to exposure did not affect spirometric responses. <i>See Section AX6.2.5 and Table AX6-13.</i>	Nightingale et al. (2000)

Table AX6-1 (cont'd). Controlled Exposure of Healthy Humans to Ozone for 1 to 2 Hours during Exercise^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions ^c	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.0 0.4	784	2 h IE 4 × 15 min at $\dot{V}_E = 18$ L/min/m ² BSA 2 exposures: 25% subjects exposed to air-air, 75% to O ₃ -O ₃	21 °C 40% RH	Weak responders 7 M, 13F Strong responders 21 M, 21 F	Healthy NS 20 to 59 years old	Significant O ₃ -induced decrements in spirometric lung function. Young adults (<35 years) were significantly more responsive than older individuals (>35 years). Sufentanil, a narcotic analgesic, largely abolished symptom responses and improved FEV ₁ in strong responders. Naloxone, an opioid antagonist, did not affect O ₃ effects in weak responders. <i>See Section AX6.2.5.1.</i>	Passannante et al. (1998)
0.0 0.4	784	2 h IE 4 × 15 min at $\dot{V}_E = 20$ L/min/m ² BSA	20 °C 40% RH	Placebo group 15 M, 1 F Antioxidant group 13 M, 2 F	Healthy NS mean age 27 years	Placebo and antioxidant groups had O ₃ -induced decrements in FEV ₁ (20 and 14%) and FVC (13 and 10%), respectively. Percent neutrophils and IL-6 levels in BAL fluid obtained 1 h postexposure were not different in the two treatment groups. <i>See Table AX6-13.</i>	Samet et al. (2001) Steck-Scott et al. (2004)
0.0 0.25	490	1 h CE $\dot{V}_E = 30$ L/min	NA Face mask exposure	32 M, 28 F	Healthy NS 22.6 ± 0.6 years old	Mean O ₃ -induced FEV ₁ decrements of 15.9% in males and 9.4% in females (gender differences not significant). FEV ₁ decrements ranged from -4 to 56%; decrements >15% in 20 subjects and >40% in 4 subjects. Uptake of O ₃ greater in males than females, but uptake not correlated with spirometric responses.	Ultman et al. (2004)

^aSee Appendix A for abbreviations and acronyms.

^bListed from lowest to highest O₃ concentration.

^cStudies conducted in exposure chamber unless otherwise indicated.

minimally affected by body size corrections to \dot{V}_E . Fitted and experimental FEV₁ decrements following a 2 h exposure at three nominal levels of \dot{V}_E are illustrated in Figure AX6-1 as a function of O₃ concentration. Their analysis indicated that C was marginally, but not significantly, more important than \dot{V}_E in predicting FEV₁ response. Additionally, the McDonnell et al. (1997) analysis revealed that some prior analyses of IE protocols may have over estimated the relative importance of C over \dot{V}_E in predicting FEV₁ responses by considering only the \dot{V}_E during exercise and ignoring the \dot{V}_E during periods of rest.

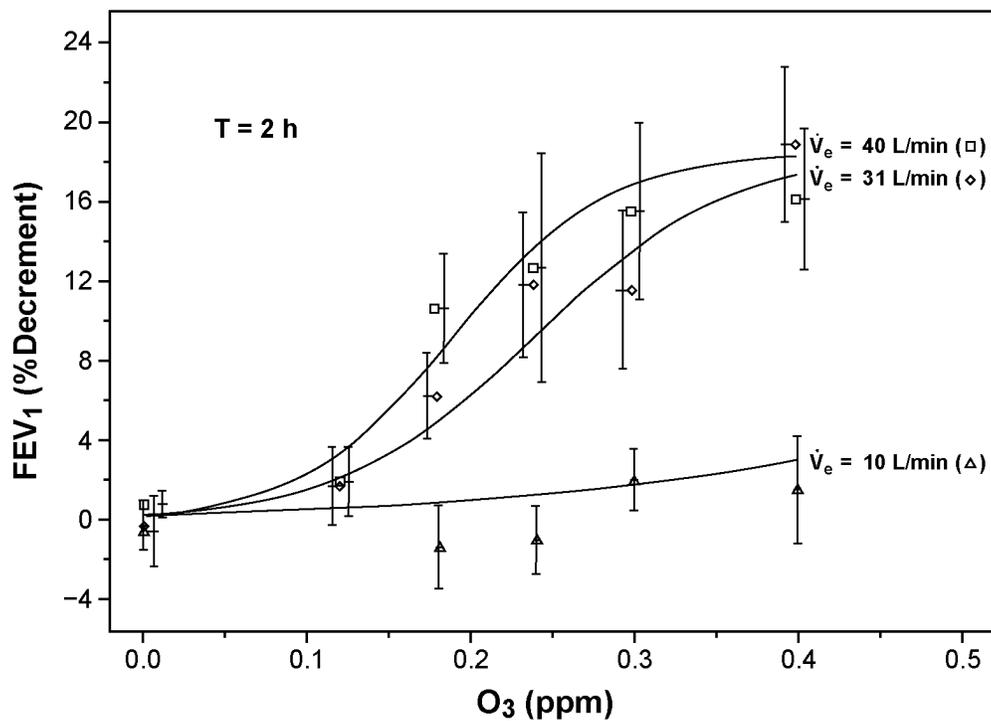


Figure AX6-1. FEV₁ decrements as a function of O₃ concentration following a 2 h exposure with incremental exercise (15 min intervals) or rest. Points are experimental data (mean \pm SE) and lines are model predictions for each activity level. Minute ventilation (\dot{V}_E) represent average across intervals of rest and exercise.

Source: McDonnell et al. (1997).

Ultman et al. (2004) measured O₃ uptake and pulmonary responses in 60 young healthy nonsmoking adults (32 M, 28 F). A bolus technique was used to quantify the uptake of O₃ as a function of the volume into the lung which the bolus penetrated. From these measurements, the volumetric depth at which 50% uptake occurred was calculated. This volumetric lung depth was correlated with conducting airways volume, i.e., a greater fraction of O₃ penetrated to deeper into the lungs of individuals with larger conducting airways volumes. Two weeks after the bolus measurements, subjects were exposed via a face mask to FA and subsequently two weeks later to 0.25 ppm O₃ for 1 h with CE at a target \dot{V}_E of 30 L/min. The breath-by-breath uptake of O₃ was measured. There was a small but significant reduction in the breath-by-breath uptake of O₃ from 90.6% on average for the first 15 minutes to 87.3% on average for the last 15 minutes of exposure. The uptake fraction was significantly greater in males (91.4%) than females (87.1%), which is consistent with the larger f_b and smaller V_T of the females than males. Uptake was not correlated with spirometric responses. However, there was a tendency for males to have greater O₃-induced FEV₁ decrements than females, 15.9% versus 9.4%, respectively. There was considerable intersubject variability in FEV₁ decrements which ranged from -4 to 56% with 20 subjects having decrements of >15% and 4 subjects with >40% decrements (*see Section AX6.4 for additional discussion regarding intersubject variability*).

Few studies have measured the effect of ozone on ventilation distribution within the lung. Foster et al. (1993) measured the effect of ozone on the vertical distribution of inspired air in the lung using planar gamma scintigraphy. Nine healthy nonsmoking males (26.7 ± 7 years old) were randomly exposed to FA or 0.33 ppm O₃ for 2 h with IE. After each exposure session, subjects inhaled a 2- to 4-ml bolus of xenon-133 while seated in front of a gamma camera. Images were acquired at the end of the first inspiration and 5-6 breaths later after the xenon had equilibrated between lung regions. Using these images, the distribution of ventilation and volume between upper-, middle-, and lower-lung regions was quantified. Post-O₃ relative to post-FA, there were significant reductions in FVC (FA, 5.23 ± 0.5; O₃, 4.88 ± 0.5 liters) and midmaximal expiratory flow (FA, 3.82 ± 0.8; O₃, 3.14 ± 0.9 liter/sec). Neither FRC nor the distribution of volume (upper, 26.5%; middle, 42.5%; lower, 31%) between lung compartments were affected by O₃ exposure. After the FA exposure, the distribution of ventilation per unit volume increased with progression from the apex to the base of the lung, i.e., the lower lung regions received the greatest ventilation. Following O₃ exposure, there was a significant

reduction in the ventilation to the lower-lung and significant increases in ventilation to the upper- and middle-lung regions relative to the FA values in 7 of the 9 subjects. The post-O₃ increase in middle-lung ventilation was correlated with the decrease in midmaximal expiratory flow ($r = 0.76, p < 0.05$).

Foster et al. (1997) measured the effect of ozone on ventilation distribution using a multiple breath nitrogen washout. Fifteen healthy nonsmoking males (25.4 ± 2 years old) were randomly exposed to FA or 0.35 ppm O₃ for 2.2 h with IE. Subjects alternated between 30 min periods of rest and treadmill exercise ($\dot{V}_E \approx 10 \times \text{FVC} \approx 50 \text{ L/min}$). The final exercise period was followed by 10 min rest period. Multiple breath nitrogen washout and spirometry were measured pre- and immediately postexposure. At 24-h post-O₃ exposure, 12 of 15 subjects returned and completed an additional multibreath nitrogen washout maneuver. Pre- to post-O₃ exposure, the mean FVC and FEV₁ were significantly decreased by 12 and 14%, respectively. Exposure to FA did not appreciably affect spirometry or the multibreath nitrogen washout. Following O₃ exposure, the washout of nitrogen was delayed and resembled a two-compartment washout, whereas pre-O₃ exposure the log-linear clearance of nitrogen as a function of expired volume resembled a single-compartment washout. The clearance rate of the slow compartment was approximated as the slope ($\text{Ln}[\text{N}_2]$ per expired volume) of the nitrogen washout between 20% and 9% nitrogen. Post-O₃, there was a pronounced slow phase evident in nitrogen washout which, on average, represented a 24% decrease in the washout rate relative to pre-O₃. Data for a single subject (see Figure 6-1) allowed for the size of the slow compartment to be determined. For this subject, the slow compartment represented 23% of the lung. This is fairly consistent with Foster et al. (1993) where ventilation to the lower-lung (31% of volume) was reduced post-O₃. At 24-h post-O₃, 6 of the 12 subjects who completed an additional nitrogen washout maneuver had a delayed washout relative to the pre-O₃ maneuver. This suggests a prolonged O₃ effect on the small airways and ventilation distribution in some individuals.

AX6.2.3 Prolonged Ozone Exposures

Between 1988 and 1994, a number of studies were completed that described the responses of subjects exposed to relatively low (0.08 to 0.16 ppm) O₃ concentrations for exposure durations of 4 to 8 h. These studies were discussed in the 1996 criteria document (U.S. Environmental Protection Agency, 1996) and only a select few are briefly discussed here. Table AX6-2 details

Table AX6-2. Pulmonary Function Effects after Prolonged Exposures to Ozone^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
<i>Studies with 4 hr Exposures</i>							
0.18	353	4 h IE (4 × 50 min) V _E = 35 L/min	23 °C 50% RH	2 M, 2 F	Adults NS, 21 to 33 years old	FVC decreased 19% and FEV ₁ decreased 29% in these four pre-screened sensitive subjects.	Adams (2000a)
0.0 0.20	0 392	4 h IE (4 × 50 min cycle ergometry or treadmill running [V _E = 40 L/min])	20 °C 50% RH	FA: 11 M, 3 F O ₃ : 9 M, 3 F	Adult NS, 19 to 41 years old	Decrease in FVC, FEV ₁ , V _T , and SRaw and increase in f _B with O ₃ exposure compared with FA; total cell count and LDH increased in isolated left main bronchus lavage and inflammatory cell influx occurred with O ₃ exposure compared to FA exposure.	Aris et al. (1993)
0.2	392	4 h IE (4 × 50 min) V _E = 25 L/min/m ² BSA	20 °C 50% RH	42 M, 24 F	Adults NS, 18 to 50 years old	FEV ₁ decreased by 18.6%; Pre-exposure methacholine responsiveness was weakly correlated with the functional response to O ₃ exposure. Symptoms were also weakly correlated with the FEV ₁ response (r = -0.31 to -0.37)	Aris et al. (1995)
0.0 0.24	0 470	4 h IE (4 × 15 min) V _E = 20 L/min	24 °C 40% RH	10 M 9 M	Healthy NS, 60 to 69 years COPD 59 to 71 years	Healthy: small, 3.3%, decline in FEV ₁ (p = 0.03 [not reported in paper], paired-t on O ₃ versus FA pre-post FEV ₁). COPD: 8% decline in FEV ₁ (p = ns, O ₃ versus FA). Adjusted for exercise, ozone effects did not differ significantly between COPD patients and healthy subjects. <i>See Section AX6.5.1.</i>	Gong et al. (1997a)
<i>Studies with >6 hr Exposures</i>							
0.0 0.06 0.08	0 118 157	6.6 h IE (6 × 50min) V _E = 20 L/min/m ² BSA	25 °C 40-60% RH	15 M, 15 F	Healthy NS Males 23.5 ± 3.0 yrs Females 22.8 ± 1.2 yrs	FEV ₁ and symptom responses after 6.6 h exposure to 0.04 and 0.06 ppm not significantly different from FA. Following exposure to 0.08 ppm, O ₃ -induced FEV ₁ (-6.1%, square-wave; -7.0%, triangular) and symptom responses significantly greater than after 0.04 and 0.06 ppm exposures. Triangular exposure to 0.08 ppm caused peak decrement in FEV ₁ at 5.6 h of exposure, whereas peak for square-wave exposure occurred at 6.6 h.	Adams (2006)
0.04 (mean, peak of 0.05) 0.06 (mean, peak of 0.09) 0.08 (mean, peak of 0.15)	78 118 157						
0.0 0.04 0.08 0.12	0 78 157 235	6.6 h IE (6 × 50min) V _E = 20 L/min/m ² BSA	23 °C 50% RH	15 M, 15 F	Healthy NS, 22.4 ± 2.4 yrs old	FEV ₁ and total symptoms after 6.6 h exposure to 0.04 ppm not significantly different from FA. FEV ₁ (-6.4%) and total symptoms significant at 6.6 h exposure to 0.08 ppm. FEV ₁ (-15.4%) at 6.6 h not significantly different between chamber and face mask exposure to 0.12 ppm.	Adams (2002)

Table AX6-2 (cont'd). Pulmonary Function Effects after Prolonged Exposures to Ozone^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.12	235	3 day-6.6h/day IE (6 × 50 min) $\dot{V}_E = 17$ L/min/m ² , 20 L/min/m ² BSA, and 23 L/min/m ² BSA	23 °C 50% RH	15 M, 15 F	Healthy NS, 18 to 31 years old	FEV ₁ at 6.6 h decreased significantly by 9.3%, 11.7%, and 13.9%, respectively at three different exercise \dot{V}_E rates, but were not significantly different from each other. Total symptoms at the highest \dot{V}_E protocol were significantly greater than for the lowest \dot{V}_E protocol beginning at 4.6 h. Largest subjects (2.2 m ² BSA) had significantly greater average FEV ₁ decrement for the three protocols, 18.5% compared to the smallest subjects (1.4 m ² BSA), 6.5%.	Adams (2000b)
(a) 0.08 (b) 0.08 (mean) varied from 0.03 to 0.15	235 235 (mean)	6.6 h IE (6 × 50 min) $\dot{V}_E = 20$ L/min/m ² BSA	23 °C 50% RH	15 M 15 F	Healthy NS, 18 to 25 years old	(a) FEV ₁ decreased 6.2% after 6.6 h in square-wave exposures. Total symptoms significantly increased at 5.6 and 6.6 h. (b) FEV ₁ decreased 5.6 to 6.2% after 4.6 to 6.6 h, respectively, in varied exposure; total symptoms significantly increased also after 4.6 to 6.6 h. No significant difference between face mask and chamber exposures.	Adams (2003a)
(a) 0.08	157	6.6 h IE (6 × 50 min) $\dot{V}_E = 20$ L/min/m ² BSA	23 °C 50% RH	15 M 15 F	Healthy NS, 18 to 25 years old	Significantly greater FEV ₁ decrement (12.4%) for 2-h, 0.30 ppm exposure than for 6.6-h, 0.08 ppm exposure (3.6%).	Adams (2003b)
(b) 0.30	588	2 h IE (4 × 15 min) $\dot{V}_E = 35$ L/min/m ² BSA					
(a) 0.12 (b) 0.12 (mean) varied from 0.07 to 0.16	235 235 (mean)	6.6 h IE (6 × 50 min) (a,b,c) $\dot{V}_E = 20$ L/min/m ² BSA (d) $\dot{V}_E = 12$ L/min/m ² BSA	23 °C 50% RH	6 M, 6 F	Healthy NS, 19 to 25 years old	(a) FEV ₁ decreased 11% at 6.6 h in square-wave exposure. Total symptoms significant from 4.6 to 6.6 h. (b) FEV ₁ decreased 13% at 6.6 h; not significantly different from square-wave exposure. Total symptoms significant from 4.6 to 6.6 h.	Adams and Ollison (1997)
(c) 0.12 (mean) varied from 0.11 to 0.13	235 (mean)					(c) FEV ₁ decreased 10.3% at 6.6 h; not significantly different from square-wave exposure. Total symptoms significant from 4.6 to 6.6 h.	
(d) 0.12	235					(d) FEV ₁ decreased 3.6% at 6.6 h; significantly less than for 20 L/min/m ² BSA protocols.	

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^aSee Appendix A for abbreviations and acronyms.

^bListed from lowest to highest O₃ concentration.

newer studies of healthy subjects undergoing prolonged exposures at O₃ concentrations ranging from 0.06 to 0.20 ppm. In most of these studies, statistically significant changes in pulmonary function, symptoms, and airway responsiveness have been observed during and after exposures to O₃ concentrations of 0.08 ppm and higher. As with studies conducted at higher O₃ concentrations for shorter periods of time, there is considerable intersubject variability in response (*see Section AX6.4*).

Folinsbee et al. (1988) first reported the effects of a 6.6 h exposure to 0.12 ppm O₃ in ten young healthy adults (25 ± 4 yr) with quasi continuous exercise that was intended to simulate a full workday of heavy physical labor. Except for a 35-min lunch break after 3 h, the subjects exercised at a moderate level ($\dot{V}_E \approx 40$ L/min) for 50 min of each hour. Ignoring the lunch break during which lung function did not change appreciably, approximately linear decreases were observed in FVC, FEV₁, and FEV₂₅₋₇₅ with duration of O₃ exposure. Correcting for FA responses, decrements of 8.2, 14.9, and 26.8% in FVC, FEV₁, and FEV₂₅₋₇₅ occurred as a result of the O₃ exposure. Using the same 6.6 h protocol, but a lower O₃ concentration of 0.08 ppm, Horstman et al. (1990) and McDonnell et al. (1991) observed decrements corrected for FA (and averaged across studies) of 5, 8, and 11% in FVC, FEV₁, and FEV₂₅₋₇₅, respectively, in 60 young adults (25 ± 5 years old). Horvath et al. (1991) observed a 4% (p = 0.03)¹ decrement in FEV₁ using the forementioned protocol (i.e., 6.6 h and 0.08 ppm O₃) in 11 healthy adults (37 ± 4 yr). The smaller decrement observed by Horvath et al. (1991) versus Horstman et al. (1990) and McDonnell et al. (1991) is consistent with response decreasing as subject age increases (*see Section AX6.5.1*).

AX6.2.3.1 Effect of Exercise Ventilation Rate on FEV₁ Response to 6.6 h Ozone Exposure

It is well known that response to O₃ exposure is a function of \dot{V}_E in studies of 2 h or less in duration (*See Section AX6.2.2*). It is reasonable to expect that response to a prolonged 6.6-h O₃ exposure is also function of \dot{V}_E , although quantitative analyses are lacking.

In an attempt to quantify this effect, Adams and Ollison (1997) exposed 12 young adults to an average O₃ concentration of 0.12 ppm for 6.6 h at varied exercise \dot{V}_E . They observed a mean FEV₁ decrements of 10 to 11% in two protocols having a mean exercise \dot{V}_E of 33 L/min

¹Based on two-tailed paired t-test of data in Table III of Horvath et al. (1991).

and a 14% decrement in a protocol with a mean exercise \dot{V}_E of 36 L/min. These FEV₁ decrements were significantly greater than the average decrement of 3.6% (not significantly different from FA response) observed at an exercise \dot{V}_E of only 20 L/min. In a subsequent study of 30 healthy adults (Adams, 2000b), the effect of smaller exercise \dot{V}_E differences on pulmonary function and symptoms responses to 6.6 h exposure to 0.12 ppm O₃ was examined. FEV₁ decrements of 9.3, 11.7, and 13.9% were observed for the exercise \dot{V}_E of 30.2, 35.5, and 40.8 L/min, respectively. Along with the tendency for FEV₁ responses to increase with \dot{V}_E , total symptoms severity was found to be significantly greater at the end of the highest \dot{V}_E protocol relative to the lowest \dot{V}_E protocol. Although the FEV₁ responses were not significantly different from each other, the power of the study to detect differences between the three \dot{V}_E levels was not reported and no analysis was performed using all of the data (e.g., a mixed effects model). Data from the Adams and Ollison (1997) and Adams (2000b) studies are illustrated in Figure AX6-2 with data from three older studies. There is a paucity of data below an exercise \dot{V}_E of 30 L/min. Existing data for exposure to 0.12 ppm O₃ suggest that FEV₁ responses increase with increasing exercise \dot{V}_E until at least 35 L/min.

AX6.2.3.2 Exercise Ventilation Rate as a Function of Body/Lung Size on FEV₁ Response to 6.6 h Ozone Exposure

Typically, with the assumption that the total inhaled O₃ dose should be proportional to the lung size of each individual, exercise \dot{V}_E in 6.6 h exposures has been set as a multiple of body surface area (BSA) (McDonnell et al., 1991) or as a product of eight times FVC (Folinsbee et al., 1988; Frank et al., 2001; Horstman et al., 1990). Utilizing previously published data, McDonnell et al. (1997) developed a statistical model analyzing the effects of O₃ concentration, \dot{V}_E , duration of exposure, age, and body and lung size on FEV₁ response. They concluded that any effect of BSA, height, or baseline FVC on percent decrement in FEV₁ in this population of 485 young adults was small if it exists at all. This is consistent with Messineo and Adams (1990), who examined pulmonary function responses in young adult women having small (n = 14) or large (n = 14) lung sizes (mean FVC of 3.74 and 5.11 L, respectively). Subjects were exposed to 0.30 ppm O₃ for 1 h with CE ($\dot{V}_E = 47$ L/min). There was no significant difference between the

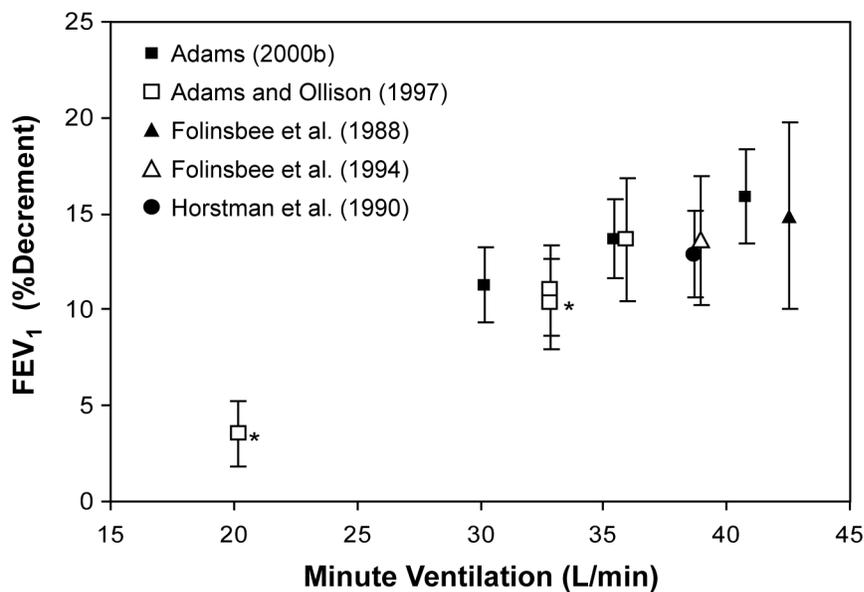


Figure AX6-2. Average FEV₁ decrements (\pm SE) for prolonged 6.6 h exposures to 0.12 ppm O₃ as a function of exercise \dot{V}_E . Since age affects response to O₃ exposure, selected studies had subjects with mean ages between 22 and 25 years. FEV₁ decrements were calculated as mean O₃ responses minus mean air responses. The SE bars illustrate variability in FEV₁ responses (pre minus post) on the O₃ exposure day in all cases except for Folinsbee et al. (1994), where post O₃ exposure variability is illustrated. In one case, the SE for \dot{V}_E of 33 L/Min (10.3% decrement) was taken as the SE of data from protocol with \dot{V}_E of 33 L/min (11% decrement). All studies used a constant 0.12 ppm O₃ exposure except two (*) which used 0.115 ppm O₃ for hours 1-2 and 5-6 and 0.13 ppm O₃ for hours 3-4 of exposure.

group FEV₁ decrements (22.1 and 25.6% for small and large lung, respectively). In addition, Messineo and Adams (1990) also did a retrospective analysis of 36 young adult males who each had completed similar 1 h exposures to 0.30 ppm O₃ with CE ($\dot{V}_E \approx 70$ L/min) and found lung size was not related to FEV₁ response.

Adams (2000b) studied a group of 30 young adult men and women exposed to 0.12 ppm O₃ for 6.6 h on three occasions while exercising 50 min of each hour at one of three different \dot{V}_E levels (viz., 17, 20, and 23 l/min/m² BSA). Their postexposure FEV₁ responses were regressed as a function of BSA (which was directly related to the absolute amount of \dot{V}_E

during exercise and, thus, primarily responsible for individual differences in total inhaled O₃ dose). The slope was significantly different from zero (p = 0.01), meaning that the smallest subjects, who had the lowest exercise \dot{V}_E (≈ 26 L/min), had a lower FEV₁ decrement (-5%) than the largest subjects (-17%), whose exercise \dot{V}_E was ≈ 44 L/min. This relationship was not a gender-based difference, as the mean female's FEV₁ decrement was -11.2%, which was not significantly different from the male's -12.2% mean value. Similarly, when total symptoms severity response was regressed against BSA, the slope was significantly different than zero (p = 0.0001), with lower values for smaller subjects than for larger subjects. Results of this study suggest that for the O₃ concentration and exposure duration used, responses are more closely related to \dot{V}_E than \dot{V}_E normalized to BSA. Further, this observation is in agreement with McDonnell et al. (1997), who observed no evidence that measurements of lung or body size were significantly related to FEV₁ response in 2 h IE exposures. These authors state that the absence of an observed relationship between FEV₁ response and BSA, height, or FVC may be due to the poor correlation between these variables and airway caliber (Collins et al., 1986; Martin et al., 1987). Also, the O₃ dosimetry study of Bush et al. (1996) indicated that normalization of the O₃ dose would be more appropriately applied as a function of anatomic dead space.

AX6.2.3.3 Comparison of 6.6 h Ozone Exposure Pulmonary Responses to Those Observed in 2 h Intermittent Exercise Ozone Exposures

It has been shown that greater O₃ concentration (Horstman et al., 1990) and higher \dot{V}_E (Adams, 2000b) each elicit greater FEV₁ response in prolonged, 6.6-h exposures, but data on the relative effect of O₃ concentration, \dot{V}_E , and T in prolonged exposures are very limited and have not been systematically compared to data from shorter (<2-h) exposures. In a recent study (Adams, 2003b), the group mean FEV₁ response for a 2-h IE exposure to 0.30 ppm O₃ was -12.4%, while that for a 6.6-h exposure to 0.08 ppm O₃ was -3.5%. The total inhaled O₃ dose (as the simple product of C × T × \dot{V}_E) was 1358 ppm·L for the 2-h exposure and 946 ppm·L for the 6.6-h exposure. Thus, the FEV₁ decrement was 3.5 times greater and the total inhaled O₃ dose was 1.44 times greater for the 2-h exposure compared to the 6.6-h exposure. This difference illustrates the limitations of utilizing the concept of total O₃ dose for comparisons between studies of vastly different exposure durations.

Adams (2003b) also examined whether prolonged 6.6 h exposure to a relatively low O₃ concentration (0.08 ppm) and the 2-h IE exposure at a relatively high O₃ concentration (0.30 ppm) elicited consistent individual subject effects, i.e., were those most or least affected in one exposure also similarly affected in the other? Individual subject O₃ exposure reproducibility was first examined via a regression plot of the postexposure FEV₁ response to the 6.6-h chamber exposure as a function of postexposure FEV₁ response to the 2-h chamber exposure. The R² of 0.40, although statistically significant, was substantially less than that observed in a comparison of individual FEV₁ response to two 2-h IE exposures by chamber and face mask, respectively (R² = 0.83). The Spearman rank order correlation for the chamber 6.6-h and chamber 2-h exposure comparison was also substantially less (0.49) than that obtained for the two 2-h exposures (0.85). The primary reason for the greater variability in the chamber 6.6-h exposure FEV₁ response as a function of that observed for the two 2-h IE exposures is very likely related to the increased variability in response upon repeated exposure to O₃ concentrations lower than 0.18 ppm (R = 0.57, compared to a mean R of 0.82 at higher concentrations) reported by McDonnell et al. (1985a). This rationale is supported by the lower R (0.60) observed by Adams (2003b) for the FEV₁ responses found in 6.6 h chamber and face mask exposures to 0.08 ppm O₃, compared to an R of 0.91 observed for responses found for the 2 h chamber and face mask exposures to 0.30 ppm O₃.

AX6.2.4 Triangular Ozone Exposures

To further explore the factors that determine responsiveness to O₃, Hazucha et al. (1992) designed a protocol to examine the effect of varying, rather than constant, O₃ concentrations. In this study, subjects were exposed to a constant level of 0.12 ppm O₃ for 8 h and to an O₃ level that increased linearly from 0 to 0.24 ppm for the first 4 h and then decreased linearly from 0.24 to 0 over the second 4 h of the 8 h exposure (triangular concentration profile). Subjects performed moderate exercise ($\dot{V}_E \approx 40$ L/min) during the first 30 minutes of each hour. The total inhaled O₃ dose (i.e., $C \times T \times \dot{V}_E$) for the constant versus the triangular concentration profile was almost identical. FEV₁ responses are illustrated in Figure AX6-3. With exposure to the constant 0.12 ppm O₃, FEV₁ declined approximately 5% by the fifth hour of exposure and then remained at that level. This observation clearly indicates a response plateau as suggested in other

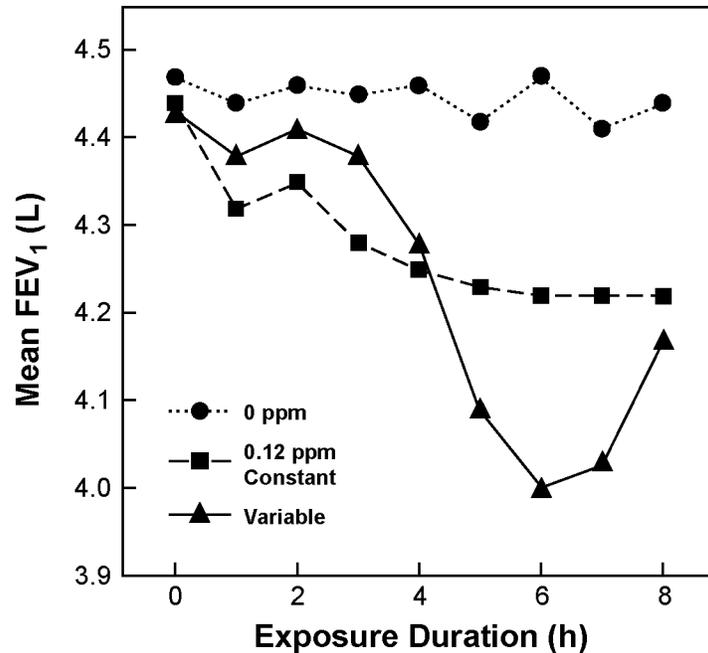


Figure AX6-3. The forced expiratory volume in 1 s (FEV₁) is shown in relation to exposure duration (hours) under three exposure conditions. Subjects exercised (minute ventilation \approx 40 L/min) for 30 min during each hour; FEV₁ was measured at the end of the intervening rest period. Standard error of the mean for these FEV₁ averages (not shown) ranged from 120 to 150 mL.

Source: Hazucha et al. (1992).

prolonged exposure studies (Horstman et al., 1990; McDonnell et al., 1991). However, with the triangular O₃ concentration profile after a minimal initial response over the first 3 h, Hazucha et al. (1992) observed a substantial change in FEV₁ corresponding to the higher average O₃ concentration that reached a maximum decrement of 10.3% at 6 h. Despite 2 h of continued exposure to a lower O₃ concentration (0.12 to 0.00 ppm, mean = 0.06 ppm), FEV₁ improved and was only reduced by 6.3% (relative to the preexposure FEV₁) at the end of the 8-h exposure. The authors concluded that total inhaled O₃ dose ($C \times \dot{V}_E \times T$) was not a sufficient index of O₃ exposure and that, as observed by others (Adams et al., 1981; Folinsbee et al., 1978; Hazucha, 1987; Larsen et al., 1991), O₃ concentration appears to be more important in determining exposure effects than is either duration or the volume of air breathed during the exposure.

However, it should be noted that the mean O₃ concentration for Hazucha et al.'s triangular exposure profile was 0.12 ppm at 4 h, 0.138 ppm at 5 h, 0.14 ppm at 6 h, and 0.133 ppm at 7 h, before falling to 0.12 ppm at 8 h. The FEV₁ responses of the last 4 hours (Figure AX6-3) follow a pattern similar to the total mean O₃ concentration over the same time period.

It has become apparent that laboratory simulations of air-pollution risk-assessment need to employ O₃ concentration profiles that more accurately mimic those encountered during summer daylight ambient air pollution episodes (Adams and Ollison, 1997; Lefohn and Foley, 1993; Rombout et al., 1986). Neither square-wave O₃ exposures or the one 8-h study by Hazucha et al. (1992) that utilized a triangular shaped varied O₃ exposure described above closely resembles the variable diurnal daylight O₃ concentration pattern observed in many urban areas experiencing air-pollution episodes (Lefohn and Foley, 1993). Recently, 6.6 h less abrupt triangular O₃ exposure profiles at lower concentrations more typical of outdoor ambient conditions have been examined (Adams, 2003a, 2006; Adams and Ollison, 1997).

Using a face-mask inhalation system, Adams and Ollison (1997) observed no significant differences in postexposure pulmonary function responses or symptoms between the 6.6-h, 0.12 ppm O₃ square-wave exposure and those observed for a triangular O₃ profile in which concentration was increased steadily from 0.068 ppm to 0.159 ppm at 3.5 h and then decreased steadily to 0.097 ppm at end exposure. Further, no attenuation in FEV₁ response during the last 2 h was observed in either the 6.6 h square-wave or the triangular exposures.

In a subsequent study (Adams, 2003a), no significant difference was observed in pulmonary function responses or symptoms between face-mask and chamber exposure systems either for a 6.6-h, 0.08 ppm O₃ square-wave profile or for the triangular O₃ exposure beginning at 0.03 ppm, increasing steadily to 0.15 ppm in the fourth hour, and decreasing steadily to 0.05 ppm at 6.6 h (mean = 0.08 ppm). For the chamber-exposure comparison, postexposure values for FEV₁ and symptoms were not significantly different from the responses for the square-wave 0.08 ppm O₃ exposure. However, analysis showed that FEV₁ response for the square-wave protocol did not become statistically significant until the 6.6-h postexposure value, while that for the triangular exposure protocol was significant at 4.6 h (when O₃ concentration was 0.15 ppm). Earlier significant FEV₁ responses for the triangular protocol were accompanied by significant increases in symptoms at 4.6 h, which continued on through the fifth and sixth

hours when the mean O₃ concentration was 0.065 ppm. Symptoms for the square-wave 0.08 ppm exposure did not become statistically significant until 5.6 h.

The FEV₁ responses during the last two hours of the triangular exposure by Adams (2003a) did not decrease as dramatically as in the Hazucha et al. (1992) study (Figure AX6-3). The most probable reason for differences in the triangular O₃ profile observations of Hazucha et al. (1992) and those of Adams (2003a) is that the increase and decrease in Hazucha et al.'s study (i.e., 0 to 0.24 ppm and back to 0) encompassed a much greater range of O₃ concentrations than those used by Adams (2003a), viz., 0.03 ppm to 0.15 ppm from 0 to 3.6 h, then decreasing to 0.05 ppm for the final hour of exposure. Nonetheless, the greatest FEV₁ decrement was observed at 6 h of Hazucha et al.'s 8 h triangular exposure (Figure AX6-3) corresponding to the time when total mean O₃ concentration was highest (0.14 ppm), with a very similar response at 7 h when total mean O₃ concentration was 0.138 ppm.

In a recent study, Adams (2006) employed three square-wave and three triangular chamber exposure profiles. Ozone concentrations for the 6.6-h exposures were 0.00, 0.06, and 0.08 ppm for square-wave profile and averaged 0.04, 0.06, and 0.08 ppm for the triangular profile. The pattern and magnitude of hourly changes in FEV₁ and symptoms during filtered air (0.0 ppm) and 0.04 ppm O₃ exposure were essentially the same. Similarly, there was no significant difference in FEV₁ and symptomatic response between the square-wave and triangular 0.06 ppm exposures. While the 6.6-h postexposure responses to the triangular exposure (mean O₃ concentration of 0.08 ppm) did not differ significantly from those observed in the square-wave exposure, FEV₁ and symptoms were significantly different from preexposure at 4.6 h (when the O₃ concentration was 0.15 ppm) in the triangular exposure, but not until 6.6 h in the square-wave exposure. These observations have confirmed and expanded findings of an earlier study (Adams, 2003a) showing a clear divergence in the peak and hourly responses in FEV₁ between the square-wave and triangular concentration profiles at the 0.08 ppm O₃ level. At the lower 0.06 ppm O₃ concentration, however, no temporal pattern differences in FEV₁ responses could be discerned between the square-wave and triangular exposure profiles. The author concluded that the results support previous evidence that O₃ concentration has a greater singular effect in the total inhaled O₃ dose than do \dot{V}_E and exposure duration.

Adams (2006) observed that at O₃ concentrations of 0.06 ppm and below differences in prolonged exposure profiles do not induce statistically different hourly responses.

Decrements in FEV₁ during square-wave O₃ exposures between 0.08 to 0.12 ppm tend to increase with time of exposure (i.e., with steadily increasing total inhaled dose), whereas FEV₁ decrements during triangular exposures (Hazucha et al., 1992; Adams, 2003a) occurred 1 to 2 h after the peak O₃ concentration and 1 h to 2 h before the maximal total O₃ inhaled dose occurred at the end of exposure. This difference, especially because O₃ concentration profiles during summer daylight air-pollution episodes rarely mimic a square-wave, implies that triangular O₃ exposure profiles most frequently observed during summer daylight hours merit further investigation. These three studies suggest that depending upon the profile of the exposure, the triangular exposure can potentially lead to higher FEV₁ responses than the square wave exposures at the overall equivalent ozone dose.

AX6.2.5 Mechanisms of Pulmonary Function Responses

Inhalation of O₃ for several hours while physically active elicits both subjective respiratory tract symptoms and acute pathophysiologic changes. The typical symptomatic response consistently reported in studies is that of tracheobronchial airway irritation. This is accompanied by decrements in lung capacities and volumes, bronchoconstriction, airway hyperresponsiveness, airway inflammation, immune system activation, and epithelial injury. The severity of symptoms and the magnitude of response depend on inhaled dose, O₃ sensitivity of an individual and the extent of tolerance resulting from previous exposures. The development of effects is time dependent during both exposure and recovery periods with considerable overlap of evolving and receding effects.

Exposure to O₃ initiates reflex responses manifested as a decline in spirometric lung function parameters (\downarrow FVC, \downarrow FEV₁, \downarrow FEF₂₅₋₇₅), bronchoconstriction (\uparrow SRaw) and altered breathing pattern (\downarrow V_T, \uparrow f_B), which becomes more pronounced as exposure progresses and symptoms of throat irritation, cough, substernal soreness and pain on deep inspiration develop. The spirometric lung function decline and the severity of symptoms during a variable (ramp) exposure profile seem to peak a short time (about 1 to 2 h) following the highest concentration of O₃ (Hazucha et al., 1992; Adams, 2003a). Exposure to a uniform O₃ concentration profile elicits the maximum spirometric response at the end of exposure (Hazucha et al., 1992; Adams, 2003a). Regardless of exposure concentration profile, as the exposure to O₃ progresses, airway inflammation begins to develop and the immune response at both cellular and subcellular level is

activated. Airway hyperreactivity develops slower than pulmonary function effects, while neutrophilic inflammation of the airways develops even more slowly and reaches the maximum 3 to 6 h postexposure. The cellular responses (e.g., release of immunoregulatory cytokines) appear to still be active as late as 20 h postexposure (Jörres et al., 2000). Following cessation of exposure, the recovery in terms of breathing pattern, pulmonary function and airway hyperreactivity progresses rapidly and is almost complete within 4 to 6 hours in moderately responsive individuals. Persisting small residual lung function effects are almost completely resolved within 24 hours. Following a 2 h exposure to 0.4 ppm O₃ with IE, Nightingale et al. (2000) observed a 13.5% decrement in FEV₁. By 3 h postexposure, however, only a 2.7% FEV₁ decrement persisted. As illustrated in Figure AX6-4, a similar postexposure recovery in FVC was observed. In hyperresponsive individuals, the recovery takes longer and as much as 48 hours to return to baseline values. More slowly developing inflammatory and cellular changes persist for up to 48 hours. The time sequence, magnitude and the type of responses of this complex series of events, both in terms of development and recovery, indicate that several mechanisms, activated at different times of exposure, must contribute to the overall lung function response (U.S. Environmental Protection Agency, 1996).

AX6.2.5.1 Pathophysiologic Mechanisms

Breathing pattern changes

Human studies consistently report that inhalation of O₃ alters the breathing pattern without significantly affecting minute ventilation. A progressive decrease in tidal volume and a “compensatory” increase in frequency of breathing to maintain steady minute ventilation during exposure suggests a direct modulation of ventilatory control. These changes parallel a response of many animal species exposed to O₃ and other lower airway irritants (Tepper et al., 1990). Although alteration of a breathing pattern could be to some degree voluntary, the presence of the response in animals and the absence of perception of the pattern change by subjects, even before appearance of the first subjective symptoms of irritation, suggests an involuntary reflex mechanism.

Direct recording from single afferent vagal fibers in animals convincingly demonstrated that bronchial C-fibers and rapidly adapting receptors are the primary vagal afferents responsible for O₃-induced changes in ventilatory rate and depth (Coleridge et al., 1993; Hazucha and

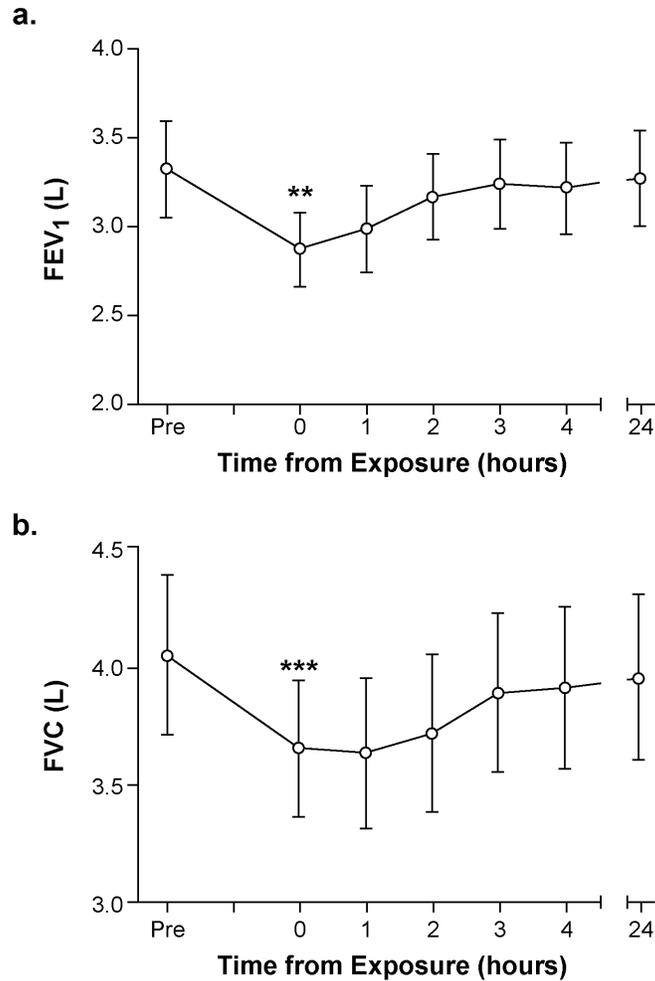


Figure AX6-4a,b. Recovery of spirometric responses following a 2 h exposure to 0.4 ppm O₃ with IE. Immediately postexposure, there were significant decrements (p < 0.001, ***p < 0.0005) in FVC (10%) and FEV₁ (13.5%) compared to preexposure values. At 3 h postexposure, FVC and FEV₁ were at 96 and 97% of preexposure values, respectively.**

Adapted from Nightingale et al. (2000).

Sant'Ambrogio, 1993). In spontaneously breathing dogs, an increase in V_T/T_i (T_i decreased more than V_T) was attributed to an increased inspiratory drive due to stimulation of rapidly adapting receptors and bronchial C-fibers by O₃ (Schelegle et al., 1993). Folinsbee and Hazucha (2000) also observed similar changes in V_T/T_i and other breath-timing parameters in humans exposed to O₃ implying activation of the same mechanisms. They also reported that Pm_{0.1} (pressure at

mouth at 0.1 sec of inspiration against a transiently occluded mouthpiece which is considered an index of inspiratory drive) increased during controlled hypercapnia without a change in the slope of $P_{m_{0.1}}$ versus pCO_2 relation suggesting that the primary mechanism is an increased inspiratory drive. Since no significant within-individual differences in ventilatory response to CO_2 between air exposure and O_3 exposure were found, the CO_2 chemoreceptors did not modulate the response. Therefore, the principal peripheral mechanism modulating changes in breathing pattern appears to be direct and indirect stimulation of lung receptors and bronchial C-fibers by O_3 and/or its oxidative products. The activity of these afferents, centrally integrated with input from other sensory pathways, drives the ventilatory controller, which determines the depth and the frequency of breathing.

The potential modulation of breathing pattern by activation of sensory afferents located in extrathoracic airways by O_3 has not yet been studied in humans. Laboratory animal studies have shown that the larynx, pharynx, and nasal mucosa are densely populated by free-ending, unmyelinated sensory afferents resembling nociceptive C-fibers (Spit et al., 1993; Sekizawa and Tsubone, 1994). They are almost certainly stimulated by O_3 and likely contribute to overall ventilatory and symptomatic responses. Nasal only exposure of rats produced O_3 -induced changes in breathing pattern that are similar to changes found in humans (Kleinman et al., 1999).

Symptoms and lung function changes

As already discussed, in addition to changes in ventilatory control, O_3 inhalation by humans will also induce a variety of symptoms, reduce vital capacity (VC) and related functional measures, and increase airway resistance. Hazucha et al. (1989) postulated that a reduction of VC by O_3 is due to a reflex inhibition of inspiration and not due to a voluntary reduction of inspiratory effort. Recently, Schelegle et al. (2001) convincingly demonstrated that a reduction of VC due to O_3 is indeed reflex in origin and not a result of subjective discomfort and consequent premature voluntary termination of inspiration. They reported that inhalation of an aerosolized topical anesthetic tetracaine substantially reduced if not abolished O_3 -induced symptoms that are known to be mediated in part by bronchial C-fibers. Yet, such local anesthesia of the upper airway mucosa had a minor and irregular effect on pulmonary function decrements and tachypnea, strongly supporting neural mediation, i.e., stimulation of both

bronchial and pulmonary C-fibers, and not voluntary inhibition of inspiration (due to pain) as the key mechanism.

The involvement of nociceptive bronchial C-fibers modulated by opioid receptors in limiting maximal inspiration and eliciting subjective symptoms in humans was studied by Passannante et al. (1998). The authors hypothesized that highly variable responses among individuals might reflect the individual's inability or unwillingness to take a full inspiration. Moreover, development of symptoms of pain on deep inspiration, cough and substernal soreness suggested that nociceptive mechanism(s) might be involved in O₃-induced inhibition of maximal inspiration. If this were so, pain suppression or inhibition by opioid receptor agonists should partially or fully reverse symptoms and lung functional impairment. Subjects for this study were pre-screened with exposure to 0.42 ppm O₃ and classified either as “weak” (FEV₁ ≥ 95% of preexposure value), “strong” (FEV₁ ≤ 85% of preexposure value), or “moderate” responders. Sixty two (28 M, 34 F) healthy volunteers (18 to 59 yrs old), known from the previous screening to be “weak” (n = 20) or “strong” (n = 42) O₃-responders, participated in this double-blind crossover study. Subjects underwent either two 2 h exposures to air, or two 2 h exposures to 0.42 ppm O₃, with 15 min IE at 17.5 l/min/m² BSA. Immediately following postexposure spirometry the “weak” responders were given (in random order) either the potent opioid receptor antagonist naloxone (0.15 mg/kg) or saline, while “strong” responders received (in random order) either the potent, rapid-acting opioid agonist and analgesic sufentanil (0.2 µg/kg), or physiologic saline administered through an indwelling catheter. Administration of saline or naloxone had no significant effect on the relatively small decrements in FEV₁ observed in “weak” responders. However, as hypothesized, sufentanil rapidly reversed both the O₃-induced symptomatic effects and spirometric decrements (FEV₁; p < 0.0001) in “strong” responders (Figure AX6-5). All the same, the reversal was not complete and the average post-sufentanil FEV₁ remained significantly below (-7.3%) the preexposure value suggesting involvement of non-opioid receptor modulated mechanisms as well. Uneven suppression of symptoms has implied involvement of both A-δ and bronchial C-fibers. The plasma β-endorphin (a potent pain suppressor) levels, though substantially elevated immediately postexposure and post-drug administration, were not related to individuals’ O₃ responsiveness. These observations have demonstrated that nociceptive mechanisms play a key role in modulating O₃-induced inhibition of inspiration. Moreover, these findings are consistent with and further support the concept that

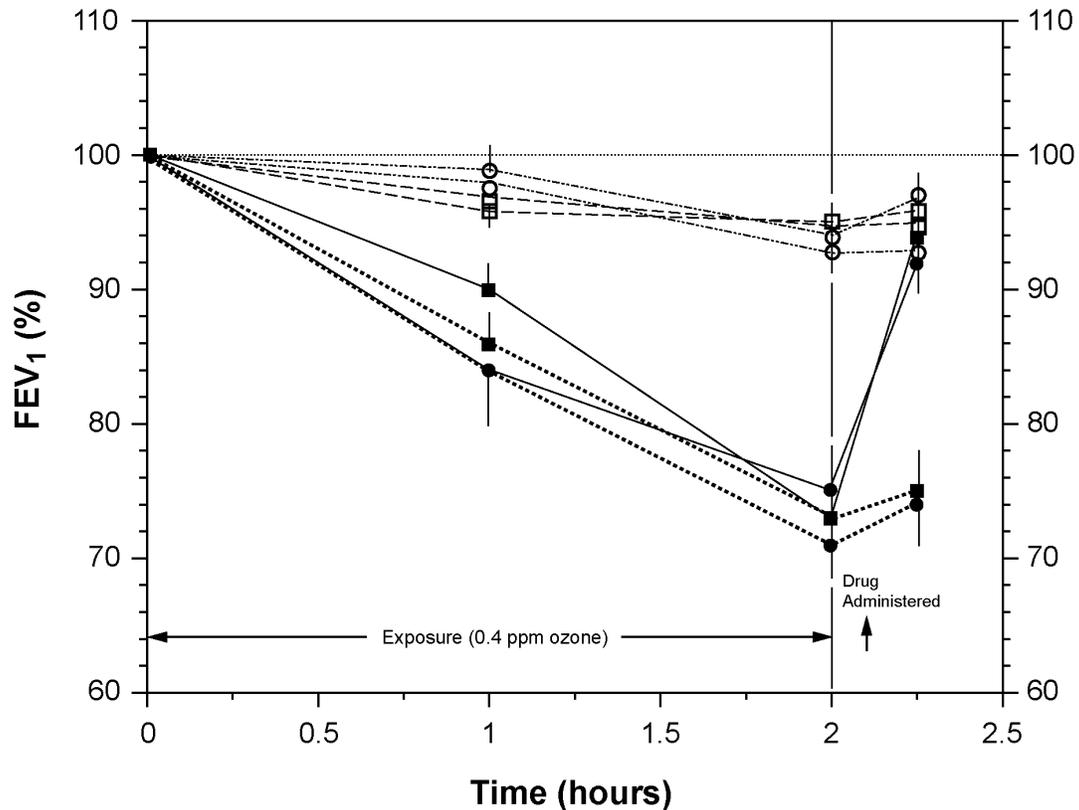


Figure AX6-5. Plot of the mean FEV₁ (% baseline) vs. time for ozone exposed cohorts. Solid lines represent data for “strong” males (n = 14; solid squares) and females (n = 15; solid circles) that received sufentanil and dotted lines represent data for the same cohorts after receiving saline. Dashed lines represent data for “weak” males (n = 5; open squares) and females (n = 10; open circles) that received naloxone and dot-dash lines represent data for the same cohorts after receiving saline. The arrow denotes the time of drug administration (~2.1 hrs). Vertical bars associated with the symbols are one-sided SEM.

Source: Adapted from Passannante et al. (1998).

the primary mechanism of O₃-induced reduction in inspiratory lung function, is an inhibition of inspiration elicited by stimulation of the C-fibers. The absence of effect of naloxone in “weak” responders shows that the weak response is not due to excessive endorphin production in those individuals. However, other neurogenic mechanisms not modulated by opioid receptors may have some though limited role in inspiratory inhibition.

Airway hyperreactivity

In addition to limitation of maximal inspiration and its effects on other spirometric endpoints, activation of airway sensory afferents also plays a role in receptor-mediated bronchoconstriction and an increase in airway resistance. Despite this common mechanism, post-O₃ pulmonary function changes and either early or late airway hyperresponsiveness (AHR) to inhaled aerosolized methacholine or histamine are poorly correlated either in time or magnitude. Fentanyl and indomethacin, the drugs that have been shown to attenuate O₃-induced lung function decrements in humans, did not prevent induction of AHR when administered to guinea pigs prior to O₃ exposure (Yeadon et al., 1992). Neither does post-O₃ AHR seem to be related to airway baseline reactivity. These findings imply that the mechanisms are either not related or are activated independently in time. Animal studies (with limited support from human studies) have suggested that an early post-O₃ AHR is, at least in part, vagally mediated (Freed, 1996) and that stimulation of C-fibers can lead to increased responsiveness of bronchial smooth muscle independently of systemic and inflammatory changes which may be even absent (Joad et al., 1996). In vitro study of isolated human bronchi have reported that O₃-induced airway sensitization involves changes in smooth muscle excitation-contraction coupling (Marthan, 1996). Characteristic O₃-induced inflammatory airway neutrophilia which at one time was considered a leading AHR mechanism, has been found in a murine model to be only coincidentally associated with AHR, i.e., there was no cause and effect relationship (Zhang et al., 1995). However, this observation does not rule out involvement of other cells such as eosinophils or T-helper cells in AHR modulation. There is some evidence that release of inflammatory mediators by these cells can sustain AHR and bronchoconstriction. In vitro and animal studies have also suggested that airway neutral endopeptidase activity can be a strong modulator of AHR (Marthan et al., 1996; Yeadon et al., 1992). Late AHR observed in some studies is plausibly due to a sustained damage of airway epithelium and continual release of inflammatory mediators (Foster et al., 2000). Thus, O₃-induced AHR appears to be a product of many mechanisms acting at different time periods and levels of the bronchial smooth muscle signaling pathways. [*The effects of O₃ on AHR are described in Section AX6.8.*]

AX6.2.5.2 Mechanisms at a Cellular and Molecular Level

Stimulation of vagal afferents by O₃ and reactive products, the primary mechanism of lung function impairment is enhanced and sustained by what can be considered in this context to be secondary mechanisms activated at a cellular and molecular level. The complexity of these mechanisms is beyond the scope of this section and the reader is directed to Section AX6.9 of this chapter for greater details. A comprehensive review by Mudway and Kelly (2000) discusses the cellular and molecular mechanisms of O₃-induced pulmonary response in great detail.

Neurogenic airway inflammation

Stimulation of bronchial C-fibers by O₃ not only inhibits maximal inspiration but, through local axon reflexes, induces neurogenic inflammation. This pathophysiologic process is characterized by release of tachykinins and other proinflammatory neuropeptides. Ozone exposure has been shown to elevate C-fiber-associated tachykinin substance P in human bronchial lavage fluid (Hazbun et al. 1993) and to deplete neuropeptides synthesized and released from C-fibers in human airway epithelium rich in substance P-immunoreactive axons. Substance P and other transmitters are known to induce granulocyte adhesion and subsequent transposition into the airways, increase vascular permeability and plasma protein extravasation, cause bronchoconstriction, and promote mucus secretion (Solway and Leff, 1991). Although the initial pathways of neurogenic, antigen-induced, and generally immune-mediated inflammation are not the same, they eventually converge leading to further amplification of airway inflammatory processes by subsequent release of cytokines, eicosanoids, and other mediators. Significantly negative correlations between O₃-induced leukotriene (LTC₄/D₄/E₄) production and spirometric decrements (Hazucha et al., 1996), and an increased level of postexposure PGE₂, a mediator known to stimulate bronchial C-fibers, show that these mediators play an important role in attenuation of lung function due to O₃ exposure (Mohammed et al., 1993; Hazucha et al., 1996). Moreover, because the density of bronchial C-fibers is much lower in the small than large airways, the reported post-O₃ dysfunction of small airways assessed by decrement in FEF₂₅₋₇₅ (Weinman et al., 1995; Frank et al., 2001) may be due in part to inflammation. Also, because of the relative slowness of inflammatory responses as compared to reflex effects, O₃-triggered inflammatory mechanisms are unlikely to initially contribute to progressive lung function reduction. It is plausible, however, that when fully activated, they sustain and

possibly further aggravate already impaired lung function. Indeed, a prolonged recovery of residual spirometric decrements following the initial rapid improvement after exposure termination could be due to slowly resolving airway inflammation. Bronchial biopsies performed 6 h postexposure have shown that O₃ caused a significant decrease in immunoreactivity to substance P in the submucosa (Krishna et al., 1997a). A strong negative correlation with FEV₁ also suggests that the release of substance P may be a contributing mechanism to persistent post-O₃ bronchoconstriction (Krishna et al., 1997a). Persistent spirometry changes observed for up to 48 h postexposure could plausibly be sustained by the inflammatory mediators, many of which have bronchoconstrictive properties (Blomberg et al., 1999).

AX6.3 PULMONARY FUNCTION EFFECTS OF OZONE EXPOSURE IN SUBJECTS WITH PREEXISTING DISEASE

This section examines the effects of O₃ exposure on pulmonary function in subjects with preexisting disease by reviewing O₃ exposure studies that utilized subjects with (1) chronic obstructive pulmonary disease (COPD), (2) asthma, (3) allergic rhinitis, and (4) ischemic heart disease. Studies of subjects with preexisting disease exposed to O₃, published subsequent to or not included in the 1996 Air Quality Criteria Document (U.S. Environmental Protection Agency, 1996), are summarized in Table AX6-3. Studies examining increased airway responsiveness after O₃ exposure are discussed in Section AX6.8.

AX6.3.1 Subjects with Chronic Obstructive Pulmonary Disease

Five studies of O₃-induced responses in COPD patients were available for inclusion in the 1996 criteria document (U.S. Environmental Protection Agency, 1996). The COPD patients in these studies were exposed during light IE (4 studies) or at rest (1 study) for 1 to 2 hours to O₃ concentrations between 0.1 and 0.3 ppm. None of these studies found significant O₃-induced changes in pulmonary function. Of the four studies examining arterial oxygen saturation, two reported small but statistically significant O₃-induced decreases in the COPD patients. These limited data suggest COPD patients experience minimal O₃-induced effects for 0.3 ppm O₃.

Table AX6-3. Ozone Exposure in Subjects with Preexisting Disease^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Condition	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
<i>Subjects with Chronic Obstructive Pulmonary or Heart Disease</i>							
0.0	0	4 h IE	24 °C	9 M	COPD patients	No significant changes in FEV ₁ , FVC, or SRaw due to ozone in COPD patients. Equivocal SaO ₂ decrement during 2 nd and 3 rd hours of ozone exposure in COPD patients. Adjusted for exercise, ozone effects did not differ significantly between COPD patients and healthy subjects.	Gong et al. (1997a)
0.24	472	15 min exercise 15 min rest V _E ≈ 20 L/min	40% RH	10 M	Age-matched healthy NS All subjects 59-71 years old		
0.3	589	3 h IE V _E ≈ 30 L/min	22 °C 50% RH	10 M	Hypertension 42-61 years old	O ₃ -induced FEV ₁ decrements of 6.7 and 7.6% in healthy and hypertensive subjects, respectively. Significant O ₃ -induced reductions in alveolar-arterial oxygen tension in both groups. No significant changes in cardiac enzymes or ECG telemetry.	Gong et al. (1998)
				6 M	Healthy 41-49 years old		
<i>Subjects with Allergic Rhinitis</i>							
0.0	0	1 h CE	20 °C	13 M, 1 F	Dust mite sensitized asthmatics	FEV ₁ decrement following O ₃ of 10% not significantly different from the 4% decrement following FA. Subjects received dust mite antigen challenge at 0.5 h FA and O ₃ postexposures and were lavaged 6 h post-challenge. Amount of allergen producing 15% FEV ₁ decrement was decreased by O ₃ compared to FA in 9 of 14 subjects. PMN in proximal airway lavage tended to be greater after O ₃ than FA (p = 0.06).	Chen et al. (2004)
0.2	392	at V _E = 25 L/min/m ² BSA	50% RH		mean age 29 ± 5 years		
0.125	245	3h IE	27 °C	5 F, 6 M	Mild bronchial asthma	Mean early-phase FEV ₁ response and number of ≥20% reductions in FEV ₁ were significantly greater after 0.25 ppm O ₃ or 4 × 0.125 ppm O ₃ . Most of the ≥15% late-phase FEV ₁ responses occurred after 4 days of exposure to 0.125 ppm O ₃ , as well as significant inflammatory effects, as indicated by increased sputum eosinophils (asthma and allergic rhinitis) and increased sputum lymphocytes, mast cell tryptase, histamine, and LDH (asthma only).	Holz et al. (2002)
0.250	490	(10 min rest, 15 min exercise on bicycle) V _E = 30 L/min	50 % RH	6 F, 16 M	20-53 years old Allergic rhinitis 19-48 years old		
0.125	245	3h IE × 4 days					
0.0	0	3 h IE,	27 °C	13 M, 11 F	Atopic mild asthma	O ₃ -induced FEV ₁ decrements of 12.5, 14.1, and 10.2% in asthmatics, allergic rhinitics and healthy subjects, respectively (group differences not significant). Methacholine responsiveness increased in asthmatics. <u>Allergen responsiveness</u> : increased significantly after O ₃ exposure in asthmatics (≈ 2 dose shift) and a smaller shift in rhinitics. No change in healthy. Neither allergen or methacholine response correlated with lung function and were not correlated with each.	Jörres et al. (1996)
0.25	490	V _E = 30 L/min 15 min ex/10 min rest/5 min no O ₃ ; every 30 min.	54% RH mouthpiece exposure	6 M, 6 F	Positive allergen and IgE tests		
				5 M, 5 F	Healthy NS		

AX6-30

Table AX6-3 (cont'd). Ozone Exposure in Subjects with Preexisting Disease^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
<i>Subjects with Asthma</i>							
0.4	784	2h IE (15 min rest, 15 min exercise on bicycle) $\dot{V}_E = 30$ L/min	NA	4 F, 5 M 7 F, 6 M	Healthy (25 ± 2 years old) Mild atopic asthma; beta agonists only (22 ± 0.7 years old)	Significant reductions in FVC (12%, 10%) and FEV ₁ (13%, 11%) for asthmatic and healthy subjects, respectively; attenuated by indomethacin in healthy subjects only. Significant reductions in mid-flows which tended to be greater in asthmatics than healthy subjects. Indomethacin treatment attenuated mid-flow-reductions somewhat more in asthmatics than healthy subjects.	Alexis et al. (2000)
0.0	0	2h IE	NA	15	Healthy adults 18-40 years old	Sputum collected 24 h before and 4-6 h post-O ₃ exposure. Baseline CD11b expression positively correlated with O ₃ -induced PMN. Increased expression of mCD14 on macrophages following O ₃ compared to FA. Asthmatic PMN response similar to healthy subjects (also see Table AX6-3). No spirometric data available.	Alexis et al. (2004)
0.4	784	4 × 15 min on bicycle, $\dot{V}_E = 40$ L/min		9	Mild atopic asthmatics 18-40 years old		
0.12	236	Rest	22 °C 40% RH	10 M, 5 F	atopic asthma	No effect of O ₃ on airway response to grass allergen.	Ball et al. (1996)
0.0	0	6 h	22 °C	5 M	Healthy NS	Similar spirometric responses in asthmatic and healthy. However, preexposure FEV ₁ and FVC were both ~0.4 L lower on O ₃ -day than FA day. More PMN's in asthmatics. IL-8 and IL-6 higher in asthmatics exposed to O ₃ . No relationship of spirometry and symptoms to inflammation.	Basha et al. (1994)
0.2	392	30 min rest/30 min exercise $\dot{V}_E \approx 25$ L/min	50% RH	5 M	Asthmatics, physician diagnosed, All 18-45 years		
0.4	784	3h 6x15 min cycle ergometer $\dot{V}_E \approx 32$ L/min 5 consecutive days	31 °C 35% RH	8 M, 2 F	Asthmatic NS adults beta-agonist use only 19-48 years old ATS criteria for asthma	FEV ₁ decreased 35% on first exposure day. Methacholine reactivity increased about ten-fold. <i>Also see Table AX6-7 for repeated exposure results.</i>	Gong et al. (1997b)
0.0	0	1 h rest	NA	9 M, 6 F	Mild allergic asthma; 18 to 49 years of age.	No effect of O ₃ on airway response to grass or ragweed allergen.	Hanania et al. (1998)
0.12	235	air-antigen O ₃ -antigen					
0.4	784	2 h IE 15 min exercise 15 min rest $\dot{V}_E \approx 20$ L/min	Head mask exposure ≈ 18 °C 60% RH	5 M, 1 F 6 M	Healthy adults Atopic asthmatics	FEV ₁ responses of healthy and asthmatic similar ($\approx 15\%$ decrease). Maximal FEV ₁ response to methacholine increased similarly in both groups (12 h postexposure). Larger increase in PC ₂₀ in healthy subjects. Both groups had increased PMN's in sputum no correlation of PMN's and lung function.	Hiltermann et al. (1995)

Table AX6-3 (cont'd). Ozone Exposure in Subjects with Preexisting Disease^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
<i>Adult Subjects with Asthma (cont'd)</i>							
0.0	0	3 h IE	27 ± 1 °C	10M, 11F	Healthy NS	No significant O ₃ -induced group differences in symptoms or spirometry. After 0.25 ppm O ₃ , there were significant decrements in FEV ₁ and FVC that tended to be greater in the asthmatics than controls. Small but significant neutrophil increase in asthmatics following 0.15 ppm O ₃ . Significant neutrophil increases following 0.25 ppm O ₃ that did not differ between groups.	Holz et al. (1999)
0.15	294	15 min rest	56 ± 7 % RH		28 ± 5 years old		
0.25	490	($\dot{V}_E = 7$ L/min)		5M, 10F	Mild Asthmatic		
0.25	490	15 min on bicycle ($\dot{V}_E = 26$ L/min)			30 ± 8 years old		
0.0	0	7.6 h	18 °C	13 M	Healthy NS, age 19-32 years.	FEV ₁ decreased 19% in asthmatics and only 10% in nonasthmatics. High responders had worse baseline airway status. More wheeze in asthmatics after O ₃ .	Horstman et al. (1995)
0.16	314	25 min treadmill, 25 min cycle/10 min rest per hour. $\dot{V}_E = 27-32$ L/min	40% RH	7 M, 10 F	Moderate Asthmatics, physician diagnosed, beta agonist users, age 19-32 years.		
0.0	0	3 h IE,	27 °C	13 M, 11 F	Atopic mild asthma	O ₃ -induced FEV ₁ decrements of 12.5, 14.1, and 10.2% in asthmatics, allergic rhinitics and healthy subjects, respectively (group differences not significant). Methacholine responsiveness increased in asthmatics. Allergen responsiveness increased after O ₃ exposure in asthmatics (=2 dose shift), a smaller shift occurred in rhinitics, no change occurred in healthy subjects. Neither allergen nor methacholine responses were correlated with each other or with lung function.	Jörres et al. (1996)
0.25	490	$\dot{V}_E = 30$ L/min	54% RH	6 M, 6 F	Positive allergen and IgE tests		
		15 min ex/10 min rest/5 min no O ₃ ; every 30 min	mouthpiece exposure	5 M, 5 F	Healthy NS		
0.16	314	7.6 h 25 min treadmill, 25 min cycle/10 min rest per hour. $\dot{V}_E = 25$ L/min	22 °C 40 % RH	4 M, 5 F	Mild atopic asthma; no meds 12 h pre-exposure 20-35 years old	Significant FEV ₁ decrease of 9.1 % following O ₃ exposure; marked individual variability with responses ranging from 2 % to 26 %.	Kehrl et al. (1999)
0.25	490	$\dot{V}_E = 25-45$ L/min	NA	8 M, 4 F	Asthmatics	Healthy 12.2% decrease in FEV ₁ , Rhinitics 10.1%, asthmatics 12.4%	Magnussen et al. (1994)
0.40	784			8 M, 10 F 22 M, 16 F	Allergic rhinitics Healthy adults		
					All <26 years old		
0.0	0	2 h IE	20 °C	6 M, 9 F	Healthy adults	O ₃ -induced FEV ₁ decrement (8%, healthy adults; 3% asthmatics) and PMN increase (20.6%, healthy adults; 15.2% asthmatics). Primary goal was to investigate relationship between antioxidant defenses and O ₃ responses in asthmatics and healthy adults (see Tables AX6-3 and AX6 -13).	Mudway et al. (2001)
0.2	392	4 × 15 min at $\dot{V}_E = 20$ L/min/m ² BSA	50% RH	9 M, 6 F	Mild asthmatics 29 years old		

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Table AX6-3 (cont'd). Ozone Exposure in Subjects with Preexisting Disease^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
<i>Adult Subjects with Asthma (cont'd)</i>							
0.2	396	2h IE (15 min rest, 15 min exercise on bicycle) $\dot{V}_E = 20 \text{ L/min/m}^2 \text{ BSA}$	22 °C 40 % RH	5 F, 4 M	Mild atopic asthma; no meds 8 h pre-exposure 21-42 years old	Significant decrease in FEV ₁ and a trend toward decreases in mean inspiratory flow, FEF ₂₅ , and FEF ₇₅ after O ₃ exposure. No significant differences in FEF ₅₀ , FVC, TLC, Raw, or sRaw. No correlation between sputum neutrophils at 6 h postexposure and FEV ₁ immediately after exposure.	Newson et al. (2000)
0.4	784	2 h rest	21 °C 40% RH	11 M, 11 F	Asthmatics sensitive to D Farinae, physician diagnosed, 18 to 35 years	Ozone resulted in nasal inflammation (increased PMN's) and caused augmented response to nasal allergen challenge.	Peden et al. (1995)
0.16	314	7.6 h 25 min treadmill, 25 min cycle/ every hour.	18 °C 40% RH	8 M	Mild asthmatics, physician diagnosed, reactive to dust mite D. Farinae.	Increased eosinophils and PMN's after O ₃ exposure more in initial (bronchial) fraction. No correlation of eosinophils and PMN's, FEV ₁ & FVC decreased 14% and 9% respectively.	Peden et al. (1997)
0.0 0.2	0 392	4h 50 min exercise, 10 min rest each hour. $\dot{V}_E \approx 45\text{-}50 \text{ L/min}$	21 °C 50% RH	12 M, 6 F	18 adult mild asthmatics mostly beta agonist users.	FVC, FEV ₁ decreased 17.6% and 25% respectively. Trend for larger increase in SRaw in asthmatics. Larger increase in PMN's and protein in asthmatics indicating more inflammation. No increase in eosinophils. Spirometry changes in asthmatics similar to healthy subjects (Aris et al., 1995; Balmes et al., 1997).	Scannell et al. (1996)

^aSee Appendix A for abbreviations and acronyms.

^bGrouped by rest and exercise; within groups listed from lowest to highest O₃ concentration.

exposures less than 2 hours in duration. These findings are also consistent decreasing O₃ effects with increasing age (*see Section AX6.5.1*).

More recently, Gong et al. (1997a) exposed 9 COPD patients (age range, 59 to 71 years; mean age 66 ± 4 years) and 10 healthy NS (age range, 60 to 69 years; mean age 65 ± 3 years) to 0.24 ppm for 4 h with interment light exercise (~20 L/min). COPD patients had decreases in FEV₁ following both clean air (-11%, p = 0.06) and O₃ (-19%, p < 0.01) exposures. These FEV₁ decrements, presumably due to exercise, were primarily attributable to four of the patients who lost greater than 14% of their FEV₁ following both the air and O₃ exposures. Relative to clean air, O₃ caused a statistically insignificant FEV₁ decrement of -8% in COPD patients which was not statistically different from the decrement of -3% in healthy subjects. Ozone-induced symptoms, sRaw, S_aO₂, and postexposure bronchial activity also exhibited little or no difference between the COPD patients and the healthy subjects.

AX6.3.2 Subjects with Asthma

Based on studies reviewed in the 1996 criteria document (U.S. Environmental Protection Agency, 1996) asthmatics appear to be at least as sensitive to acute effects of O₃ as healthy nonasthmatic subjects. At rest, neither adolescent asthmatics nor healthy controls had significant responses as a result of an hour exposure to 0.12 ppm O₃. Exposure of adult asthmatics to 0.25 ppm O₃ for 2 h at rest also caused no significant responses. Preexposure to between 0.10 and 0.25 ppm O₃ for 1 hr with light IE does not appear to exacerbate exercise-induced asthma (Fernandes et al., 1994; Weymer et al., 1994). At higher exposures (0.4 ppm O₃ with heavy IE for 2 h), Kreit et al. (1989) and Eschenbacher et al. (1989) demonstrated significantly greater FEV₁ and FEF₂₅₋₇₅ decrements in asthmatics than in healthy controls. With longer duration exposures to lower O₃ levels (0.12 ppm with moderate IE for 6.5 h), asthmatics have also shown a tendency for greater FEV₁ decrements than healthy nonasthmatics (Linn et al., 1994). Newer clinical studies (*see Table AX6-3*) continue to suggest that asthmatics are at least as sensitive as healthy controls to O₃-induced responses.

Studies of less than 3 h duration have reported similar or tendencies for increased O₃-induced spirometric responses up to O₃ concentrations of 0.4 ppm. Similar group decrements in FEV₁ and FVC were reported by Hiltermann et al. (1995), who exposed 6 asthmatics and 6 healthy subjects to 0.4 ppm O₃ for 2 h with light IE. Alexis et al. (2000) exposed 13 mild

atopic asthmatics and 9 healthy subjects for 2 h to 0.4 ppm O₃ with IE ($\dot{V}_E = 30$ L/min). Similar O₃-induced group decrements in FEV₁ and FVC were also reported by these investigators. A tendency, however, for an increased O₃-induced reduction in mid-flows (viz., FEF₂₅, FEF₅₀, FEF_{60p}, FEF₇₅) was reported for the asthmatics relative to the healthy subjects. In a larger study, Jörres et al. (1996) exposed 24 asthmatics, 12 allergic rhinitis, and 10 healthy subjects to 0.25 ppm O₃ for 3 h with IE. Statistically significant O₃-induced decreases in FEV₁ occurred in all groups, but tended to be lower in healthy controls (allergic rhinitis, -14.1%; asthmatics, -12.5%; healthy controls, -10.2%). Holz et al. (1999) exposed 15 asthmatics and 21 healthy controls to 0.15 and 0.25 ppm O₃ for 3-h with light IE. After the 0.25 ppm O₃ exposure, there were significant decrements in FEV₁ and FVC that tended to be slightly greater in the asthmatics than controls. One study reported that asthmatics tended to have less of an FEV₁ response to O₃ than healthy controls (Mudway et al., 2001). In that study, however, the asthmatics also tended to be older than the healthy subjects which could partially explain their lesser response.

Studies between 4 and 8 h duration, with O₃ concentrations of 0.2 ppm or less, also suggest a tendency for increased O₃-induced pulmonary function responses in asthmatics relative to healthy subjects. Scannell et al. (1996) exposed 18 asthmatics to 0.2 ppm O₃ for 4 h with IE ($\dot{V}_E \approx 25$ L/min/m² BSA). Baseline and hourly pulmonary function measurements of FEV₁, FVC, and sRaw were obtained. Asthmatic responses were compared to 81 healthy subjects who underwent similar experimental protocols (Aris et al., 1995; Balmes et al., 1996). Asthmatic subjects experienced a significant O₃-induced increase in sRaw, FEV₁ and FVC. The O₃-induced increase in sRaw tended to be greater in asthmatics than the healthy subjects, whereas similar group decrements in FEV₁ and FVC were observed. Basha et al. (1994) also reported similar spirometric responses between 5 asthmatic and 5 healthy subjects exposed to 0.2 ppm O₃ for 6 h with IE. However, the mean preexposure FEV₁ in the asthmatics was about 430 mL less (i.e., ~12% decreased) on the O₃-day relative to the air-day. In a longer exposure duration (7.6 h) study, Horstman et al. (1995) exposed 17 asthmatics and 13 healthy controls to 0.16 ppm O₃ or FA with alternating periods of exercise (50 min, $\dot{V}_E \approx 30$ L/min) and rest (10 min). Both groups had significant O₃-induced decrements in FEV₁, FVC, and FEV₂₅₋₇₅. The asthmatic and healthy subjects had similar O₃-induced reductions in FVC. The FEV₁ decrement experienced by the asthmatics was significantly greater in the healthy controls (19% versus 10%, respectively).

There was also tendency for a greater O₃-induced decrease in FEF₂₅₋₇₅ in asthmatics relative to the healthy subjects (24% versus 15%, respectively).

With repeated O₃ exposures asthmatics, like healthy subjects (*see Section AX6.6*) develop tolerance. Gong et al. (1997b) exposed 10 asthmatics to 0.4 ppm O₃, 3 h per day with IE ($\dot{V}_E \approx 32$ L/min), for 5 consecutive days. Symptom and spirometric responses were greatest on the first (-35 % FEV₁) and second (-34 % FEV₁) exposure days, and progressively diminished toward baseline levels (-6 % FEV₁) by the fifth exposure day. Similar to healthy subjects, asthmatics lose their tolerance to O₃ after 4 to 7 days without O₃ exposure.

Other published studies with similar results (e.g., McBride et al., 1994; Basha et al., 1994; Peden et al., 1995, 1997; Peden, 2001a; Scannell et al., 1996; Hiltermann et al., 1997, 1999; Michelson et al., 1999; Vagaggini et al., 1999; Newson et al., 2000; Holz et al., 2002) also reported that asthmatics have a reproducible and somewhat exaggerated inflammatory response to acute O₃ exposure (*see Section AX6.9*). For instance, Scannell et al. (1996) performed lavages at 18 h post-O₃ exposure to assess inflammatory responses in asthmatics. Asthmatic responses were compared to healthy subjects who underwent a similar experimental protocol (Balmes et al., 1996). Ozone-induced increases in BAL neutrophils and total protein were significantly greater in asthmatics than healthy subjects. There was also a trend for an ozone related increased IL-8 in the asthmatics relative to healthy subjects. Inflammatory responses do not appear to be correlated with lung function responses in either asthmatic or healthy subjects (Balmes et al., 1996, 1997; Holz et al., 1999). This lack of correlations between inflammatory and spirometric responses may be due to differences in the time kinetics of these responses (Stenfors et al., 2002). In addition, airway responsiveness to inhaled allergens is increased by O₃ exposure in subjects with allergic asthma for up to 24 h (*see Section AX6.8*).

One of the difficulties in comparing O₃-induced spirometric responses of healthy subjects versus asthmatics is the variability in responsiveness of asthmatics. Most of the asthma studies were conducted on subjects with a clinical history of mild disease. However, classification of asthma severity is not only based on functional assessment (e.g., percent predicted FEV₁), but also on clinical symptoms, signs, and medication use (Table AX6-4). Although “mild atopic asthmatics” are frequently targeted as an experimental group, the criteria for classification has varied considerably within and across the available published studies. Although the magnitude of group mean changes in spirometry may not be significantly different between healthy and

Table AX6-4. Classification of Asthma Severity¹

Classification	Step	Days with symptoms	Nights with symptoms	Lung Function ²		Medications ³	
				FEV1 or PEF % predicted oral	PEF variability (%)	Daily	Quick relief
Severe persistent	4	Continual	Frequent	≤60	>30	High-dose inhaled steroids (ICS) and long-acting inhaled β ₂ -agonist If needed, add oral steroids	Short-acting inhaled β ₂ -agonist, as needed; oral steroids may be required
Moderate persistent	3	Daily	>1/week	between 60 and 80	>30	Low-to-medium-dose ICS and long-acting β ₂ -agonist (preferred) Or Medium-dose ICS (another preferred option for children ages <5 years) Or Low-to-medium-dose ICS and either leukotriene modifier or theophylline	Short-acting inhaled β ₂ -agonist, as needed; oral steroids may be required
Mild persistent	2	>2/week, but <1 time/day	>2/week	≥80	20-30	Low-dose inhaled steroids (preferred) Or Cromolyn leukotriene modifier, or (except for children aged <5 years) nedocromil or sustained release theophylline to serum concentration of 5-15 μg/mL	Short-acting inhaled β ₂ -agonist, as needed; oral steroids may be required
Mild intermittent	1	≤2/week	<2/month	≥80	<20	No daily medicine needed	Short-acting inhaled β ₂ -agonist, as needed; oral steroids may be required

¹ Sources: Centers for Disease Control (2003); National Institutes of Health (1997, 2003).

² For adults and children aged >5 years who can use a spirometer or peak flow meter.

³ The medications listed here are appropriate for treating asthma at different levels of severity. The preferred treatments, dosage, and type of medication recommended vary for adults and children and are detailed in the *EPR-Update 2002* stepwise approach to therapy. The stepwise approach emphasizes that therapy should be stepped up as necessary and stepped down when possible to identify the least amount of medication required to achieve goals of therapy. The stepwise approach to care is intended to assist, not replace, the clinical decision-making required to meet individual patient needs.

asthmatic subjects, many of the studies have reported clinically significant changes in some individuals.

Alexis et al. (2000) explored the possibility that the mechanisms of O₃-induced spirometric responses may differ between asthmatics and healthy subjects. Physician-diagnosed mild atopic asthmatics and healthy subjects were pretreated with 75 mg/day of indomethacin (a COX inhibitor) or placebo and then exposed for 2 h to 0.4 ppm O₃ or to FA during mild IE ($\dot{V}_E = 30$ L/m). The number and severity of O₃-induced symptoms were significantly increased in both asthmatics and healthy subjects. These symptom responses were similar between the subject groups and unaffected by indomethacin pretreatment. Asthmatics and healthy subjects also had similar O₃-induced reductions in FVC and FEV₁. These restrictive-type responses, occurring due to the combined effects of bronchoconstriction and reflex inhibition of inspiration (*see Section AX6.2.1*), were attenuated by indomethacin in the healthy subjects but not the asthmatics. Thus, in healthy subjects but not asthmatics, COX metabolites may contribute to O₃-induced reductions in FVC and FEV₁. As assessed by the magnitude of reductions in mid-flows (*viz.* FEF₂₅, FEF₅₀, FEF_{60p}, FEF₇₅), the small airways of the asthmatics tended to be more affected than the healthy subjects. This suggests asthmatics may be more sensitive to small airway effects of O₃, which is consistent with the observed increases in inflammation and airway responsiveness. Indomethacin pretreatment attenuated some of these O₃-induced small airways effects (FEF₅₀ in healthy subjects, FEF_{60p} in asthmatics).

AX6.3.3 Subjects with Allergic Rhinitis

Most O₃ exposure studies in humans with existing respiratory disease have focused on lung diseases like COPD and asthma. However, chronic inflammatory disorders of the nasal airway, especially allergic rhinitis, are very common in the population. People with allergic rhinitis have genetic risk factors for the development of atopy that predispose them to increased upper airway responsiveness to specific allergens as well as nonspecific air pollutants like O₃. Studies demonstrating the interaction between air pollutants and allergic processes in the human nasal airways and rhinoconjunctival tissue have been reviewed by Peden (2001b) and Riediker et al. (2001), respectively. Ozone exposure of subjects with allergic rhinitis has been shown to induce nasal inflammation and increase airway responsiveness to nonspecific bronchoconstrictors, although to a lesser degree than experienced by asthmatics.

McDonnell et al. (1987) exposed nonasthmatic adults with allergic rhinitis to 0.18 ppm O₃. The allergic rhinitics were no more responsive to O₃ than healthy controls, based on symptoms, spirometry, or airway reactivity to histamine although they had a small but significantly greater increase in SRaw. The data on subjects with allergic rhinitis and asthmatic subjects suggest that both of these groups have a greater rise in Raw to O₃ with a relative order of airway responsiveness to O₃ being normal < allergic < asthmatic.

Bascom et al. (1990) studied the upper respiratory response to acute O₃ inhalation, nasal challenge with antigen, and the combination of O₃ plus antigen in subjects with allergic rhinitis. Exposure to O₃ caused significant increases in upper and lower airway symptoms, a mixed inflammatory cell influx with a seven-fold increase in nasal lavage PMNs, a 20-fold increase in eosinophils, and a 10-fold increase in mononuclear cells, as well as an apparent sloughing of epithelial cells. McBride et al. (1994) also observed increased nasal PMN's after O₃ exposure in atopic asthmatics. Peden et al. (1995), who studied allergic asthmatics exposed to O₃, found that O₃ causes an increased response to nasal allergen challenge in addition to nasal inflammatory responses. Their data suggested that allergic subjects have an increased immediate response to allergen after O₃ exposure. In a follow-up study, Michelson et al. (1999) reported that 0.4 ppm O₃ did not promote early-phase-response mediator release or enhance the response to allergen challenge in the nasal airways of mild, asymptomatic dust mite-sensitive asthmatic subjects. Ozone did, however, promote an inflammatory cell influx, which helps induce a more significant late-phase response in this population.

Jörres et al. (1996) found that O₃ causes an increased response to bronchial allergen challenge in subjects with allergic rhinitis. This study also compared responses in subjects with mild allergic asthma (*see Sections AX6.3.2 and AX6.8*). The subjects were exposed to 0.25 ppm O₃ for 3 h with IE. Airway responsiveness to methacholine was determined 1 h before and after exposure; responsiveness to allergen was determined 3 h after exposure. Statistically significant decreases in FEV₁ 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. Airway responsiveness to an individual's historical allergen (either grass and birch pollen, house dust mite, or animal dander) was significantly increased after O₃ exposure when compared to FA exposure. In subjects with asthma and allergic rhinitis, a maximum percent fall in FEV₁ of 27.9 % and 7.8%, respectively,

occurred 3 days after O₃ exposure when they were challenged with of the highest common dose of allergen. The authors concluded that subjects with allergic rhinitis, but without asthma, could be at risk if a high O₃ exposure is followed by a high dose of allergen.

Holz et al. (2002) extended the results of Jörres et al. (1996) by demonstrating that repeated daily exposure to lower concentrations of O₃ (0.125 ppm for 4 days) causes an increased response to bronchial allergen challenge in subjects with preexisting allergic airway disease, with or without asthma. There was no major difference in the pattern of bronchial allergen response between subjects with asthma or rhinitis, except for a 10-fold increase in the dose of allergen required to elicit a similar response ($\geq 20\%$ decrease in FEV₁) in the asthmatic subjects. Early phase responses were more consistent in subjects with rhinitis and late-phase responses were more pronounced in subjects with asthma. There also was a tendency towards a greater effect of O₃ in subjects with greater baseline response to specific allergens chosen on the basis of skin prick test and history (viz., grass, rye, birch, or alder pollen, house dust mite, or animal dander). These data suggest that the presence of allergic bronchial sensitization, but not a history of asthma, is a key determinant of increased airway allergen responsiveness with O₃.

[A more complete discussion of airway responsiveness is found in Section AX6.8]

AX6.3.4 Subjects with Cardiovascular Disease

Superko et al. (1984) exposed six middle-aged males with angina-symptom-limited exercise tolerance for 40 min to FA and to 0.2 and 0.3 ppm O₃ while they were exercising continuously according to a protocol simulating their angina-symptom-limited exercise training prescription (mean $\dot{V}_E = 35$ L/min). No significant pulmonary function impairment or evidence of cardiovascular strain induced by O₃ inhalation was observed. Gong et al. (1998) exposed hypertensive (n = 10) and healthy (n = 6) adult males, 41 to 78 years of age, to FA and on the subsequent day to 0.3 ppm O₃ for 3 h with IE at 30 L/min. The ECG was monitored by telemetry, blood pressure by cuff measurement, and a venous catheter was inserted for measurement of routing blood chemistries and cardiac enzymes. Pulmonary artery and radial artery catheters were placed percutaneously for additional blood sampling and for measurement of hemodynamic pressures, cardiac output, and S_aO₂. Other hemodynamic variables were calculated, including cardiac index, stroke volume, pulmonary and systemic vascular resistance, left and right ventricular stroke-work indices, and rate-pressure product. Spirometric volumes

(FVC, FEV₁) and symptoms of breathing discomfort were measured before and after the O₃ exposures. There were significant O₃-induced FEV₁ decrements in both subject groups that did not differ between groups (hypertensive, 7.6%; healthy, 6.7%). The overall results did not indicate any major acute cardiovascular effects of O₃ in either the hypertensive or normal subjects. However, statistically significant O₃ effects for both groups combined were increases in HR, rate-pressure product, and the alveolar-to-arterial PO₂ gradient, suggesting that impaired gas exchange was being compensated for by increased myocardial work. These effects might be more important in some patients with severe cardiovascular disease. *[See Section AX6.10 for discussion of extrapulmonary effects of O₃ exposure.]*

AX6.4 INTERSUBJECT VARIABILITY AND REPRODUCIBILITY OF RESPONSE

Analysis of the factors that contribute to intersubject variability is important for the understanding of individual responses, mechanisms of response, and health risks associated with acute O₃ exposures. Bates et al. (1972) noted that variation between individuals in sensitivity and response was evident in respiratory symptoms and pulmonary function following O₃ exposure. A large degree of intersubject variability in response to O₃ has been consistently reported in the literature (Adams et al., 1981; Aris et al., 1995; Folinsbee et al., 1978; Kulle et al., 1985; McDonnell et al., 1983). Kulle et al. (1985) noted that the magnitude of variability between individuals in FEV₁ responses increases with O₃ concentration. Similarly, McDonnell et al. (1983) observed FEV₁ decrements ranging from 3 to 48% (mean 18%) in 29 young adult males exposed to 0.40 ppm O₃ for 2 h during heavy IE. At a lower O₃ concentration of 0.18 ppm, 20 similarly exposed subjects had FEV₁ decrements ranging from 0 to 23% (mean = 6%), while those exposed to FA (n = 20) had decrements ranging from -2% to 6% (mean = 1%) (McDonnell et al., 1983). All of the subjects in these studies were young adult males. *(Intersubject variability related to age and gender is discussed in Sections AX6.5.1 and AX6.5.2, respectively.)*

More recently, McDonnell (1996) examined the FEV₁ response data from three 6.6 h exposure studies of young adult males conducted at the EPA Health Effects Research Laboratory in Chapel Hill, NC (Folinsbee et al., 1988; Horstman et al., 1990; McDonnell et al., 1991).

The response distributions for subjects at each of four O₃ concentrations (0.0, 0.08, 0.10, and 0.12 ppm) are illustrated in Figure AX6-6. It is apparent that the FEV₁ responses in FA are small with most tightly grouped around zero. With increasing O₃ concentration, the mean response increases as does the variability about the mean. At higher O₃ concentrations, the distribution of response becomes asymmetric with a few individuals experiencing large FEV₁ decrements. The response distribution in Figure AX6-6 allows estimates of the number or percentage of subjects responding in excess of a certain level. With FA exposure, none of 87 subjects had a FEV₁ decrement in excess of 10%; however, 26%, 31%, and 46% exceeded a 10% decrement at 0.08, 0.10, and 0.12 ppm, respectively. FEV₁ decrements as large as 30 to 50% were even observed in some individuals. In 6.6-h face mask exposures of young adults (half women) to 0.08 ppm O₃, Adams (2002) found that 6 of 30 subjects (20%) had >10% decrements in FEV₁. The response distributions in Figure AX6-6 underlines the wide range of response to O₃ under prolonged exposure conditions and reinforces the observations by others consequent to 2 h IE exposures at higher O₃ concentrations (Horvath et al., 1981; McDonnell et al., 1983).

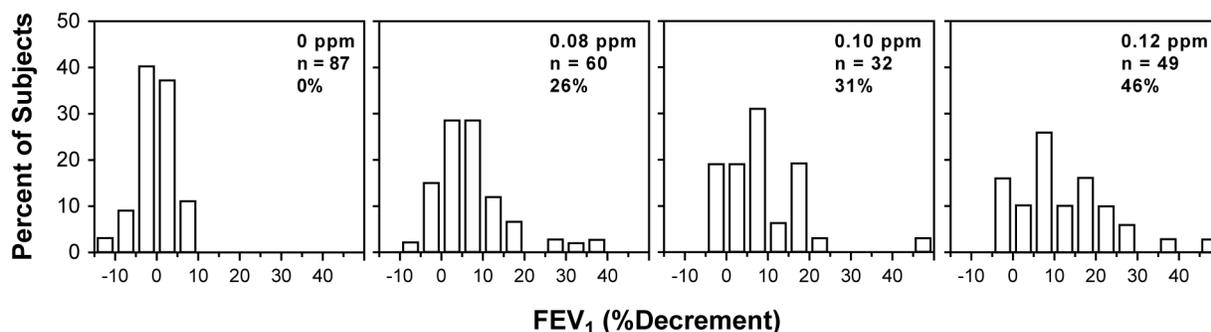


Figure AX6-6. Frequency distributions of FEV₁ decrements following 6.6-h exposures to O₃ or filtered air. During each hour of the exposures, subjects were engaged in moderate exercise for 50 minutes. With increasing O₃ concentration, the distribution of responses becomes asymmetric, with a few individuals exhibiting large FEV₁ decrements. The percentage in each panel indicates the portion of subjects having a FEV₁ decrement in excess of 10%.

Source: McDonnell (1996).

Some of the intersubject variability in response to O₃ inhalation may be due to intrasubject variability, i.e., how reproducible the measured responses are in an individual between several O₃ exposures. The more reproducible the subject's response, the more precisely it indicates his/her intrinsic responsiveness. McDonnell et al. (1985a) examined the reproducibility of individual responses to O₃ in healthy human subjects (n = 32) who underwent repeated exposures within a period of 21 to 385 days (mean = 88 days; no median reported) at one of five O₃ concentrations ranging from 0.12 to 0.40 ppm. Reproducibility was assessed using the intraclass correlation coefficient (R). The most reproducible responses studied were FVC (R = 0.92) and FEV₁ (R = 0.91). However, at the lowest concentration, 0.12 ppm, relatively poor FEV₁ reproducibility was observed (R = 0.58) due, in part, to a lack of specific O₃ response or a uniformly small response in the majority of subjects. McDonnell et al. (1985a) concluded that for 2 h IE O₃ exposures equal to or greater than 0.18 ppm, the intersubject differences in magnitude of change in FVC and FEV₁ are quite reproducible over time and likely due to differences in intrinsic responsiveness of individual subjects. Hazucha et al. (2003) exposed 47 subjects on three occasions for 1.5 h, with moderate intensity IE, to 0.40 to 0.42 ppm O₃. Reproducibility of FEV₁ responses was related to the length of time between re-exposures, with a Spearman correlation R of 0.54 obtained between responses for exposures 1 and 2 (median = 105 days), and an R of 0.85 between responses for exposures 2 and 3 (median = 7 days).

Identification of mechanisms of response and health risks associated with acute O₃ exposures are complicated by a poor association between various O₃-induced responses. For example, McDonnell et al. (1983) observed a very low correlation between changes in sRaw and FVC (r = -0.16) for 135 subjects exposed to O₃ concentrations ranging from 0.12 to 0.40 ppm for 2.5 h with IE. In a retrospective study of 485 male subjects (ages 18 to 36 yrs) exposed for 2 h to one of six O₃ concentrations at one of three activity levels, McDonnell et al. (1999) observed significant, but low, Spearman rank order correlations between FEV₁ response and symptoms of cough (R = 0.39), shortness of breath (R = 0.41), and pain on deep inspiration (R = 0.30). The authors concluded from their data that the O₃-induced responses are related mechanistically to some degree, but that there is not a single factor which is responsible for the observed individual differences in O₃ responsiveness across the spectrum of symptom and lung function responses. This conclusion is supported by differences in reproducibility observed by

McDonnell et al., (1985a). Compared to the intraclass correlation coefficient for FEV₁ (R = 0.91), relatively low but statistically significant R values for symptoms ranged from 0.37 to 0.77, with that for sRaw being 0.54. The reproducibility correlations for f_B (R = -0.20) and V_T (R = -0.03) were not statistically significant.

The effect of this large intersubject variability on the ability to predict individual responsiveness to O₃ was demonstrated by McDonnell et al. (1993). These investigators analyzed the data of 290 male subjects (18 to 32 years of age) who underwent repeat 2 h IE exposures to one or more O₃ concentrations ranging from 0.12 to 0.40 ppm in order to identify personal characteristics (i.e., age, height, baseline pulmonary functions, presence of allergies, and past smoking history) that might predict individual differences in FEV₁ response. Only age contributed significantly to intersubject responsiveness (younger subjects were more responsive), accounting for just 4% of the observed variance. Interestingly, O₃ concentration accounted for only 31% of the variance, strongly suggesting the importance of as yet undefined individual characteristics that determine FEV₁ responsiveness to O₃. A more general form of this model was developed to investigate the O₃ exposure FEV₁ response relationship (McDonnell et al., 1997). These authors used data from 485 male subjects (age = 18 to 36 years) exposed once for 2 h to one of six O₃ concentrations (ranging from 0.0 to 0.40 ppm) at one of 3 activity levels (rest, n = 78; moderate IE, n = 92; or heavy IE, n = 314). In addition to investigating the influence of subject's age, the model focused on determining whether FEV₁ response was more sensitive to changes in C than to changes in \dot{V}_E , and whether the magnitude of responses is independent of differences in lung size. It was found that the unweighted proportion of the variability in individual responses explained by C, \dot{V}_E , T, and age was 41%, with no evidence that the sensitivity of FEV₁ response to \dot{V}_E was different than changes in C, and no evidence that magnitude of response was related to measures of body or lung size. The authors concluded that much inter-individual variability in FEV₁ response to O₃ remains unexplained.

AX6.5 INFLUENCE OF AGE, GENDER, ETHNIC, ENVIRONMENTAL AND OTHER FACTORS

AX6.5.1 Influence of Age

On the basis of results reported from epidemiologic studies, children and adolescents are considered to be at increased risk, but not necessarily more responsive, to ambient oxidants than adults. However, findings of controlled laboratory studies that have examined the acute effects of O₃ on children and adolescents do not completely support this assertion (Table AX6-5). Children experience about the same decrements in spirometric endpoints as young adults exposed to comparable O₃ doses (McDonnell et al., 1985b; Avol et al., 1987). In contrast to young adults, however, they had no symptomatic response, which may put them at an increased risk for continued exposure. Similarly, young adults (Linn et al., 1986; Avol et al., 1984) have shown comparable spirometric function response when exposed to low O₃ dose under similar conditions. Among adults, however, it has been repeatedly demonstrated that older individuals respond to O₃ inhalation with less intense lung function changes than younger adults. Thus, children, adolescents, and young adults appear to be about equally responsive to O₃, but more responsive than middle-aged and older adults when exposed to a comparable dose of O₃ (U.S. Environmental Protection Agency, 1996).

Gong et al. (1997a) studied ten healthy men (60 to 69 years old) and nine COPD patients (59 to 71 years old) from the Los Angeles area who were exposed to 0.24 ppm O₃ while intermittently exercising every 15 min at a light load (~20 L/min) for 4 h. Healthy subjects showed a small but significant O₃-induced FEV₁ decrement of 3.3% (p = 0.03 [not reported in paper] paired-t on O₃ versus FA pre-post FEV₁)². Small but statistically nonsignificant changes were also observed for respiratory symptoms, airway resistance and arterial O₂ saturation. In the COPD patients, there was an 8% FEV₁ decrement due to O₃ exposure which was not significantly different from the response in the healthy subjects. The authors have concluded that typical ambient concentrations of O₃ are unlikely to induce “a clinically significant acute lung dysfunction” in exposed older men. However, they also acknowledged that the “worst case” scenario of O₃ exposure used in their study causes acute spirometric responses.

²Personal communication from authors, correction to Table 2 in Gong et al. (1997a), the %FEV₁ change at the end of the ozone exposure for subject ID 2195 should read 4.9 and not the published value of -4.3, the mean and standard deviation reported in the table are correct.

Table AX6-5. Age Differences in Pulmonary Function Responses to Ozone^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.40	784	2 h IE (15' ex/15' rest) $\dot{V}_E \approx 33\text{-}45$ L/min (47 subjects only)	≈ 22 °C 40% RH treadmill	146 M 94 F	Healthy NS 18 to 60 years old	Young individuals of both gender (<35 years) significantly more responsive than older subjects. Strong responses are less common over the age of 35 years, especially in women. The variability of an individual's responsiveness to repeated exposures to O ₃ decreases with age.	Hazucha et al. (2003)
0.42	823	1.5 h IE (20' ex/10' rest) $\dot{V}_E \approx 33\text{-}45$ L/min (All subjects)					
0.0	0	2 h, IE (15' ex/15' rest)	21 °C	28 M	Healthy NS	Significant decrements in spirometric lung function in all groups. Young males and females (<35 years) were significantly more responsive than older individuals (>35 years).	Passannante et al. (1998)
0.40	784	$\dot{V}_E \approx 18$ L/min/m ² BSA 2 exposures: 25% of subj. exposed to air-air, 75% exposed to O ₃ -O ₃	40% RH treadmill	34 F	Healthy NS 18 to 59 years old		
0.0	0	4 h, IE (15' ex/15' rest)	24 °C	10 M	Healthy NS	Healthy: small, 3.3%, decline in FEV ₁ (p = 0.03 [not reported in paper], paired-t on O ₃ versus FA pre-post FEV ₁). COPD: 8% decline in FEV ₁ (p = ns, O ₃ versus FA). Adjusted for exercise, ozone effects did not differ significantly between COPD patients and healthy subjects.	Gong et al. (1997a)
0.24	470	$\dot{V}_E = 20$ L/min	40% RH	9 M	COPD 59 to 71 years old		
0.0	0	2 h rest or IE	22 °C	485 WM (each subject exposed at one activity level to one O ₃ concentration)	Healthy NS	Statistical analysis of 8 experimental chamber studies conducted between 1980 and 1993 by the U.S. EPA in Chapel Hill, NC. O ₃ -induced decrement in FEV ₁ predicted to decrease with age. FEV ₁ response of a 30 year old predicted to be 50% the response of a 20 year old. <i>Also see Table 6-1</i>	McDonnell et al. (1997)
0.12	235	(4 × 15 min	40% RH		18 to 36 years old		
0.18	353	at $\dot{V}_E = 25$ or 35			mean age 24 years		
0.24	471	L/min/m ² BSA)					
0.30	589						
0.40	784						
0.0	0	2.33 h IE	22 °C	371 (WM, BM, WF, BF; ~25% per group) each subject exposed to one O ₃ concentration	Healthy NS	Statistical analysis of experimental data collected between 1983 and 1990 by the U.S. EPA in Chapel Hill, NC. O ₃ -induced decrement in FEV ₁ predicted to decrease with age. FEV ₁ response of a 30 year old predicted to be 65% the response of a 20 year old. No effect of menstrual cycle phase on FEV ₁ response. Inconsistent effect of social economic status on FEV ₁ response.	Seal et al. (1996)
0.12	235	(4 × 15 min	40% RH		18 to 35 years old		
0.18	353	at $\dot{V}_E = 25$			mean age 24 years		
0.24	471	L/min/m ² BSA)					
0.30	589						
0.40	784						

AX6-46

Table AX6-5 (cont'd). Age Differences in Pulmonary Function Responses to Ozone^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.18 0.24 0.30 0.40	353 470 588 784	2.33 h IE $\dot{V}_E = 20$ L/min/m ² BSA	NA	48 WF, 55 BF	Healthy NS, 18 to 35 years old, black and white	Older women had smaller changes in FEV ₁ than younger women. No age- related differences in SRaw or cough score.	Seal et al. (1993)
0.45	882	1 h, CE $\dot{V}_E \approx 26$ L/min 2 h, IE $\dot{V}_E \approx 26$ L/min	≈ 23 °C 58% RH cycle/treadmill	7 M 5 F	Healthy NS, 60 to 79 years old (all in 60s except one 79 years old)	Comparison of 1-h CE protocol and 2-h IE protocol indicated no difference between the changes in pulmonary function following the two protocols.	Drechsler-Parks et al. (1990)
0.45	882	2 h, IE (20' ex/20' rest) Male: $\dot{V}_E = 28.5$ L/min Female: $\dot{V}_E = 26.1$ L/min	23 °C 46% RH cycle/treadmill	10 M, 6 F	Healthy NS, 60 to 89 years old	Mean decrement in FEV ₁ = 5.7%; eight subjects had a 5% or greater difference between their response to O ₃ and FA, and the other eight had less than a 5% difference between their responses to FA and 0.45 ppm O ₃ .	Bedi et al. (1989)
0.45	882	2 h, IE (20' ex/20' rest) $\dot{V}_E \approx 26$ L/min	≈ 24 °C 63% RH cycle	8 M 8 F	Healthy NS, 51 to 69 years old Healthy NS, 56 to 76 years old	13 subjects had decrements in FEV ₁ on three separate exposures to 0.45 ppm within 5% of their mean response to the three exposures. The other three subjects were not reproducible. Symptom reports did not correlate well with pulmonary function changes.	Bedi et al. (1988)
0.12	235	1 h IE (mouthpiece) $\dot{V}_E = 4$ to $5 \times$ resting	22 °C 75% RH treadmill	5 M, 7 F	Healthy NS, 12 to 17 years old	No significant changes in any pulmonary function in healthy subjects.	Koenig et al. (1988)
0.20 0.30	392 588	1 h (mouthpiece) 50' rest/10' ex for first 7 males, 20' rest/10' ex for remaining subjects Male: $\dot{V}_E \approx 29$ L/min Female: $\dot{V}_E \approx 23$ L/min	≈ 22 °C $\geq 75\%$ RH treadmill	9 M, 10 F	Healthy NS, 55 to 74 years old	No spirometric changes for either group. Females had 13% increase in R _T at 3 and 22 min after 0.30-ppm exposure.	Reisenauer et al. (1988)
0.113 ^c + other ambient pollutants	221	1 h CE (bicycle) $\dot{V}_E \approx 22$ L/min	32.7 °C $\approx 43\%$ RH cycle	33 M, 33 F	NS for both groups, mean age = 9.4 years old	No differences in responses of boys and girls. Similar decrements (<5% on average) following both purified air and ambient air (O ₃ at 0.11 ppm) exposures.	Avol et al. (1987)

AX6-47

Table AX6-5 (cont'd). Age Differences in Pulmonary Function Responses to Ozone^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.45	882	2 h, IE (20' ex/20' rest) $\dot{V}_E \approx 26$ L/min	≈ 23 °C 53% RH cycle	8 M, 8 F	Healthy NS, 51 to 76 years old	Mean decrement in FEV ₁ = $5.6 \pm 13\%$; range of decrements = 0 to 12%.	Drechsler-Parks et al. (1987a,b)
0.12	235	40 min (mouthpiece) IE, 10 min exercise at $\dot{V}_E = 32.6$ L/min	NA treadmill	3 M, 7 F	Healthy NS, 14 to 19 years old	No significant change in FEV ₁ ; increased R _T with exposure to 0.18 ppm O ₃ . Some subjects responded to 5 to 10 mg/mL methacholine after 0.18-ppm O ₃ exposure, whereas none responded to 25 mg/mL methacholine at baseline bronchochallenge.	Koenig et al. (1987)
0.18	353	40 min (mouthpiece) IE, 10 min exercise at $\dot{V}_E = 41.3$ L/min		4 M, 6 F			

^aSee Appendix A for abbreviations and acronyms.

^bListed from lowest to highest O₃ concentration.

^cOzone concentration is the mean of a range of ambient concentrations.

Although Gong et al. (1997a) and others (see Table AX6-5) have examined responses to O₃ exposure in subjects of various ages, the exposure conditions differ between most studies so that age effects remain uncertain. Three recent studies, which analyzed large data sets (≥ 240 subjects) of similarly exposed subjects, show clearly discernable changes in FEV₁ responses to O₃ as a function of age.

Seal et al. (1996) analyzed O₃-induced spirometric responses in 371 young nonsmokers (18 to 35 years of age). The subject population was approximately 25% white males, 25% white females, 25% black males, and 25% black females. Each subject was exposed once to 0.0, 0.12, 0.18, 0.24, 0.30, or 0.40 ppm ozone for 2.3 h during IE at a \dot{V}_E of 25 L/min/m² BSA. A logistic function was used to model and test the significance of age, socioeconomic status (SES), and menstrual cycle phase as predictors of FEV₁ response to O₃ exposure. Menstrual cycle phase was not a significant. SES was inconsistent with the greatest response observed in the medium SES and the lowest response in high SES. FEV₁ responses decreased with subject age. On average, regardless of the O₃ concentration, the response of 25, 30, and 35 year old individuals are predicted to be 83, 65, and 48% (respectively) of the response in 20 year olds. For example, in 20 year old exposed to 0.12 ppm ozone (2.3 h IE, $\dot{V}_E = 25$ L/min/m² BSA) a 5.4% decrement in FEV₁ is predicted, whereas, a similarly exposed 35 yr old is only predicted to have a 2.6% decrement. The Seal et al. (1996) model is limited to predicting FEV₁ responses immediately postexposure in individuals exposed for 2.3 h during IE at a \dot{V}_E of 25 L/min/m² BSA.

McDonnell et al. (1997) examined FEV₁ responses in 485 healthy white males (18 to 36 years of age) exposed once for 2 h to an O₃ concentration of 0.0, 0.12, 0.18, 0.24, 0.30, or 0.40 ppm at rest or one of two levels of IE (\dot{V}_E of 25 and 35 L/min/m² BSA). FEV₁ was measured preexposure, after 1 h of exposure, and immediately postexposure. Decrements in FEV₁ were modeled by sigmoid-shaped curve as a function of subject age, O₃ concentration, \dot{V}_E , and duration of exposure. Regardless of the O₃ concentration or duration of exposure, the average responses of 25, 30, and 35 year old individuals are predicted to be 69, 48, and 33% (respectively) of the response in 20 year olds. The McDonnell et al. (1997) model is best suited to predicting FEV₁ responses in white males exposed to O₃ for 2 h or less under IE conditions.

Hazucha et al. (2003) analyzed the distribution of O₃ responsiveness in subjects (146 M, 94 F) between 18 and 60 years of age. Subjects were exposed to 0.42 ppm O₃ for 1.5 h with IE

at $\dot{V}_E = 20 \text{ L/min/m}^2 \text{ BSA}$. Figure AX6-7 illustrates FEV₁ responses to O₃ exposure as a function of subject age. Consistent with the discussion in Section 6.4, a large degree of intersubject variability is evident in Figure AX6-7. Across all ages, 18% of subjects were weak responders ($\leq 5\%$ FEV₁ decrement), 39% were moderate responders, and 43% were strong responders ($\geq 15\%$ FEV₁ decrement). Younger subjects (≤ 35 years of age) were predominately strong responders, whereas, older subjects (>35 years of age) were mainly weak responders. In males, the FEV₁ responses of 25, 35, and 50 year olds are predicted to be 94, 83, and 50% (respectively) of the average response in 20 year olds. In females, the FEV₁ responses of 25, 35, and 50 year olds are predicted to be 82, 46, and 18% (respectively) of the average response in 20 year olds. The Hazucha et al. (1996) model is limited to predicting FEV₁ responses immediately postexposure in individuals exposed to 0.42 ppm O₃ for 1.5 h during IE at a \dot{V}_E of 20 L/min/m² BSA.

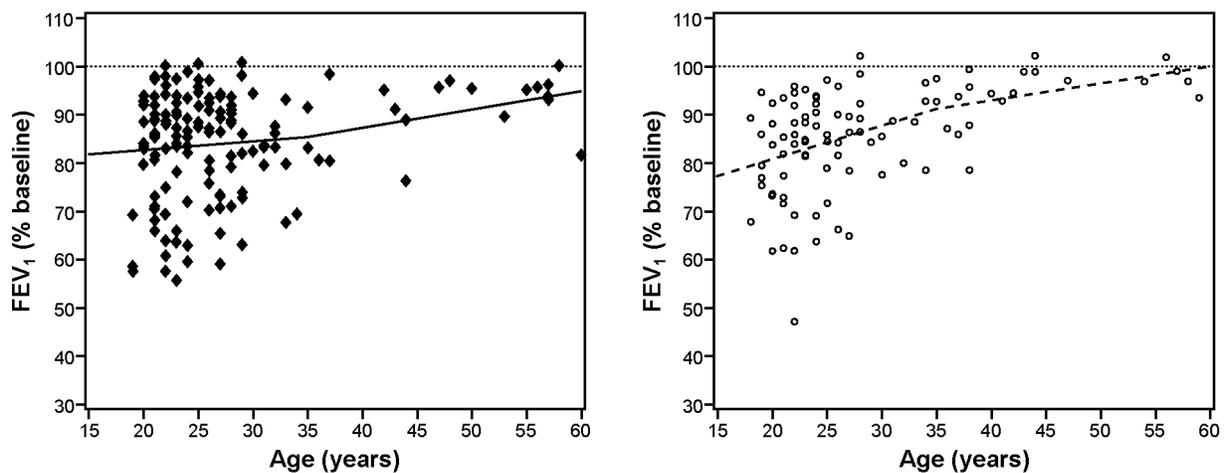


Figure AX6-7. Effect of O₃ exposure (0.42 ppm for 1.5 h with IE) on FEV₁ as a function of subject age. Left panel data for males (n = 146; 19 to 60 yrs old), right panel data for females (n = 94; 18 to 59 yrs old). In a 45 yr old male and 52 yr old female, FEV₁ decreased to 37 and 72% of baseline, respectively. These two outliers, not illustrated above, demonstrate that some individuals may still experience substantial responses despite increasing age.

Source: Adapted from Hazucha et al. (2003).

The pathophysiologic mechanisms behind the pronounced age-dependent, gender-differential rate of loss of O₃ responsiveness are unclear. Passannante et al. (1998) have previously demonstrated that O₃-induced spirometric decrements (FEV₁) in healthy young and middle-aged adults are principally neural in origin, involving opioid-modulated sensory bronchial C-fibers. (*The methodological details of this study are presented in Section AX6.2.3 of this chapter.*) The peripheral afferents are most likely the primary site of action, which would be compatible with a reflex action as well as a cortical mechanism. The pattern of progressive decline, as well as the subsequent rate of recovery of spirometric lung function, suggest involvement of both direct and indirect (possibly by PGE_{2α}) stimulation and/or sensitization of vagal sensory fibers. (*For details, see Section AX6.2.3.1 of this chapter.*)

The additional pulmonary function data published since the release of last O₃ criteria document (U.S. Environmental Protection Agency, 1996) and reviewed in this section reinforce the conclusions reached in that document. Children and adolescents are not more responsive to O₃ than young adults when exposed under controlled laboratory conditions. However, they are more responsive than middle-aged and older individuals. Young individuals between the age of 18 and 25 years appear to be the most sensitive to O₃. With progressing age, the sensitivity to O₃ declines and at an older age (>60 yrs) appears to be minimal except for some very responsive individuals. Endpoints other than FEV₁ may show a different age-related pattern of responsiveness.

AX6.5.2 Gender and Hormonal Influences

The few late 1970 and early 1980 studies specifically designed to determine symptomatic and lung function responses of females to O₃ were inconsistent. Some studies have concluded that females might be more sensitive to O₃ than males, while others found no gender differences (U.S. Environmental Protection Agency, 1996). During the subsequent decade, seven studies designed to systematically explore gender-based differences in lung function following O₃ exposure were completed (Table AX6-6). Protocols included mouthpiece and chamber exposures, young and old individuals, normalization of ventilation to BSA or FVC, continuous and intermittent exercise, control for menstrual cycle phase, and the use of equivalent effective dose of O₃ during exposures. These studies have generally reported no statistically significant differences in pulmonary function between males and females (Adams et al., 1987; Drechsler-

Table AX6-6. Gender and Hormonal Differences in Pulmonary Function Responses to Ozone^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions ^c	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.0 0.25	490	1 h CE $\dot{V}_E = 30$ L/min	NA Face mask exposure	32 M, 28 F	Healthy NS 22.6 ± 0.6 years old	Mean O ₃ -induced FEV ₁ decrements of 15.9% in males and 9.4% in females (gender differences not significant). FEV ₁ decrements ranged from -4 to 56%; decrements >15% in 20 subjects and >40% in 4 subjects. Uptake of O ₃ greater in males than females, but uptake not correlated with spirometric responses.	Ultman et al. (2004)
0.40 0.42	784 823	2 h, IE (15' ex/15' rest) $\dot{V}_E = 33-45$ L/min 1.5 h IE (20' ex/10' rest) $\dot{V}_E = 33-45$ L/min	22 °C 40% RH treadmill	146 M 94 F	Healthy NS, 18 to 60 years old	No significant gender differences in FEV ₁ among young (<35 years) and older individuals. Strong responses are less common over the age of 35 years, especially in women.	Hazucha et al. (2003)
0.0 0.35	0 686	1.25 h, IE (30' ex/15' rest/30' ex) $\dot{V}_E = 40$ L/min	22 °C 40% RH treadmill	19 F	O ₃ responders 22.1 ± 2.7 years old	FVC and FIVC changes about the same, -13%, FEV ₁ -20%. Increased airway responsiveness to methacholine. Persistence of small effects on both inspired and expired spirometry past 18 h. Chemoreceptors not activated but ventilatory drive was accelerated.	Folinsbee and Hazucha (2000)
0.0 0.4	0 784	2 h, IE (15' ex/15' rest) $\dot{V}_E \approx 18$ L/min/m ² BSA 2 exposures: 25% of subj. exposed to air-air, 75% exposed to O ₃ -O ₃	21 °C 40% RH treadmill	28 M 34 F	Healthy NS, 20-59 years old	Significant decrements in spirometric lung function. No significant differences in FEV ₁ between young females and males and older females and males either in responders or nonresponders subgroups.	Passannante et al. (1998)
0 0.12 0.24 0.30 0.40	0 235 470 588 784	2.33 h IE (15' ex/15' rest) $\dot{V}_E = 20$ L/min/m ² BSA one exposure per subject	22 °C 40% RH treadmill	48 WF, 55 BF	Healthy NS, 18 to 35 years old	Significant menstrual cycle phase × race interaction for FEV ₁ . No significant menstrual cycle phase effect when blacks and whites were analyzed separately. No significant menstrual phase effects for SRaw or cough score.	Seal et al. (1996)

Table AX6-6 (cont'd). Gender and Hormonal Differences in Pulmonary Function Responses to Ozone^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions ^c	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference																																																																			
ppm	µg/m ³																																																																									
0.0	0	2.15 h, IE (30' ex/30' rest)	19-24 °C	12 M	Healthy NS, 5 F follicular and 7 luteal phase exposure, regular menstrual cycles, 18 to 35 years old	Changes in FVC, FEV ₁ , FEF ₂₅₋₇₅ , $\dot{V}_{max50\%}$, and $\dot{V}_{max25\%}$ were similar during both the follicular and luteal phases. No significant difference between males and females.	Weinmann et al. (1995)																																																																			
0.35	686		48-55% RH treadmill	12 F				0.3	588	1 h CE $\dot{V}_E \approx 50$ L/min	NA	9 F	Healthy NS, regular menstrual cycles, 20 to 34 years old	FEV ₁ decreased 13.1% during the mid-luteal phase and 18.1% during the follicular phase. Decrement in FEF ₂₅₋₇₅ was significantly larger during the follicular phase than the mid-luteal phase. Changes in FVC were similar in both phases.	Fox et al. (1993)	0	0	2.33 h (15' ex/15' rest) $\dot{V}_E = 25$ L/min/m ² BSA (one exposure/subject)	22 °C	30 to 33 F and 30 to 33 M in each concentration group; total of 372 individuals participated	Healthy NS, 18 to 35 years old, blacks and whites	Decrements in FEV ₁ , increases in SRaw and cough, correlated with O ₃ concentration. There were no significant differences between the responses of males and females.	Seal et al. (1993)	0.12	235	40% RH	0.18	353	treadmill	0.24	470	0.30	588	0.40	784	0	0	1 h (mouthpiece), CE $\dot{V}_E \approx 47$ L/min exposures ≥ 4 days apart	21 to 25 °C	14 F	FVC = 5.11 ± 0.53 L, NS, 20 to 24 years old	Small lung group, FVC = 3.74 ± 0.30 L. Large lung group, FVC = 5.11 ± 0.53 L. Significant concentration-response effect on FVC and FEV ₁ ; lung size had no effect on percentage decrements in FVC or FEV ₁ .	Messineo and Adams (1990)	0.18	353	45 to 60% RH	14 F	FVC = 3.74 ± 0.30 L, NS, 19 to 23 years old	0.30	588	cycle	0.0	0	2 h, IE (20' ex/20' rest) $\dot{V}_E = 28.5$ L/min for M $\dot{V}_E = 26.1$ L/min for F repeated O ₃ exposures	23.1 °C	10 M	Healthy NS, 60 to 89 years old	Mean decrement in FEV ₁ = 5.7%. Decrements in FVC and FEV ₁ were the only pulmonary functions significantly altered by O ₃ exposure. No significant differences between responses of men and women.	Bedi et al. (1989)	0.45	882	46.1% RH cycle/treadmill	6 F	Healthy NS, 64 to 71 years old	0	0	1 h (mouthpiece) IE (50' rest/10' ex first 7 M) (20' rest/10' ex all others) $\dot{V}_E \approx 28$ L/min for M $\dot{V}_E \approx 23$ L/min for F	≈ 22 °C	9 M, 10 F	Healthy NS, 55 to 74 years old	No change in any spirometric measure for either group. Females had 13% increase in R _T after 0.30-ppm exposure. Gender differences not evaluated.	Reisenauer et al. (1988)	0.20	392
0.3	588	1 h CE $\dot{V}_E \approx 50$ L/min	NA	9 F	Healthy NS, regular menstrual cycles, 20 to 34 years old	FEV ₁ decreased 13.1% during the mid-luteal phase and 18.1% during the follicular phase. Decrement in FEF ₂₅₋₇₅ was significantly larger during the follicular phase than the mid-luteal phase. Changes in FVC were similar in both phases.	Fox et al. (1993)																																																																			
0	0	2.33 h (15' ex/15' rest) $\dot{V}_E = 25$ L/min/m ² BSA (one exposure/subject)	22 °C	30 to 33 F and 30 to 33 M in each concentration group; total of 372 individuals participated	Healthy NS, 18 to 35 years old, blacks and whites	Decrements in FEV ₁ , increases in SRaw and cough, correlated with O ₃ concentration. There were no significant differences between the responses of males and females.	Seal et al. (1993)																																																																			
0.12	235		40% RH																																																																							
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0.30	588																																																																									
0.40	784																																																																									
0	0	1 h (mouthpiece), CE $\dot{V}_E \approx 47$ L/min exposures ≥ 4 days apart	21 to 25 °C	14 F	FVC = 5.11 ± 0.53 L, NS, 20 to 24 years old	Small lung group, FVC = 3.74 ± 0.30 L. Large lung group, FVC = 5.11 ± 0.53 L. Significant concentration-response effect on FVC and FEV ₁ ; lung size had no effect on percentage decrements in FVC or FEV ₁ .	Messineo and Adams (1990)																																																																			
0.18	353		45 to 60% RH	14 F	FVC = 3.74 ± 0.30 L, NS, 19 to 23 years old																																																																					
0.30	588		cycle																																																																							
0.0	0	2 h, IE (20' ex/20' rest) $\dot{V}_E = 28.5$ L/min for M $\dot{V}_E = 26.1$ L/min for F repeated O ₃ exposures	23.1 °C	10 M	Healthy NS, 60 to 89 years old	Mean decrement in FEV ₁ = 5.7%. Decrements in FVC and FEV ₁ were the only pulmonary functions significantly altered by O ₃ exposure. No significant differences between responses of men and women.	Bedi et al. (1989)																																																																			
0.45	882		46.1% RH cycle/treadmill	6 F	Healthy NS, 64 to 71 years old																																																																					
0	0	1 h (mouthpiece) IE (50' rest/10' ex first 7 M) (20' rest/10' ex all others) $\dot{V}_E \approx 28$ L/min for M $\dot{V}_E \approx 23$ L/min for F	≈ 22 °C	9 M, 10 F	Healthy NS, 55 to 74 years old	No change in any spirometric measure for either group. Females had 13% increase in R _T after 0.30-ppm exposure. Gender differences not evaluated.	Reisenauer et al. (1988)																																																																			
0.20	392		$\geq 75\%$ RH																																																																							
0.30	588		treadmill																																																																							

Table AX6-6 (cont'd). Gender and Hormonal Differences in Pulmonary Function Responses to Ozone^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions ^c	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.3	588	1 h (mouthpiece), CE $\dot{V}_E \approx 70$ L/min for men $\dot{V}_E \approx 50$ L/min for women	21 to 25 °C 45 to 60% RH cycle	20 M 20 F	NS, 18 to 30 years old NS, 19 to 25 years old	Significant decrements in FVC, FEV ₁ , and FEV ₂₅₋₇₅ following O ₃ exposure. No significant differences between men and women for spirometry or SRaw.	Adams et al. (1987)
0.0 0.45	0 882	2 h, IE (20' rest/ 20' ex) $\dot{V}_E \approx 27.9$ L/min for M $\dot{V}_E \approx 25.4$ L/min for F repeated O ₃ exposures	24 °C 58% RH cycle	8 M 8 F	Healthy NS, 51 to 69 years old Healthy NS, 56 to 76 years old	Range of responses in FEV ₁ : 0 to -12% (mean = -5.6%). No significant difference in responses of men and women. Tendency for women to have greater effects.	Drechsler-Parks et al. (1987a,b)
0.48	941	2 h, IE $\dot{V}_E \approx 25$ L/min	21 °C (WBGT) cycle	10 F	Healthy NS, 19 to 36 years old	Mean decrement in FEV ₁ = 22.4%. Significant decrements in all spirometric measurements. Results not significantly different from a similar study on males (Drechsler-Parks et al., 1984).	Horvath et al. (1986)

^a See Appendix A for abbreviations and acronyms.

^b Listed from lowest to highest O₃ concentration.

^c WBGT = 0.7 T_{wet bulb} + 0.3 T_{dry bulb or globe}

Parks et al., 1987a; Messineo and Adams, 1990; Seal et al., 1993; Weinmann et al., 1995) although in some studies females appeared to experience a slightly greater decline than males (Drechsler-Parks et al., 1987a; Messineo and Adams, 1990). The comparative evaluations were based on responses that included spirometry, airway resistance, nonspecific bronchial responsiveness (NSBR) determinations, and changes in frequency and severity of respiratory symptoms. However, depending on how the O₃ dose was calculated and normalized, the findings of at least three studies may be interpreted as showing that females are more sensitive to O₃ than males. The findings of the seven studies are presented in detail in Section 7.2.1.3 of the previous O₃ criteria document (U.S. Environmental Protection Agency, 1996).

Some support for a possible increased sensitivity of females to O₃ comes from a study of uric acid concentration in nasal lavage fluid (NLF). Housley et al. (1996) found that the NLF of females contains smaller amounts of uric acid than the NLF of males. The primary source of uric acid is plasma; therefore, lower nasal concentrations would reflect lower plasma concentrations of this antioxidant. The authors have speculated that in females, both lower plasma and NLF levels (of uric acid) can plausibly make them more susceptible to oxidant injury, since local antioxidant protection may not be as effective as with higher levels of uric acid, and consequently more free O₃ can penetrate deeper into the lung.

Several studies also have suggested that anatomical differences in the lung size and the airways between males and females, and subsequent differences in O₃ distribution and absorption, may influence O₃ sensitivity and potentially differential O₃ response. The study of Messinio and Adams (1990) have, however, convincingly demonstrated that the effective dose to the lung, and not the lung size, determines the magnitude of (FEV₁) response. Furthermore, the O₃ dosimetry experiments of Bush et al. (1996) have shown that despite gender differences in longitudinal distribution of O₃, the absorption distribution in conducting airways was the same for both sexes when expressed as a ratio of penetration to anatomic dead space volume. This implies that gender differences, if any, are not due to differences in (normal) lung anatomy. The data also have shown that routine adjustment of O₃ dose for body size and gender differences would be more important if normalized to anatomic dead space rather than the usual FVC or BSA.

One of the secondary objectives of a study designed to examine the role of neural mechanisms involved in limiting maximal inspiration following O₃ exposure has been to

determine if gender differences occur. A group of healthy males (n = 28) and females (n = 34) were exposed to 0.42 ppm O₃ for 2 h with IE. The methodological details of the study are presented in Section AX6.2.5.1 of this document. As Figure AX6-4 shows, the differences between males and females were, at any condition, measurement point, and O₃ sensitivity status only minimal and not significant (Passannante et al., 1998).

In another investigation, Folinsbee and Hazucha (2000) exposed a group of 19 O₃-responsive young females (average age of 22 years, prescreened for O₃ responsiveness by earlier exposure) to air and 0.35 ppm O₃. The randomized 75-min exposures included two 30-min exercise periods at a \dot{V}_E of 40 L/min. In addition to standard pulmonary function tests, they employed several techniques used for the first time in human air pollution studies assessment of O₃ effects. The average lung function decline from a pre-exposure value was 13% for FVC, 19.9 % for FEV₁, and 30% for FEF₂₅₋₇₅. The infrequently measured forced inspiratory vital capacity (FIVC) was the same as FVC suggesting that the lung volume limiting mechanisms are the same. The reduction in peak inspiratory flow (PIF) most likely reflects an overall reduction in inspiratory effort associated with neurally mediated inhibition of inspiration. Persistence of small inspiratory and expiratory spirometric effects, airway resistance, and airway responsiveness to methacholine for up to 18 h postexposure suggests that recovery of pulmonary function after O₃ exposure involves more than the simple removal of an irritant. Incomplete repair of damaged epithelium and still unresolved airway inflammation are the likely causes of the residual effects that in some individuals persisted beyond 24 h postexposure. However, by 42 hours no residual effects were detected. No significant changes were found in ventilatory response to CO₂ between air and O₃ exposures, suggesting that chemoreceptors were not affected by O₃. However, O₃ inhalation did result in accelerated timing of breathing and a modest increase in inspiratory drive. These observations are consistent with, and further supportive of, the primary mechanisms of O₃-induced reduction in inspiratory lung function, namely an inhibition of inspiration elicited by stimulation of the C-fibers and other pulmonary receptors. Because the measures of inspiratory and chemical drive to assess O₃ effects were not reported in any previous human study, no comparisons are possible. Because no male subjects were recruited for the study, it is not possible to compare gender effects. Despite being O₃-responsive, however, the average post-O₃ decline in expiratory lung function from preexposure (13% for FVC; 19.9% for FEV₁; 30% for FEF₂₅₋₇₅) was similar to that seen in female cohorts studied by

other investigators under similar conditions of exposure. These were the same studies that found no gender differences in O₃ sensitivity (Adams et al., 1987; Messineo and Adams, 1990).

The study by Hazucha et al. (2003), discussed in the previous section, has in addition to aging also examined gender differences in O₃ responsiveness. The male (n = 146) and female (n = 94) cohorts were classified into young (19 to 35 year-old) and middle-aged (35 to 60 year-old) groups. This classification was selected in order to facilitate comparison with data reported previously by other laboratories. Using a linear regression spline model (with a break point at 35 years), the authors reported that the rate of loss of sensitivity is about three times as high in young females as in young males (p < 0.003). In young females, the average estimated decline in FEV₁ response is 0.71% per year, while in young males it is 0.19% per year. Middle-aged groups of both genders show about the same rate of decline (0.36 to 0.39%, respectively). At 60 years of age, the model estimates about a 5% post-O₃ exposure decline in FEV₁ for males, but only a 1.3% decline for females. These observations suggest that young females lose O₃ sensitivity faster than young males, but by middle age, the rate is about the same for both genders. Descriptive statistics show that there were practically no differences in the mean value, standard error of the mean, and coefficient of variation for % FEV₁ decrement between the group of young males (n = 125; 83.7 ± 1.1%; CV = 13.5%) and young females (n = 73; 83.4 ± 1.25%; CV = 12.8%). A straight linear regression model of these data was illustrated in Figure AX6-7. The slopes, significant in both males (r = 0.242; p = 0.003) and females (r = 0.488; p = 0.001), represent the decline in responsiveness of 0.29% and 0.55% per year respectively, as assessed by FEV₁.

Two earlier studies of the effects of the menstrual cycle phase on O₃ responsiveness have reported conflicting results (U.S. Environmental Protection Agency, 1996). Weinmann et al. (1995) found no significant lung function effects related to menstrual cycle, although during the luteal phase the effects were slightly more pronounced than during the follicular phase; while Fox et al., (1993) reported that follicular phase enhanced O₃ responsiveness. In a more recent investigation of possible modulatory effects of hormonal changes during menstrual cycle on O₃ response, young women (n = 150) 18 to 35 years old were exposed once to one of multiple O₃ concentrations (0.0, 0.12, 0.18, 0.24, 0.30, 0.40 ppm) for 140 min with IE at 35 L/min/m² BSA. The women's menstrual cycle phase was determined immediately prior to O₃ exposure. Post-O₃, no significant differences in % predicted FEV₁ changes that could be related to the menstrual

cycle phase were found. Admittedly, a less precise method of determining menstrual cycle phase used in this study could have weakened the statistical power. Unfortunately, the direction and magnitude of O₃ response as related to the menstrual cycle phases were not reported (Seal et al., 1996). Considering the inconclusiveness of findings of this study and the inconsistency of results between the two earlier studies, it is not possible to make any firm conclusions about the influence of the menstrual cycle on responses to O₃ exposure.

Additional studies presented in this section clarify an open-ended conclusion reached in the previous O₃ criteria document (U.S. Environmental Protection Agency, 1996) regarding the influence of age on O₃ responsiveness. Healthy young males and females are about equally responsive to O₃, although the rate of loss of sensitivity is higher in females than in males. Middle-aged men and women are generally much less responsive to O₃ than younger individuals. Within this range, males appear to be slightly more responsive than females, but the rate of age-related loss in FEV₁ is about the same. The O₃ sensitivity may vary during the menstrual cycle; however, this variability appears to be minimal.

AX6.5.3 Racial, Ethnic, and Socioeconomic Status Factors

In the only laboratory study designed to compare spirometric responses of whites and blacks exposed to a range of O₃ concentrations (0 to 0.4 ppm), Seal et al. (1993) reported inconsistent and statistically insignificant FEV₁ differences between white and black males and females within various exposure levels. Perhaps, with larger cohorts the tendency for greater responses of black than white males may become significant. Thus, based on this study it is still unclear if race is a modifier of O₃ sensitivity, although the findings of epidemiologic studies reported in the previous criteria document “can be considered suggestive of an ethnic difference” (U.S. Environmental Protection Agency, 1996). However, as Gwynn and Thurston (2001) pointed out, it appears that it is more the socioeconomic status (SES) and overall quality of healthcare that drives PM₁₀- and O₃-related hospital admissions than an innate or acquired sensitivity to pollutants.

This assertion is somewhat supported by the study of Seal et al. (1996) who employed a family history questionnaire to examine the influence of SES on the O₃ responsiveness of 352 healthy, 18- to 35-year-old black and white subjects. Each subject was exposed once under controlled laboratory conditions to either air or 0.12, 0.18, 0.24, 0.30, 0.40 ppm O₃ for 140 min

with 15 min IE at 35 L/min/m² BSA. An answer to the “Education of the father” question was selected as a surrogate variable for SES status. No other qualifying indices of SES were used or potential bias examined. Of the three SES categories, individuals in the middle SES category showed greater concentration-dependent decline in % predicted FEV₁ (4-5% @ 0.4 ppm O₃) than low and high SES groups. The authors did not have an “immediately clear” explanation for this finding. The SES to %predicted FEV₁ relationship by gender-race group was apparently examined as well; however, these results were not presented. Perhaps a more comprehensive and quantitative evaluation of SES status would have identified the key factors and clarified the interpretation of these findings. With such a paucity of data it is not possible to discern the influence of racial or other related factors on O₃ sensitivity.

AX6.5.4 Influence of Physical Activity

Apart from the importance of increased minute ventilation on the inhaled dose of O₃ during increased physical activity, including work, recreational exercise, and more structured exercise like sports, no systematic effort has been made to study other potential physical factors that may modulate O₃ response. The typical physiologic response of the body to exercise is to increase both the rate and depth of breathing, as well as increase other responses such as heart rate, blood pressure, oxygen uptake, and lung diffusion capacity.

Physical activity increases minute ventilation in proportion to work load. At rest, and during light exercise, the dominant route of breathing is through the nose. The nose not only humidifies air, among other physiologic functions, but also absorbs O₃ thus decreasing the overall dose. As the intensity of exercise increases, the minute ventilation increases and the breathing switches from nasal to oronasal mode. There is considerable individual variation in the onset of oronasal breathing, which ranges from 24 to 46 L/min (Niinimaa et al., 1980). During heavy exercise, ventilation is dominated by oral breathing. Consequently, the residence time of inhaled air in the nose and the airways is shorter, reducing the uptake of O₃ (Kabel et al., 1994). Moreover, increasing inspiratory flow and tidal volume shifts the longitudinal distribution of O₃ to the peripheral airways, which are more sensitive to injury than the larger, proximal airways. Ozone uptake studies of human lung showed that at simulated quiet breathing, 50% of O₃ was absorbed in the upper airways, 50% in the conducting airways, and none reached the small airways (Hu et al. 1994). With ventilation simulating heavy exercise

(60 L/min), the respective O₃ uptakes were 10% (upper airways), 65% (conducting airways), and 25% (small airways). These observations imply that equal O₃ dose ($C \times T \times \dot{V}_E$) will have a greater effect on pulmonary function and inflammatory responses when inhaled during heavy physical activity than when inhaled during lighter activity. Although, Ultman et al. (2004) recently reported that spirometric response are not correlated with O₃ uptake. (*See Chapter 4 of this document for more information on the dosimetry of O₃.*)

Other physiologic factors activated in response to physical activity are unlikely to have as much impact on O₃ responsiveness as does minute ventilation; however, their potential influence has not been investigated.

AX6.5.5 Environmental Factors

Since the 1996 O₃ criteria document, not a single human laboratory study has examined the potential influence of environmental factors such as rural versus urban environment, passive cigarette smoke exposure, and bioactive admixtures such as endotoxin on healthy individual's pulmonary function changes due to O₃ (U.S. Environmental Protection Agency, 1996).

Some of the unresolved issues, e.g., health effects of ETS and O₃ interaction, which need to be examined in human studies were explored very recently in laboratory animal studies (*see Chapter 5 for more details*). In one study on mice, preexposure of animals to sidestream cigarette smoke (ETS surrogate), which elicited no immediate effects, resulted in a potentiation of subsequent O₃-induced inflammatory response. This finding suggests that typical adverse effects of ETS do not necessarily have to elicit an immediate response to ETS, but may in fact potentiate the effects of a subsequent exposure to another pollutant like O₃ (Yu et al., 2002). The key mechanism by which smoke inhalation may potentiate subsequent oxidant injury appears to be damage to cell membranes and the resulting increase in epithelial permeability. Disruption of this protective layer may facilitate as well as accelerate injury to subepithelial structures when subsequently exposed to other pollutants (Bhalla, 2002). Although this may be a plausible mechanism in nonsmokers and acute smokers exposed to ETS and other pollutants, studies involving chronic smokers who most likely already have chronic airway inflammation do not seem to show exaggerated response with exposure to O₃.

More than 25 years ago, Hazucha et al. (1973) reported that the spirometric lung function of smokers declined significantly less than that of nonsmokers when exposed to 0.37 ppm O₃.

The findings of this study have been confirmed and expanded (Table AX6-7). Frampton et al. (1997a) found that exposure of current smokers (n = 34) and never smokers (n = 56) to 0.22 ppm O₃ for 4 h with IE for 20 min of each 30 min period at 40 to 46 L/min, induced a substantially smaller decline in FVC, FEV₁ and SGaw of smokers than never smokers. Smokers also demonstrated a much narrower distribution of spirometric endpoints than never smokers. Similarly, nonspecific airway responsiveness to methacholine was decreased in smokers. However, both groups showed the consistency of response from exposure to exposure. It should be noted that despite seemingly lesser response, the smokers were more symptomatic post air exposure than never smokers, but the opposite was true for O₃ exposure. This would suggest that underlying chronic airway inflammation present in smokers has blunted stimulation of bronchial C-fibers and other pulmonary receptors, the receptors substantially responsible for post-O₃ lung function decrements. In addition to desensitization, the other “protective” mechanisms active in smokers may be an increase in the mucus layer conferring not only a mechanical protection, but also acting as an O₃ scavenger. Another plausible explanation of a diminished responsiveness of smokers may be related to elevated levels of reduced glutathione (GSH), an antioxidant, found in epithelial lining fluid of chronic but not acute smokers (MacNee et al., 1996).

Despite some differences in a release of proinflammatory cytokines and subsequent recruitment of inflammatory cells, both smokers and nonsmokers developed airway inflammation following O₃ exposure. This was demonstrated by the Torres et al. (1997) study that involved exposures of about equal size cohorts of otherwise healthy young smokers, nonsmoker O₃ nonresponders (<5% FEV₁ post-O₃ decrement) and nonsmoker O₃ responders (>15% FEV₁ post-O₃ decrement) to air and two 0.22 ppm O₃ atmospheres for 4 hours, alternating 20 min of moderate exercise (25 L/min/m² BSA) with 10 min of rest. Both O₃ exposures were followed by nasal lavage (NL) and bronchoalveolar lavage (BAL) performed immediately post one of exposures and 18 hr later following the other exposure. Neither O₃ responsiveness nor smoking alters the magnitude or the time course of O₃-induced airway inflammation. The overall cell recovery was lower immediately postexposure but higher, particularly in nonsmokers, 18 h post-O₃ exposure when compared to control (air) in all groups. Recovery of lymphocytes, PMNs and AMs in both alveolar and bronchial lavage fluid showed the largest increase in response to O₃ in all groups, with nonsmokers showing greater relative increases than

Table AX6-7. Influence of Ethnic, Environmental, and Other Factors

Ozone Concentration		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$						
0.0	0	2 h	20 °C	15 M, 1 F	Placebo group: healthy NS avg age 27 yrs.	PF decrements in the supplementation group were signif. smaller for FVC ($p < 0.046$) and near significant for FEV ₁ ($p < 0.055$). The inflammatory response (BAL) showed no significant differences between the two groups either in the recovery of cellular components or the concentrations and types of inflammatory cytokines.	Samet et al. (2001)
0.4	780	IE, 15' ex/15' rest $\dot{V}_E = 20 \text{ L}/\text{min}/\text{m}^2$ BSA	40% RH	13 M, 2 F	Antiox. Suppl. Gr.: Healthy NS avg age 27 yrs.		
0.0	0	0.75 h	60% RH	5 M, 12 F	Asthmatics sensitive to SO ₂ 19 to 38 yrs old	No significant differences due to O ₃ between placebo and antioxidant supplement cohort in either spirometric responses or bronchial hyperresponsiveness to 0.1 ppm SO ₂ .	Trenka et al. (2001)
0.12	235	IE, 15' ex/15' rest $\dot{V}_E = 40\text{-}46 \text{ L}/\text{min}$					
0.0	0	4 h	21 °C	25 (M/F)	Healthy NS	Glutathione peroxidase (GPx) activity and eGPx protein level were significantly ($p = 0.0001$) depleted in ELF for at least 18 h postexp. In BAL both endpoints were elevated (ns). No association between cell injury, PF, or GPx activity.	Avisar et al. (2000) ^b
0.22	431	IE, 20' ex/10' rest	37% RH		O ₃ responders and nonresponders		
0.22	431	$\dot{V}_E = 40\text{-}46 \text{ L}/\text{min}$			18 to 40 yrs old		
0.0	0	2.17 h	22 °C or 30 °C	5 M, 4 F	Healthy NS	FEV ₁ decreased ($p < 0.5$) by ~8% at 22 °C and ~6.5% at 30 °C. 19 h postexp decline of 2.3% still signif. ($p < 0.05$). SGaw signif. ($p < 0.05$) declined at 30 °C but not at 22 °C. The AHR assessed 19 h postexp. as PC ₅₀ sGaw methacholine signif. ($p < 0.05$) higher at both temperatures.	Foster et al. (2000)
0.12-	235-470 ^a	IE, 10' ex/ 10' rest	45-55% RH		24 to 32 yrs old		
0.24 ^a		$\dot{V}_E = 36\text{-}39 \text{ L}/\text{min}$					

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Table AX6-7 (cont'd). Influence of Ethnic, Environmental, and Other Factors

Ozone Concentration		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$						
0.0	0	2 h		6 M, 9 F	Healthy NS	Corticosteroid pretreatment had no effects on post-O ₃ decline in PF, PMN response, and sputum cell count under both the placebo and treatment conditions. Methacholine PC ₂₀ FEV ₁ was equally decreased in both cond. 4 h after exposure. No changes in exhaled NO and CO.	Nightingale et al. (2000)
0.40	780	IE, 20' ex/ 10' rest \dot{V}_E = mild to mod.			avg age 31 yrs.		
0.0	0	4 h	21 °C	90 M	56 never smokers	Smokers are less responsive to O ₃ as assessed by spirometric and plethysmographic variables. Neither age, gender, nor methacholine responsiveness were predictive of O ₃ response.	Frampton et al. (1997a,c) ^b
0.22	431	IE 20' ex/10' rest \dot{V}_E = 40-46 L/min	37% RH		34 current smokers 18 to 40 yrs. old		
0.0	0	4 h	21 °C	10 M, 2 F	NS, O ₃ nonresp., avg age 25 yrs.;	Neither O ₃ responsiveness nor smoking has altered the magnitude and the time course of O ₃ -induced airway inflammation. Inflammation involved all types of cells accessible by BAL. The recovery profile of these cells over time was very similar for all groups showing highest values 18 h postexposure.	Torres et al. (1997) ^b Frampton et al. (1997a,c) ^b
0.22	431	IE, 20' ex/10' rest	37% RH	10 M, 3 F	NS, O ₃ resp., avg age 25 yrs;		
0.22	431	\dot{V}_E = 25 L/min/m ² BSA		11 M, 2 F	smokers avg age 28 yrs		

^aRamp exposure from 0.12 ppm to 0.24 ppm and back to 0.12 ppm at the end of exposure.

^bRelated studies, sharing of some subjects .

smokers. Of the two cytokines, IL-6 and IL-8, IL-6 was substantially and significantly ($p < 0.0002$) elevated immediately postexposure but returned back to control 18 h later in all groups; but only nonsmokers' effects were significantly higher ($p < 0.024$). IL-8 showed a similar pattern of response but the increase in all groups, though still significant ($p < 0.0001$), was not as high as for IL-6. Between group differences were not significant. This inflammatory response involved all types of cells present in BAL fluid and the recovery profile of these cells over time was very similar for all groups. In contrast to BAL, NL did not prove to be a reliable marker of airway inflammation. The lack of association between lung function changes (spirometry) and airway inflammation for all three groups confirms similar observations reported from other laboratories. This divergence of mechanisms is further enhanced by an observation that a substantially different spirometric response between O₃ responders and nonresponders, the airway inflammatory response of the two groups was very similar, both in terms of magnitude and pattern (Torres et al., 1997).

The influence of ambient temperature on pulmonary effects induced by O₃ exposure in humans has been studied infrequently under controlled laboratory conditions. Several experimental human studies published more than 20 years ago reported additive effects of heat and O₃ exposure (see U.S. Environmental Protection Agency, 1986, 1996). In the study of Foster et al. (2000) 9 young (mean age 27 years) healthy subjects (4F/5M) were exposed for 130 min (IE 10 min @ 36 to 39 l/min) to filtered air and to ramp profile O₃ at 22° and 30 °C, 45-55% RH. The order of exposures was randomized. The O₃ exposure started at 0.12 ppm, reached the peak of 0.24 ppm mid-way through and subsequently declined to 0.12 ppm at the end of exposure. Ozone inhalation decreased V_T and increased f_B as compared to baseline at both temperatures. At the end of exposure FEV₁ decreased significantly ($p < 0.5$) by ~8% at 22 °C and ~6.5% at 30 °C. One day (19 h) later, the decline of 2.3% from baseline was still significant ($p < 0.05$). FVC decrements were smaller and significant only at 22 °C immediately postexposure. SGaw significantly ($p < 0.05$) declined at 30 °C but not at 22 °C. A day later, sGaw was elevated above the baseline for all conditions. The nonspecific bronchial responsiveness (NSBR) to methacholine assessed as PC₅₀ sGaw was significantly ($p < 0.05$) higher one day following O₃ exposure at both temperatures but more so at 30 °C. Thus, these findings indicate that elevated temperature has partially attenuated spirometric response but enhanced airway reactivity. Numerous studies have reported an increase in NSBR immediately

after exposure to O₃. Whether the late NSBR reported in this study is a persistent residual effect of an earlier increase in airway responsiveness, or is a true one day lag effect cannot be determined from this study. Whatever the origin, however, a delayed increase in airway responsiveness raises a question of potentially increased susceptibility of an individual to respiratory impairment, particularly if the suggested mechanism of disrupted epithelial membrane holds true.

AX6.5.6 Oxidant-Antioxidant Balance

Oxidant-antioxidant balance has been considered as one of the determinants of O₃ responsiveness. Amateur cyclists who took antioxidant supplements (vitamins C, E, and β-carotene) for three months showed no decrements in spirometric lung function when cycling on days with high O₃ levels. In contrast, matched control group of cyclists not pretreated with vitamin supplements experienced an almost 2% decline in FVC and FEV₁ and >5% reduction in PEF during the same activity period. Adjustment of data for confounders such as PM₁₀ and NO₂ did not change the findings. Apparently, substantially elevated levels of plasma antioxidants may afford some protection against lung function impairment (Grievink et al., 1998, 1999).

Both laboratory animal and human studies have repeatedly demonstrated that antioxidant compounds present the first line of defense against the oxidative stress. Thus, upregulation of both enzymatic and nonenzymatic antioxidant systems is critical to airway epithelial protection from exposure to oxidants such as O₃ and NO₂ (*see Table AX6-7*). As an extension of an earlier study focused on pulmonary function changes (Frampton et al., 1997a), Avissar et al. (2000) hypothesized that concentration of glutathione peroxidase (GPx), one of the antioxidants in epithelial lining fluid (ELF), is related to O₃ and NO₂ responsiveness. They exposed healthy young nonsmokers (n = 25), O₃-responders, and nonresponders to filtered air and twice to 0.22 ppm O₃ for 4 h (IE, 20' ex /10' rest, @ \dot{V}_E 40 to 46 L/min). In the NO₂ part of the study, subjects were exposed to air and twice to NO₂ (0.6 and 1.5 ppm) for 3 h, with IE of 10 min of each 30 min @ \dot{V}_E of 40 L/min. Ozone exposure elicited a typical pulmonary function response with neutrophilic airway inflammation in both responders and nonresponders. The GPx activity was significantly reduced (p = 0.0001) and eGPx protein significantly depleted (p = 0.0001) in epithelial lining fluid (ELF) for at least 18 h postexposure. In contrast, both GPx and eGPx were slightly elevated in bronchoalveolar lavage fluid (BALF). However, neither of the two NO₂

exposures had a significant effect on pulmonary function, airway neutrophilia, epithelial permeability, GPx activity, or eGPx protein level in either ELF or BALF. The lack of a significant response to NO₂ has been attributed to the weak oxidative properties of this gas. No association has been observed between cell injury, assessed by ELF albumin, or pulmonary function and GPx activity for O₃ exposure. Thus, it is unclear what role antioxidants may have in modulation of O₃-induced lung function and inflammatory responses. The authors found a negative association between lower baseline eGPx protein concentration in ELF and post-O₃ neutrophilia to be an important predictor of O₃-induced inflammation; however, the causal relationship has not been established.

The effects of dietary antioxidant supplementation on O₃-induced pulmonary and inflammatory response of young healthy individuals has been investigated by Samet et al. (2001). Under controlled conditions, subjects received ascorbate restricted diet for three weeks. After the first week of prescribed diet, subjects were randomly assigned into two groups, and exposed to air (2 h, IE every 15 min at 20 L/min/m² BSA). Thereafter, one group received daily placebo pills and the other a daily supplement of ascorbate, α-tocopherol and a vegetable juice for the next two weeks. At the end of a two week period subjects were exposed to 0.4 ppm O₃ under otherwise similar conditions as in sham exposures. Serum concentration of antioxidants determined prior to O₃ exposure showed that subjects receiving supplements had substantially higher concentrations of ascorbate, tocopherol and carotenoid in blood than the control group. Plasma levels of glutathione and uric acid (cellular antioxidants) remained essentially the same. Ozone exposure reduced spirometric lung function in both groups; however, the average decrements in the supplementation group were smaller for FVC (p = 0.046) and FEV₁ (p = 0.055) when compared to the placebo group. There was no significant correlation between individual lung function changes and respective plasma levels of antioxidants. Individuals in both groups experienced typical post-O₃ subjective symptoms of equal severity. Similarly, the inflammatory response as assessed by BALF showed no significant differences between the two groups either in the recovery of cellular components or the types and concentrations of inflammatory cytokines. Because of the complexity of protocol, the study was not designed as a cross-over type. However, it is unlikely that the fixed air-O₃ sequence of exposures influenced the findings in any substantial way. Although the study did not elucidate the protective mechanisms, it has demonstrated the value of dietary antioxidants in attenuating lung function

effects of O₃. This observation may appear to contradict the findings of Avissar's and colleagues study (2000) discussed above; however, neither study found association between lung function changes and glutathione levels. The lack of such association suggests that activation of antioxidant protective mechanisms is seemingly independent of mechanisms eliciting lung-function changes and that dietary antioxidants afford protection via a different pathway than tissue-dependent antioxidant enzymes. Moreover, the findings of this study have provided additional evidence that symptomatic, functional, inflammatory, and antioxidant responses are operating through substantially independent mechanisms.

Further evidence that the levels and activity of antioxidant enzymes in ELF may not be predictive or indicative of O₃-induced lung function or inflammatory effects has been provided by a study of Blomberg et al. (1999). No association was found between the respiratory tract lining fluid redox potential level, an indicator of antioxidants balance, and either spirometric or inflammatory changes induced by a moderate exposure of young individuals to O₃ (0.2 ppm/2 h, intermittent exercise at 20 L/min/m² BSA). However, O₃ exposure caused a partial depletion of antioxidants (uric acid, GSH, EC-SOD) in nasal ELF and a compensatory increase in plasma uric acid, affording at least some local protection (Mudway et al. 1999). More recently, Mudway et al. (2001) investigated the effect of baseline antioxidant levels on response to a 2-h exposure to 0.2 ppm O₃ in 15 asthmatic and 15 healthy subjects. In the BALF of 15 healthy subjects, significant O₃-induced reductions in ascorbate and increases in glutathione disulphide and EC-SOD were observed, whereas, levels were unaffected by O₃ exposure in the asthmatics. In both groups, BALF levels of uric acid and α -Tocopherol were unaffected by O₃.

Trenga et al. (2001) studied the potential protective effects of dietary antioxidants (500 mg vitamin C and 400 IU of vitamin E) on bronchial responsiveness of young to middle-aged asthmatics. Recruited subjects were prescreened by exposure to 0.5 ppm SO₂ for 10 min while exercising on a treadmill and selected for study participation if they experienced a >8% decrease in FEV₁. Prior to the 1st exposure, subjects took either two supplements or two placebo pills at breakfast time for 4 weeks. They continued taking respective pills for another week when the 2nd exposure took place. The 45-min exposures to air and 0.12 ppm O₃ (15 min IE, $\dot{V}_E \approx 3 \times$ resting rate) via mouthpiece were randomized. Each exposure was followed by two 10-min challenges to 0.10 and 0.25 ppm SO₂ with exercise to determine bronchial hyperresponsiveness. Due to potential variability of baseline lung function between days, and the way the data have

been presented, it is difficult to interpret the results. All spirometric measures (FEV_1 , FVC, FEF_{25-75} , and PEF) were significantly decreased from baseline at subsequent time points following both the FA and O_3 exposures. Exposure to O_3 caused significant decrements in FEV_1 and PEF. The post FA and O_3 exposure decrements in lung function were not affected by the treatment regimen (placebo versus vitamin). Bronchial hyperresponsiveness to 0.1 ppm SO_2 was also unaffected by treatment regimen. Based on the prescreening SO_2 challenge, subjects were ranked by their bronchial responsiveness to SO_2 as “less-severe” (8 to 16% FEV_1 decrements) and “more-severe” (27 to 44% FEV_1 decrements). The authors concluded O_3 exposure increases bronchial responsiveness to SO_2 in asthmatics and that antioxidant supplementation has a protective effect against this responsiveness, especially in the “more-severe” responders.

AX6.5.7 Genetic Factors

It has been repeatedly postulated that genetic factors may play an important role in individual responsiveness to ozone. Recent studies (Bergamaschi et al., 2001; Corradi et al., 2002; Romieu et al., 2004) have indeed found that genetic polymorphisms of antioxidant enzymes, namely NAD(P)H:quinone oxidoreductase (NQO1) and glutathione-S-transferase M1 (GSTM1), may play an important role in attenuating oxidative stress of airway epithelium. Bergamaschi and colleagues (2001) studied young nonsmokers (15 F, 9 M; mean age 28.5 years) who cycled for two hours on a cycling circuit in a city park on days with the average ozone concentration ranging from 32 to 103 ppb. There was no control study group nor the intensity of bicycling has been reported. Since spirometry was done within 30 min post-ride, it is difficult to gauge how much of the statistically significant ($p = 0.026$) mean decrement of 160 ml in FEV_1 of 8/24 individuals with NQO1 wild type (NQO1wt) and GSTM1null (GSTM1null) genotypes was due to ozone. Individuals with other genotype combinations including GSTM1null had a mean post-ride decrement of FEV_1 of only 40 mL. The post-ride serum level of Clara cell protein (CC16), a biomarker of airway permeability, has been elevated in both subgroups. Only a “susceptible” subgroup carrying NQO1wt in combination with GSTM1null genotype, serum concentration of CC16 showed positive correlation with ambient concentration of ozone and negative correlation with FEV_1 changes. Despite some interesting observations, the study results should be interpreted cautiously.

A subsequent study from the same laboratory was conducted in a more controlled environment (Corradi et al., 2002). Healthy young (mean 30.1 yrs) individuals (12 M, 10 F) underwent a single exposure to 0.1 ppm O₃ for 2 h while intermittently exercising at a moderate load on a bicycle ergometer. The study design did not incorporate sham exposure, though the authors have stated that in a separate experiment the effects of exercise on markers of inflammation in blood and EBC were negligible. The eight subjects with NQO1wt and GSTM1null genotype, the “susceptible” group, indeed showed an increase in markers of inflammation (IL-6, IL-8, TBARS, LTB₄) and oxidative stress (8-isoprostane, H₂O₂) immediately post and 18 hrs postexposure. The fourteen subjects with other combination of genotypes showed small and inconsistent response in EBC and blood biomarkers, though PMN activity in both groups was significantly increased by exposure. The DNA adduct 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, was elevated immediately postexposure in both groups but only in the “susceptible” group the increase became significant. The spirometric endpoints (not reported) were not affected by the exposure at any time point, which contrasts the previous study. The incomplete study design calls for a careful interpretation of the findings.

It is of interest to note, that human nasal mucosa biopsies of GSTM1 deficient subjects showed higher antioxidant enzymes activity than biopsies of GSTM1 positive individuals when incubated for 24 h in 120 ppb O₃ environment (Otto-Knapp et al., 2003).

The influence of functional polymorphism of inflammatory and other genes on O₃ susceptibility was studied by Yang et al. (2005). In this study 54 nonsmoking subjects (11 healthy subjects, 15 mild asthmatics, 25 with rhinitis) were exposed to 250 ppb O₃ for 3 h (44 subjects), 200 ppb for 4 h (4 subjects), and 400 ppb for 2 h (3 subjects). During these exposures subjects intermittently exercised (~14 L/min/m² BSA). The pooled data of the tumor necrosis factor α (TNF-α), lymphotoxin-α (LTA), Toll-like receptor 4 (TLR4), superoxide dismutase (SOD2) and glutathione peroxidase (GPX1) genes appear to show only TNF-α as a promising genetic factors of susceptibility. However, as the authors stated “the functional significance of individual TNF-α polymorphisms remains controversial” (Yang et al., 2005).

More specific genotyping has shown that O₃ responsiveness and asthma risk may be related to the presence of variant Ser allele for NQO1. In a field study of susceptibility to ambient O₃ in Mexico City, 4- 17 yrs old asthmatic children (n = 218) were genotyped, including variant alleles

(David et al., 2003). The risk of asthma was related to the 1-h daily max ambient O₃ which ranged from 12 to 309 ppb. Relative to Pro/Pro genotype the presence of at least one NQO1 Ser allele variant lowered the risk of asthma in these children (RR = 0.8). In children with GSTM1null genotype combined with at least one NQO1 Ser allele variant the decreased risk of asthma became statistically significant (RR = 0.4). The presence of Ser allele which renders NQO1 less active, thus affecting the conjugation of quinones and formation of ROS subsequently reducing the oxidative stress, may plausibly explain the protective effect of this genotypic combination.

Another field study of asthmatic children (n = 158) exposed to ambient O₃ (12-309 ppb 1-h max during the 12 week study period) has found that in children with genetic deficiency of GSTM1 the decrements in FEF₂₅₋₇₅ were related to the previous day 1-h daily max O₃. The association was more pronounced in moderate to severe asthmatics. Children with GSTM1pos variant showed no significant decrement in lung function. Randomly administered antioxidant supplementation (vit. C 250 mg/day and vit. E 50 mg/day) attenuated post-ozone lung function response in GSTM1null children (Romieu et al., 2004).

These recent studies have shown that individual's innate susceptibility to ozone may be linked to genetic background of an individual. Although a number of potential ozone susceptibility genes have been identified, additional better designed and controlled studies are needed to ascertain the link between susceptibility and polymorphism.

AX6.6 REPEATED EXPOSURES TO OZONE

Repeated daily exposure to O₃ in the laboratory for 4 or 5 days leads to attenuated changes in pulmonary function responses and symptoms (Hackney et al., 1977a; U.S. Environmental Protection Agency, 1986, 1996). A summary of studies investigating FEV₁ responses to repeated daily exposure for up to 5 days is given in Table AX6-8. The FEV₁ responses to repeated O₃ exposure typically have shown an increased response on the second exposure day (Day 2) compared to the initial (Day 1) exposure response. This is readily apparent in repeated exposures to a range of concentrations from 0.4 to 0.5 ppm O₃ accompanied by moderate exercise (Folinsbee et al., 1980; Horvath et al., 1981; Linn et al., 1982), and at lower concentrations, 0.20 to 0.35 ppm, when accompanied by heavy exercise (Brookes et al., 1989;

Table AX6-8. Changes in Forced Expiratory Volume in One Second After Repeated Daily Exposure to Ozone^a

Ozone Concentration ^b		Exposure Duration and Activity ^c	Number and Gender of Subjects	Percent Change in FEV ₁ on Consecutive Exposure Days					References ^d
ppm	µg/m ³			First	Second	Third	Fourth	Fifth	
0.12	235	6.6 h, IE (40)	17 M	-12.79	-8.73	-2.54	-0.6	0.2	Folinsbee et al. (1994)
0.20	392	2 h, IE (30)	10 M	+1.4	+2.7	-1.6	—	—	Folinsbee et al. (1980)
0.20	392	2 h, IE (18 and 30)	8 M, 13 F	-3.0	-4.5	-1.1	—	—	Gliner et al. (1983)
0.20	392	2 h, IE (18 and 30)	9	-8.7	-10.1	-3.2	—	—	Gliner et al. (1983)
0.20	392	1 h, CE (60)	15 M	-5.02	-7.8	—	—	—	Brookes et al. (1989)
0.25	490	1 h, CE (63)	4 M, 2 F	-20.2	-34.8	—	—	—	Folinsbee and Horvath (1986)
			5 M, 2 F	-18.8	—	-22.3	—	—	
0.35	686	2 h, IE (30)	10 M	-5.3	-5.0	-2.2	—	—	Folinsbee et al. (1980)
0.35	686	1 h, CE (60)	8 M	-31.0	-41.0	-33.0	-25.0	—	Foxcroft and Adams (1986)
0.35	686	1 h, CE (60)	10 M	-16.1	-30.4	—	—	—	Schonfeld et al. (1989)
			10 M	-14.4	—	-20.6	—	—	
0.35	686	1 h, CE (60)	15 M	-15.9	-24.6	—	—	—	Brookes et al. (1989)
0.40	784	3 h, IE (4-5 × resting)	13 M ^f	-9.2	-10.8	-5.3	-0.7	-1.0	Kulle et al. (1982)
0.40	784	3 h, IE (4-5 × resting)	11 F ^f	-8.8	-12.9	-4.1	-3.0	-1.6	Kulle et al. (1982)
0.4	784	2 h, IE (65)	8 M	-18.0	-29.9	-21.1	-7.0	-4.4	Folinsbee et al. (1998)
0.4	784	3 h, IE (32)	8 M, 2 F ^h	-34.7	-31.1	-18.5	-12.0	-6.2	Gong et al. (1997b)
0.42	823	2 h, IE (30)	24 M	-21.1	-26.4	-18.0	-6.3	-2.3	Horvath et al. (1981)
0.45	882	2 h, IE (27)	1 M, 5 F	-13.3	—	-22.8	—	—	Bedi et al. (1985)
0.45	882	2 h, IE (27)	10 M, 6 F	-5.8	-5.6	-1.9	—	—	Bedi et al. (1989)
0.47	921	2 h, IE (3 × resting)	8 M, 2 F ^g	-11.4	-22.9	-11.9	-4.3	—	Linn et al. (1982)
0.5	980	2 h, IE (30)	8 M	-8.7	-16.5	-3.5	—	—	Folinsbee et al. (1980)
0.5	980	2.5 h, IE (2 × resting)	6	-2.7	-4.9	-2.4	-0.7	—	Hackney et al. (1977a)

^aSee Appendix A for abbreviations and acronyms.

^bListed from lowest to highest O₃ concentration.

^cExposure duration and intensity of IE or CE were variable; \dot{V}_E (number in parentheses) given in liters per minute or as a multiple of resting ventilation.

^dFor a more complete discussion of these studies, see Table AX6-9 and U.S. Environmental Protection Agency (1986).

^eSubjects were especially sensitive on prior exposure to 0.42 ppm O₃ as evidenced by a decrease in FEV₁ of more than 20%. These nine subjects are a subset of the total group of 21 individuals used in this study.

^fBronchial reactivity to a methacholine challenge also was studied.

^gSeven subjects completed entire experiment.

^hSubjects had mild asthma.

Folinsbee and Horvath, 1986; Foxcroft and Adams, 1986; Schonfeld et al., 1989). Mechanisms for enhanced pulmonary function responses on Day 2 have not been established, although persistence of acute O₃-induced damage for greater than 24 h may be important (Folinsbee et al., 1993). An enhanced Day 2 FEV₁ response was less obvious or absent in exposures at lower concentrations or those that caused relatively small group mean O₃-induced decrements. For example, Bedi et al. (1988) found no enhancement of the relatively small pulmonary function responses in older subjects (median age, 65 years) exposed repeatedly to O₃. Three reports (Bedi et al., 1985; Folinsbee and Horvath, 1986; Schonfeld et al., 1989) demonstrated that enhanced pulmonary function responsiveness was present within 12 h, lasted for at least 24 h and possibly 48 h, but was absent after 72 h.

After 3 to 5 days of consecutive daily exposures to O₃, FEV₁ responses are markedly diminished or absent. One study (Horvath et al., 1981) suggested that the rapidity of this decline in FEV₁ response was related to the magnitude of the subjects' initial responses to O₃ or their "sensitivity." A summary of studies examining the effects of repeated exposures to O₃ on FEV₁ and other pulmonary function, symptoms, and airway inflammation is given in Table AX6-9. Studies examining persistence of the attenuation of pulmonary function responses following 4 days of repeated exposure (Horvath et al., 1981; Kulle et al., 1982; Linn et al., 1982) indicate that attenuation is relatively short-lived, being partially reversed within 3 to 7 days and typically abolished within 1 to 2 weeks. Repeated exposures separated by 1 week (for up to 6 weeks) apparently do not induce attenuation of the pulmonary function response (Linn et al., 1982). Gong et al. (1997b) studied the effects of repeated exposure to 0.4 ppm O₃ in a group of mild asthmatics and observed a similar pattern of responses as those seen previously in healthy subjects. The attenuation of pulmonary responses reached after 5 days of consecutive O₃ exposure was partially lost at 4 and 7 days postexposure.

In addition to the significant attenuation or absence of pulmonary function responses after several consecutive daily O₃ exposures, symptoms of cough and chest discomfort usually associated with O₃ exposure generally are substantially reduced or absent (Folinsbee et al., 1980, 1994; Foxcroft and Adams, 1986; Linn et al., 1982). Airway responsiveness to methacholine is increased with an initial O₃ exposure (Holtzman et al., 1979; Folinsbee et al., 1988), may be further increased with subsequent exposures (Folinsbee et al., 1994), and shows a tendency for the increased response to diminish with repeated exposure (Dimeo et al., 1981; Kulle et al.,

Table AX6-9. Pulmonary Function Effects with Repeated Exposures to Ozone^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.25	490	2 h IE ₂ (30 min rest, 30 min exercise), $\dot{V}_E = 39$ L/min	21.4 °C 43.9% RH 4 days consecutive FA exposure; 4 days consecutive O ₃ exposure	5 M, 3 F	Healthy, NS	FVC and FEV ₁ decrements were significantly attenuated on Day 4 of O ₃ exposure compared to day 1 of O ₃ exposure. Significant small airway function depression accompanied by significant neutrophilia in BALF one day following the end of O ₃ exposure.	Frank et al. (2001)
0.2	392	4 h IE (4 × 30 min exercise), $\dot{V}_E = 14.8$ L/min/m ² BSA	1 day FA, 1 day, O ₃ ; 4 days consecutive exposure to O ₃	15 M, 8 F	Healthy, NS 21 to 35 years old	FEV ₁ decrement and symptoms significantly reduced on Day 4 of O ₃ exposure compared to Day 1 of O ₃ exposure. Airway inflammation of mucosa persisted on Day 4 although some inflammatory markers in BALF attenuated significantly.	Jörres et al. (2000)
0.2	392	4 h IE (4 × 30 min exercise), $\dot{V}_E = 25$ L/min/m ² BSA	20 °C 50% RH (1 day, O ₃ ; 4 days consecutive exposure to O ₃)	9 M, 6 F	Healthy, NS 23 to 37 years old	Significant decrease in FVC, FEV ₁ , SRaw, and symptoms on Day 4 of O ₃ exposure compared to a single day of O ₃ exposure. Number of PMNs, fibronectin, and IL6 in BALF were significantly decreased on Day 4 compared to a single day of O ₃ exposure.	Christian et al. (1998)
0.4	784	3h/day for 5 days IE (15 min rest, 15 min exercise) $\dot{V}_E = 32$ L/min	31 °C 35% RH 5 consecutive days plus follow up @ 4 or 7 days	8 M, 2 F	Mild asthma adult	FEV ₁ decreased 35% on day 1 and only 6% on day 5. Bronchial reactivity increased after day 1 and remained elevated. Adaptation of asthmatics is similar to healthy subjects but may be slower and less complete.	Gong et al. (1997b)
0.12	235	6.6 h 50 min exercise/10 min rest, 30 min lunch $\dot{V}_E = 38.8$ L/min	18 °C 40% RH five consecutive daily exposures	17 M	Healthy NS	FEV ₁ responses were maximal on first day of exposure (-13%), less on second day (-9%), absent thereafter. Symptoms only the first 2 days. Methacholine airway responsiveness was at least doubled on all exposure days, but was highest on the second day of O ₃ . Airway responsiveness was still higher than air control after 5 days of O ₃ exposure. Trend to lessened response, but it was not achieved after 5 days.	Folinsbee et al. (1994)

Table AX6-9 (cont'd). Pulmonary Function Effects with Repeated Exposures to Ozone^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.4	784	2 h IE (15 min rest, 15 min exercise) V _E ≈ 60 L/min	5 days consecutive O ₃ exposure	16 M	Healthy NS	O ₃ -exposure FEV ₁ decrement was greater on day 2, 29.9%, than day 1, 18.0%, then decreased on day 3, 21.1%, day 4, 7% and day 5, 4.4%	Folinsbee et al. (1998) Devlin et al. (1997)
0.45	882	2 h IE (3 × 20 min exercise) V _E = 27 L/min	23.3 °C 63% RH Exposed for 3 consecutive days, not exposed for 2 days, then exposed to 0.45 ppm again for 1 day	10 M, 6 F	Healthy NS 60 to 89 years old median 65 years old; mean FVC = 3.99 L; mean FEV ₁ = 3.01 L; FEV ₁ /FVC range = 61 to 85%	Overall increase in symptoms, but no single symptom increased significantly. FVC decreased 111 mL and 104 mL on Days 1 and 2, respectively. FEV ₁ fell by 171 and 164 mL, and FEV ₃ fell by 185 and 172 mL. No significant changes on Days 3 and 4 or with FA. FEV ₁ changes were -5.8, -5.6, -1.9, and -1.7% on the four O ₃ days.	Bedi et al. (1989)
0.20/0.20 0.35/0.20 0.35/0.35	392/392 686/392 686/686	1 h CE at 60 L/min	21 to 25 °C 40 to 60% RH (three 2-day sets of exposures)	15 M	Healthy aerobically trained NS, FVC = 4.24 to 6.98 L	Consecutive days of exposure to 0.20 ppm produced similar FEV ₁ responses on each day (-5.02, -7.80); 0.35/0.20 ppm pair caused increased response to 0.20 ppm on second day (-8.74); 0.35/0.35 ppm caused much increased response on Day 2 (-15.9, -24.6). Symptoms were worse on the second exposure to 0.35 ppm, but not with second exposure to 0.20 ppm.	Brookes et al. (1989)
0.35	686	60 min CE V _E = 60 L/min	21 to 25 °C 40 to 60% RH (two exposures for each subject separated by 24, 48, 72, or 120 h)	40 M (4 groups of 10)	NS; nonallergic, non-Los Angeles residents for >6 mo; =25 years old	No differences between responses to exposures separated by 72 or 120 h. Enhanced FEV ₁ response at 24 h (-16.1% vs. -30.4%). Possible enhanced response at 48 h (-14.4% vs. -20.6%). Similar trends observed for breathing pattern and SRaw.	Schonfeld et al. (1989)
0.45	882	2 h IE (3 × 20 min exercise) V _E = 26 L/min	23.3 °C 62.5% RH (three exposures with a minimum 1-week interval)	8 M, 8 F	Healthy NS, 61 years old for M and 65 years old for F (FVC = 4.97 L for M and 3.11 L for F)	Spirometric changes were not reproducible from time to time after O ₃ exposure (R < 0.50). Repeat exposures to air yielded consistent responses.	Bedi et al. (1988)

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Table AX6-9 (cont'd). Pulmonary Function Effects with Repeated Exposures to Ozone^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.18	353	2 h IE (heavy) $\dot{V}_E \approx 60$ to 70 L/min (35 L/min/m ² BSA)	31 °C 35% RH (screen exposures in spring 1986; second exposures in summer/fall 1986 and winter 1987 and spring 1987 for responders and nonresponders only)	59 adult Los Angeles residents 12 responsive 13 nonresponsive	Responders: 19 to 40 years old 6 atopic, 2 asthmatic, 4 normal Nonresponders: 18 to 39 years old, 13 normal	Responders had $\Delta FEV_1 = -12.4\%$ after initial screening; nonresponders had no change. Responders had nonsignificant response in late summer or early winter, but were responsive again in early spring (spring 1986, -385 mL; Autumn 1986, -17 mL; winter 1987, $+16$ mL; spring 1987, -347 mL). Nonresponders did not change with season. Suggests that responders responses may vary with ambient exposure, but nonresponders generally remain nonresponsive.	Linn et al. (1988) (also see Hackney et al., 1989)
0.45 (+0.30 PAN)	882	2 h IE (20 min rest, 20 min exercise) $\dot{V}_E = 27$ L/min	22 °C 60% RH 5 days consecutive exposure to PAN + O ₃	3 M, 5 F	Healthy NS, Mean age = 24 years	FEV ₁ decreased $\approx 19\%$ with O ₃ alone, $\approx 15\%$ on Day 1 of O ₃ + PAN, $\approx 5\%$ on Day 5 of O ₃ + PAN, $\approx 7\%$ 3 days after 5 days of O ₃ + PAN, $\approx 15\%$ after 5 days of O ₃ + PAN. Similar to other repeated O ₃ exposure studies, O ₃ responses peaked after 2 days, were depressed 3 days later, and responses returned 7 days later. PAN probably had no effect on repeated to O ₃ exposure responses.	Drechsler-Parks et al. (1987b) (also see Table AX6-14)
0.35	686	≈ 1 h CE (see paper for details)	22 to 25 °C 35 to 50% RH (1 day FA; 1 day O ₃ ; 4 days consecutive exposure to O ₃)	8 M	Aerobically trained healthy NS (some were known O ₃ sensitive), 22.4 \pm 2.2 years old	Largest FEV ₁ decrease on second of 4 days O ₃ exposure (-40% mean decrease). Trend for attenuation of pulmonary function response not complete in 4 days. $\dot{V}O_{2max}$ decreased with single acute O ₃ exposure (-6%) but was not significant after 4 days of O ₃ exposure (-4%). Performance time was less after acute O ₃ (211 s) exposure than after FA (253 s).	Foxcroft and Adams (1986)

^aSee Appendix A for abbreviations and acronyms.

^bListed from lowest to highest O₃ concentration.

1982). The initially enhanced and then lessened response may be related to changes that occur during the repair of pulmonary epithelia damaged as a consequence of O₃ exposure.

Inflammatory responses (Koren et al., 1989a), epithelial damage, and changes in permeability (Kehrl et al., 1987) might explain a portion of these responses. By blocking pulmonary function responses and symptoms with indomethacin pretreatment, Schonfeld et al. (1989) demonstrated that in the absence of an initial response, pulmonary function and symptoms effects were not enhanced on Day 2 by repeated exposure to 0.35 ppm O₃. These results suggest that airway inflammation and the release of cyclooxygenase products of arachidonic acid play a role in the enhanced pulmonary function responses and symptoms observed upon reexposure to O₃ within 48 h.

Response to laboratory O₃ exposure as a function of the season of the year in the South Coast Air Basin of Los Angeles, CA, has been examined in several studies (Avol et al., 1988; Hackney et al., 1989; Linn et al., 1988). Their primary purpose was to determine whether O₃ responsive subjects would remain responsive after regular ambient exposure during the “smog season”. The subjects were exposed to 0.18 ppm O₃ for 2 h with heavy IE on four occasions, spring, fall, winter, and the following spring. The marked difference in FEV₁ response between responsive and nonresponsive subjects seen initially (-12.4% versus +1%) no longer was present after the summer smog season (fall test) or 3 to 5 months later (winter test). However, when the subjects were exposed to O₃ during the following spring, the responsive subjects again had significantly larger changes in FEV₁, suggesting a seasonal variation in response.

Brookes et al. (1989) and Gliner et al. (1983) tested whether initial exposure to one O₃ concentration could alter response to subsequent exposure to a different O₃ concentration. Gliner et al. (1983) showed that FEV₁ response to 0.40 ppm O₃ was not influenced by previously being exposed to 0.20 ppm O₃ for 2 h on 3 consecutive days. Brookes et al. (1989) found enhanced FEV₁ and symptoms upon exposure to 0.20 ppm after previous exposure to 0.35 ppm O₃. These observations suggest that, although preexposure to low concentrations of O₃ may not influence responses to higher concentrations, preexposure to a high concentration of O₃ can significantly increase responses to a lower concentration on the following day.

Foxcroft and Adams (1986) demonstrated that decrements in exercise performance seen after 1 h of exposure to 0.35 ppm O₃ with heavy CE were significantly less after 4 consecutive days exposure than they were after a single acute exposure. Further, exercise performance,

$\dot{V}O_{2\max}$, $\dot{V}_{E\max}$ and HR_{\max} were not significantly different after 4 days of O_3 exposure compared to those observed in a FA exposure. Despite the change in exercise performance, Foxcroft and Adams (1986) did not observe a significant attenuation of FEV_1 response, although symptoms were significantly reduced. However, these investigators selected known O_3 -sensitive subjects whose FEV_1 decrements exceeded 30% on the first 3 days of exposure. The large magnitude of these responses, the trend for the responses to decrease on the third and fourth day, the decreased symptoms, and the observations by Horvath et al. (1981) that O_3 -sensitive subjects adapt slowly, suggest that attenuation of response would have occurred if the exposure series had been continued for another 1 or 2 days. These observations support the contention advanced by Horvath et al. (1981) that the progression of attenuation of response is a function of initial “ O_3 sensitivity.”

Drechsler-Parks et al. (1987b) examined the response to repeated exposures to 0.45 ppm O_3 plus 0.30 ppm peroxyacetyl nitrate (PAN) in 8 healthy subjects and found similar FEV_1 responses to exposures to O_3 (-19%) and to O_3 plus PAN (-15%). Thus, PAN did not increase responses to O_3 . Further, repeated exposure to the PAN plus O_3 mixture resulted in similar changes to those seen with repeated O_3 exposure alone. The FEV_1 responses fell to less than -5% after the fifth day, with the attenuation of response persisting 3 days after the repeated exposures, but being absent after 7 days. These observations suggest that PAN does not influence the attenuation of response to repeated O_3 exposure. If the PAN responses are considered negligible, this study confirms the observation that the attenuation of O_3 responses with chamber exposures lasts no longer than 1 week. [*More discussion on the interaction of O_3 with other pollutants can be found in Section AX6.11.*]

Folinsbee et al. (1993) exposed a group of 16 healthy males to 0.4 ppm O_3 for 2 h/day on 5 consecutive days. Subjects performed heavy IE ($\dot{V}_E = 60$ to 70 L/min). Decrement in FEV_1 averaged 18.0, 29.9, 21.1, 7.0, and 4.4% on the 5 exposure days. However, baseline preexposure FEV_1 decreased from the first day's preexposure measurement and was depressed by an average of about 5% by the third day. This study illustrates that, with high-concentration and heavy-exercise exposures, pulmonary function responses may not be completely recovered within 24 h. During this study, BALF also was obtained immediately after the Day 5 exposure, with results reported by Devlin et al. (1997). These authors found that some inflammation and cellular responses associated with acute O_3 exposure were also attenuated after 5 consecutive days of O_3

exposure (compared to historical data for responses after a single-day exposure), although indicators of epithelial cell damage—not seen immediately after acute exposure—were present in BALF after the fifth day of exposure. When reexposed again 2 weeks later, changes in BALF indicated that epithelial cells appeared fully repaired (Devlin et al., 1997).

Frank et al. (2001) exposed 8 healthy young adults to 0.25 ppm O₃ for 2 h with moderate IE (exercise $\dot{V}_E = 40$ L/min) on 4 consecutive days. In addition to standard pulmonary function measures, isovolumetric FEF₂₅₋₇₅, $\dot{V}_{\max 50}$ and $\dot{V}_{\max 75}$ were grouped into a single value representing small airway function (SAW_{grp}). Exercise ventilatory pattern was also monitored each day, while peripheral airway resistance was measured by bronchoscopy followed by lavage on Day 5. The authors observed two patterns of functional response in their subjects—attenuation and persistent. Values of FVC and FEV₁ showed significant attenuation by Day 4 compared to Day 1 values. However, SAW_{grp} and rapid shallow breathing during exercise persisted on Day 4 compared to Day 1, and were accompanied by significant neutrophilia in BALF 1 day following the end of O₃ exposure. Frank et al. (2001) suggested that both types of functional response (i.e., attenuation and persistence) are linked causally to inflammation. They contend that the attenuation component is attributable at least in part to a reduction in local tissue dose during repetitive exposure that is likely to result from the biochemical, mechanical, and morphological changes set in motion by inflammation. They speculated that the persistent component represents the inefficiencies incurred through inflammation. Whether the persistent small airway dysfunction is a forerunner of more permanent change in the event that oxidant stress is extended over lengthy periods of time is unknown.

Early repeated multihour (6 to 8 h) exposures focused on exposures to low concentrations of O₃ between 0.08 and 0.12 ppm (Folinsbee et al., 1994; Horvath et al., 1991; Linn et al., 1994). Horvath et al. (1991) exposed subjects for 2 consecutive days to 0.08 ppm using the 6.6-h prolonged exposure protocol (see Table AX6-2). They observed small pre- to postexposure changes in FEV₁ (-2.5%) on the first day, but no change on the second day. Linn et al. (1994) observed a 1.7% decrease in FEV₁ in healthy subjects after 6.6 h exposure to 0.12 ppm O₃. A second consecutive day exposure to O₃ yielded even smaller (<1%) responses. In a group of asthmatics exposed under similar conditions (Linn et al., 1994), the FEV₁ response on the first day was -8.6% which was reduced to -6.7% on day 2, both significantly greater than those observed for the nonasthmatics group. The observations of Horvath et al. (1991) and Linn et al.

(1994) elicited a somewhat different pattern of response (no enhancement of response after the first exposure) than that seen at higher concentrations in 2 h exposures with heavy exercise (Tables AX6-8 and AX6-9). However, the subjects studied by Horvath et al. (1991) were exposed only to 0.08 ppm O₃ and were somewhat older (30 to 43 yrs) than the subjects studied by Folinsbee et al. (1994), mean age of 25 yrs, while the nonasthmatic subjects studied by Linn et al. (1994) were also older (mean = 32 yrs), had lower exercise \dot{V}_E (-20%) and were residents of Los Angeles who often encountered ambient levels of O₃ at or above 0.12 ppm.

Folinsbee et al. (1994) exposed 17 subjects to 0.12 ppm O₃ for 6.6 h, with 50 min of moderately heavy exercise ($\dot{V}_E = 39$ L/min) each hour, on 5 consecutive days. Compared with FA, the percentage changes in FEV₁ over the five days were -12.8%, -8.7%, -2.5%, -0.06%, and +0.18%. A parallel attenuation of symptoms was observed, but the effect of O₃ in enhancing airway responsiveness (measured by increase in SRaw upon methacholine challenge) over 5 days was not attenuated (3.67, 4.55, 3.99, 3.24, and 3.74, compared to 2.22 in FA control). Nasal lavage revealed no increases in neutrophils except on the first O₃ exposure day.

Christian et al. (1998) exposed 15 adults (6 females and 9 males; mean age = 29.1 yrs) to 4 consecutive days at 0.20 ppm O₃ for 4 h, with 30 min of IE (exercise $\dot{V}_E = 25$ L/min/m²) each hour. Measures of FEV₁, FVC, and symptoms were all significantly reduced on Day 1, further decreased on Day 2, and then attenuated to near FA control values on Day 4. The pattern of SRaw response was similar, being greatest on Day 2 and no different from FA control on Day 4. BAL was done on Day 5 and showed that neutrophil recruitment to the respiratory tract was attenuated with repeated short-term exposures, compared to Day 1 control O₃ exposure, while airway epithelial injury appeared to continue as reflected by no attenuation of IL-6, IL-8, total protein, and LDH. The authors concluded that such injury might lead to airway remodeling, which has been observed in several animal studies (Brummer et al., 1977; Schwartz et al., 1976; Tepper et al., 1989; Van Bree et al., 1989). In a similar study to that of Christian et al. (1998), Jörres et al. (2000) exposed 23 adults (8 females and 15 males; mean age = 27.9 yrs) on 4 consecutive days to 0.20 ppm O₃ for 4 h, with 30 min of IE (exercise $\dot{V}_E = 26$ L/min) each hour. The authors observed that FEV₁ was significantly reduced and symptoms were significantly increased on Day 1. On Day 2, FEV₁ was further decreased, while symptoms remained unchanged. By Day 4, both FEV₁ and symptoms were attenuated to near FA, control values. Twenty hours after the Day 4 exposure, BAL and bronchial mucosal biopsies were

performed. These authors found via bronchial mucosal biopsies that inflammation of the bronchial mucosa persisted after repeated O₃ exposure, despite attenuation of some inflammatory markers in BALF and attenuation of lung function responses and symptoms. Further, Jörres et al. (2000) observed persistent although small decrease in baseline FEV₁ measured before exposure, thereby suggesting that there are different time scales of the functional responses to O₃, which may reflect different mechanisms. The levels of protein remaining elevated after repeated exposures confirms the findings of others (Christian et al., 1998; Devlin et al., 1997), and suggests that there is ongoing cellular damage irrespective of the attenuation of cellular inflammatory responses with the airways. [*Further discussion on the inflammatory responses to O₃ can be found in Section AX6.9.*]

Based on studies cited here and in the previous O₃ criteria documents (U.S. Environmental Protection Agency, 1986, 1996), several conclusions can be drawn about repeated 1- to 2-h O₃ exposures. Repeated exposures to O₃ can cause an enhanced (i.e., greater) lung function response on the second day of exposure. This enhancement appears to be dependent on the interval between the exposures (24 h is associated with the greatest increase) and is absent with intervals >3 days. As shown in Figure AX6-8, an enhanced response also appears to depend on O₃ concentration and to some extent on the magnitude of the initial response. Small responses to the first O₃ exposure are less likely to result in an enhanced response on the second day of O₃ exposure. Repeated daily exposure also results in attenuation of pulmonary function responses, typically after 3 to 5 days of exposure. This attenuated response persists for less than 1 week or as long as 2 weeks. In temporal conjunction with the pulmonary function changes, symptoms induced by O₃, such as cough and chest discomfort, also are attenuated with repeated exposure. Ozone-induced changes in airway responsiveness attenuate more slowly than pulmonary function responses and symptoms. Attenuation of the changes in airway responsiveness appear to persist longer than changes in pulmonary function, although this has been studied only on a limited basis. In longer-duration (6.6 h), lower-concentration studies that do not cause an enhanced second-day response, the attenuation of response to O₃ appears to proceed more rapidly. Inflammatory markers from BALF on the day following both 2 h (Devlin et al., 1997) and 4 h (Christian et al., 1998; Jörres et al., 2000) repeated O₃ exposure for 4 days indicate that there is ongoing cellular damage irrespective of the attenuation of some cellular inflammatory responses of the airways, lung function responses and symptoms.

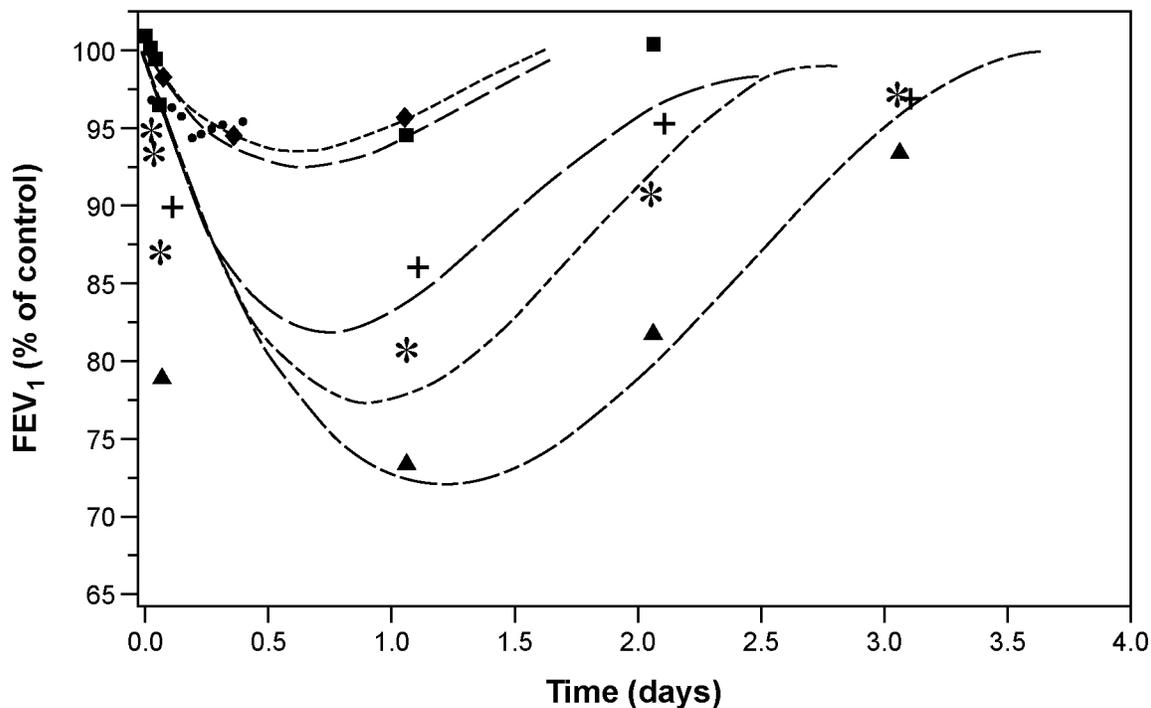


Figure AX6-8. Regression curves were fitted to day-by-day postexposure FEV₁ values obtained after repeated daily acute exposures to O₃ for 2 to 3 h with intermittent exercise at a V_E of 24 to 43 L/min (adaptation studies). Symbols represent the results from individual studies conducted at 0.2 ppm for 2 h (◆), 0.35 ppm for 2 h (■), 0.4 ppm for 2 h (⊕), 0.5 ppm for 2 h (*), and 0.54 ppm for 3 h (▲). Also shown for comparison are the FEV₁ values obtained after exposure to 0.12 ppm O₃ for 10 h (●).

Source: Modified from Hazucha (1993).

AX6.7 EFFECTS ON EXERCISE PERFORMANCE

AX6.7.1 Introduction

In an early epidemiologic study examining race performances in Los Angeles area high school cross-country runners, Wayne et al. (1967) observed that endurance exercise performance was depressed by inhalation of ambient oxidant air pollutants. The authors concluded that the detrimental effects of oxidant air pollutants on race performance might have been related to the associated discomfort in breathing, thus limiting the runners' motivation to perform at high levels, although physiologic effects limiting O₂ availability could not be ruled out.

Subsequently, the effects of acute O₃ inhalation on endurance exercise performance have been examined in numerous controlled laboratory studies. These studies were discussed in the previous O₃ criteria document (U.S. Environmental Protection Agency, 1996) in two categories: (1) those that examined the effects of acute O₃ inhalation on maximal oxygen uptake ($\dot{V}O_{2\max}$) and (2) those that examined the effects of acute O₃ inhalation on the ability to complete strenuous continuous exercise protocols of up to 1 h in duration. In this section, major observations in these studies are briefly reviewed with emphasis on reexamining the primary mechanisms causing decrements in $\dot{V}O_{2\max}$ and endurance exercise performance consequent to O₃ inhalation. A summary of major studies of O₃ inhalation effects on endurance exercise performance, together with observed pulmonary function and symptoms of breathing discomfort responses, is given in Table AX6-10.

AX6.7.2 Effect on Maximal Oxygen Uptake

Three early studies (Folinsbee et al., 1977; Horvath et al., 1979; Savin and Adams, 1979) examining the effects of acute O₃ exposures on $\dot{V}O_{2\max}$ were reviewed in an earlier O₃ criteria document (U.S. Environmental Protection Agency, 1986). Briefly, Folinsbee et al. (1977) observed that $\dot{V}O_{2\max}$ was significantly decreased (10.5%) following a 2-h exposure to 0.75 ppm O₃ with light (50 Watts) IE. Reduction in $\dot{V}O_{2\max}$ was accompanied by a decrease in maximal ventilation, maximal heart rate, and a large decrease in maximal tidal volume. In addition, the 2-h IE O₃ exposure resulted in a 22.3% decrease in FEV₁ and significant symptoms of cough and chest discomfort. In contrast, Horvath et al. (1979) did not observe a change in $\dot{V}O_{2\max}$ or other maximal cardiopulmonary endpoints in subjects exposed for 2 h at rest to either 0.50 or 0.75 ppm, although FVC was significantly decreased 10% following the latter exposure. Without preliminary exposure to O₃, Savin and Adams (1979) examined the effects of a 30-min exposure to 0.15 and 0.30 ppm O₃ while performing a progressively incremented exercise test to volitional fatigue (mean = 31.5 min in FA). No significant effect on maximal work time or $\dot{V}O_{2\max}$ was observed compared to that observed upon FA exposure. Further, no significant effect on pulmonary function, maximal heart rate, and maximal tidal volume was observed, although maximal \dot{V}_E was significantly reduced 7% in the 0.30 ppm O₃ exposure. Results of these early studies suggest that $\dot{V}O_{2\max}$ is reduced if the incremented maximal exercise

Table AX6-10. Ozone Effects on Exercise Performance^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.06-0.07 0.12-0.13	120-140 245-260	CE ($\dot{V}_E = 30$ to 120 L/min) 16 to 28 min progressive maximum exercise protocol	23 to 24.5 °C 50 to 53% RH	12 M, 12 F	Athletic	Reduced maximum performance time and increased symptoms of breathing discomfort during O ₃ exposure.	Linder et al. (1988)
0.18	353	1 h CE or competitive simulation at mean $\dot{V}_E = 94$ L/min	NA	# not given; all males	Well-trained distance runners	Maximal treadmill run time reduced from 71.7 min in FA to 66.2 min during O ₃ exposure with no decrease in arterial O ₂ saturation.	Folinsbee et al. (1986)
0.35	686	50 min CE $\dot{V}_E = 60$ L/min	22 to 25 °C 35 to 50% RH	8 M	Trained nonathletes	V_T decreased, f_B increased with 50-min O ₃ exposures; decrease in FVC, FEV ₁ , FEF ₂₅₋₇₅ , performance time, VO _{2max} , \dot{V}_{Emax} , and HR _{max} from FA to 0.35-ppm O ₃ exposure.	Foxcroft and Adams (1986)
0.12 0.20	235 392	1 h CE $\dot{V}_E = 89$ L/min	31 °C	15 M, 2 F	Highly trained competitive cyclists	Decrease in \dot{V}_{Emax} , $\dot{V}O_{2max}$, V_{Tmax} , workload, ride time, FVC, and FEV ₁ with 0.20 ppm O ₃ exposure, but not significant with 0.12-ppm O ₃ exposure, as compared to FA exposure.	Gong et al. (1986)
0.12 0.18 0.24	235 353 470	1 h competitive simulation exposures at mean $\dot{V}_E = 87$ L/min	23 to 26 °C 45 to 60% RH	10 M	Highly trained competitive cyclists	Decrease in exercise time of 7.7 min and 10.1 min for subjects unable to complete the competitive simulation at 0.18 and 0.24 ppm O ₃ , respectively; decrease in FVC and FEV ₁ for 0.18- and 0.24-ppm O ₃ exposure compared with FA exposure.	Schelegle and Adams (1986)
0.21	412	1 h CE at 75% $\dot{V}O_{2max}$	19 to 21 °C 60 to 70% RH	6 M, 1 F	Well-trained cyclists	Decrease in FVC, FEV ₁ , FEF ₂₅₋₇₅ , and MVV with 0.21 ppm O ₃ compared with FA exposure.	Folinsbee et al. (1984)
0.20 0.35	392 686	1 h CE or competitive simulation at mean $\dot{V}_E = 77.5$ L/min	23 to 26 °C 45 to 60% RH	10 M	Well-trained distance runners	V_T decreased and f_B increased with continuous 50-min O ₃ exposures; decrease in FVC, FEV ₁ , and FEF ₂₅₋₇₅ from FA to 0.20 ppm and FA to 0.35-ppm O ₃ exposure in all conditions; three subjects unable to complete continuous and competitive protocols at 0.35 ppm O ₃ .	Adams and Schelegle (1983)
0.25 0.50 0.75	490 980 1,470	2 h rest	NA	8 M, 5 F		FVC decreased with 0.50- and 0.75-ppm O ₃ exposure compared with FA; 4% nonsignificant decrease in mean VO _{2max} following 0.75 ppm O ₃ compared with FA exposure.	Horvath et al. (1979)
0.15 0.30	294588	~30 min, progressively incremented exercise to voluntary exhaustion	23 °C 50% RH	9 M	Healthy, NS 21 to 44 years old	Exposure to 0.15 and 0.30 ppm O ₃ did not decrease maximal exercise performance or VO _{2max} compared to FA. No significant pulmonary function or symptom responses were observed, although a trend (P < .10) was evident.	Savin and Adams (1979)
0.75	1,470	2 h IE (4 × 15 min light [50 W] bicycle ergometry)	NA	13 M	4 light S, 9 NS	Decrease in FVC, FEV ₁ , ERV, IC, and FEF _{50%} after 1-h 0.75-ppm O ₃ exposure; decrease in VO _{2max} , V_{Tmax} , \dot{V}_{Emax} , maximal workload, and HR _{max} following 0.75-ppm O ₃ exposure compared with FA.	Folinsbee et al. (1977)

^aSee Appendix A for abbreviations and acronyms.

^bListed from lowest to highest O₃ concentration.

test is preceded by an O₃ exposure of sufficient total inhaled dose of O₃ to result in significant pulmonary function decrements and symptoms of breathing discomfort.

Using trained nonathletes, Foxcroft and Adams (1986) observed significant ($p < 0.05$) reductions in rapidly incremented $\dot{V}O_{2\max}$ exercise performance time (-16.7%), $\dot{V}O_{2\max}$ (-6.0%), maximal \dot{V}_E (-15.0%), and maximal heart rate (-5.6%) immediately following an initial 50-min exposure to 0.35 ppm O₃ during heavy CE ($\dot{V}_E = 60$ L/min). These decrements were accompanied by a significant reduction in FEV₁ (-23%) and the occurrence of marked symptoms of breathing discomfort. Similarly, Gong et al. (1986) found significant reductions in rapidly incremented $\dot{V}O_{2\max}$ exercise performance time (-29.7%), $\dot{V}O_{2\max}$ (-16.4%), maximal \dot{V}_E (-18.5%), and maximal workload (-7.8%) in endurance cyclists immediately following a 1-h exposure to 0.20 ppm O₃ with very heavy exercise ($\dot{V}_E = 89$ L/min), but not following exposure to 0.12 ppm. Gong et al. (1986) observed only a 5.6% FEV₁ decrement and mild symptoms following exposure to 0.12 ppm, but a large decrement in FEV₁ (-21.6%) and substantial symptoms of breathing discomfort following the 0.20 ppm exposure, which the authors contended probably limited maximal performance and $\dot{V}O_{2\max}$.

AX6.7.3 Effect on Endurance Exercise Performance

A number of studies of well trained endurance athletes exposed to O₃ have consistently observed an impairment of 1-h continuous heavy exercise performance of some individuals (Adams and Schelegle, 1983; Avol et al., 1984; Folinsbee et al., 1984; Gong et al., 1986). The performance impairment is indicated by an inability to complete the prescribed O₃ exposures (even at concentrations as low as 0.16 ppm) that subjects were able to complete in FA (Avol et al., 1984). Other indications of impaired endurance exercise performance upon exposure to O₃ include a -7.7% reduced endurance treadmill running time when exposed to 0.18 ppm O₃ (Folinsbee et al., 1986), which was accompanied by significantly decreased FEV₁ and significantly elevated symptoms of breathing discomfort. Another study (Schelegle and Adams, 1986) observed the failure of some trained endurance athletes to complete a 1-h competitive simulation protocol upon exposure to O₃ (30 min warm-up, followed immediately by 30 min at the maximal workload that each subject could just maintain in FA; mean $\dot{V}_E = 120$ L/min). In this study, all subjects (n = 10) completed the FA exposure, whereas one, five, and seven

subjects could not complete the 0.12, 0.18, and 0.24 ppm O₃ exposures, respectively. Following the 0.18 ppm and 0.24 ppm O₃ exposures, but not the 0.12 ppm exposure, FEV₁ was reduced significantly and symptoms were significantly increased. Linder et al. (1988) also observed small decrements in performance time (1 to 2 min) during a progressive maximal exercise test (mean = 21.8 min) at O₃ concentrations of 0.065 and 0.125 ppm. These small effects were accompanied by a significant increase in subjective perception of overall effort at 0.125 ppm, but with no significant reduction in FEV₁ at either O₃ concentration. Collectively, reduced endurance exercise performance and associated pulmonary responses are clearly related to the total inhaled dose of O₃ (Adams and Schelegle, 1983; Avol et al., 1984; Schelegle and Adams, 1986).

Mechanisms limiting $\dot{V}O_{2\max}$ and maximal exercise performance upon O₃ exposure have not been precisely identified. Schelegle and Adams (1986) observed no significant effect of O₃ on cardiorespiratory responses, and there was no indirect indication that arterial O₂ saturation was affected. The latter is consistent with the observation that measured arterial O₂ saturation at the end of a maximal endurance treadmill run was not affected by O₃ (Folinsbee et al., 1986). In studies in which O₃ inhalation resulted in a significant decrease in $\dot{V}O_{2\max}$, and/or maximal exercise performance, significantly decreased FEV₁ and marked symptoms of breathing discomfort were observed (Adams and Schelegle, 1983; Avol et al., 1984; Folinsbee et al., 1977, 1984, 1986; Foxcroft and Adams, 1986; Gong et al., 1986; Schelegle and Adams, 1986). However, Gong et al. (1986) observed rather weak correlations between FEV₁ impairment and physiological variable responses during maximal exercise (R = 0.26 to 0.44). Rather, these authors concluded that substantial symptoms of breathing discomfort consequent to 1 h of very heavy exercise while exposed to 0.20 ppm O₃, probably limited maximal performance and $\dot{V}O_{2\max}$ either voluntarily or involuntarily (Gong et al., 1986). Strong support for this contention is provided by the observation of significant increases in $\dot{V}O_{2\max}$ (4.7%) and maximal performance time (8.8%) following four consecutive days of 1 h exposure to 0.35 ppm O₃ with heavy exercise ($\dot{V}_E = 60$ L/min) compared to initial O₃ exposure (Foxcroft and Adams, 1986). These improvements, which were not significantly different from those for FA, were accompanied by a significant reduction in symptoms of breathing discomfort with no significant attenuation of FEV₁ and other pulmonary function responses. In this regard, Schelegle et al. (1987) observed a disparate effect of indomethacin pretreatment (an inhibitor of the cyclo-

oxygenation of arachidonic acid to prostaglandins associated with inflammatory responses) on O₃-induced pulmonary function response (significant reduction) and an overall rating of perceived exertion and symptoms of pain on deep inspiration and shortness of breath (no significant effect).

AX6.8 EFFECTS ON AIRWAY RESPONSIVENESS

Increased airway responsiveness, also called airway hyperresponsiveness or bronchial hyperreactivity, indicates that the airways are more reactive to bronchoconstriction induced by a variety of stimuli (e.g., specific allergens, exercise, SO₂, cold air) than they would be when normoreactive. In order to determine the level of airway responsiveness, airway function (usually assessed by spirometry or plethysmography) is measured after the inhalation of small amounts of an aerosolized specific (e.g., antigen, allergen) or nonspecific (e.g., methacholine, histamine) bronchoconstrictor agent or measured stimulus (e.g., exercise, cold air). The dose or concentration of the agent or stimulus is increased from a control, baseline level (placebo) until a predetermined degree of airway response, such as a 20% drop in FEV₁ or a 100% increase in Raw, has occurred (Cropp et al., 1980; Sterk et al., 1993). The dose or concentration of the bronchoconstrictor agent that produced the increased responsiveness often is referred to as the “PD₂₀FEV₁” or “PC₂₀FEV₁” (i.e., the provocative dose or concentration that produced a 20% drop in FEV₁) or the “PD₁₀₀SRaw” (i.e., the provocative dose that produced a 100% increase in SRaw). A high level of bronchial responsiveness is a hallmark of asthma. The range of nonspecific bronchial responsiveness, as expressed by the PD₂₀ for example, is at least 1,000-fold from the most sensitive asthmatics to the least sensitive healthy subjects. Unfortunately, it is difficult to compare the PD₂₀FEV₁ or PD₁₀₀SRaw across studies because of the many different ways of presenting dose response to bronchoconstrictor drugs, for example, by mg/mL, units/mL, and molar solution; or by cumulative dose (CIU or CBU) and doubling dose (DD). Further confounding comparisons by affecting the site of drug delivery, dose, and ultimately bronchial responses, the size of aerosolized agents used in challenges can vary between nebulizers and as a function of supply air pressure in otherwise identical systems. Other typical bronchial challenge tests with nonspecific bronchoconstrictor stimuli are based on exercise intensity or temperature of inhaled cold air.

Increases in nonspecific airway responsiveness were previously reported as an important consequence of exposure to O₃ (e.g., Golden et al., 1978; Table AX6-11). König et al. (1980) and Holtzman et al. (1979) found the increased airway responsiveness after O₃ exposure in healthy subjects appeared to be resolved after 24 h. Because atopic subjects had similar increases in responsiveness to histamine after O₃ exposure as nonatopic subjects, Holtzman et al. (1979) concluded that the increased nonspecific bronchial responsiveness after O₃ exposure was not related to atopy. Folinsbee and Hazucha (1989) showed increased airway responsiveness in 18 female subjects 1 and 18 h after exposure to 0.35 ppm O₃. Taken together, these studies suggest that O₃-induced increases in airway responsiveness usually resolve 18 to 24 h after exposure, but may persist in some individuals for longer periods.

Gong et al. (1986) found increased nonspecific airway responsiveness in elite cyclists exercising at competitive levels with O₃ concentrations as low as 0.12 ppm. Folinsbee et al. (1988) found an approximate doubling of the mean methacholine responsiveness in a group of healthy volunteers exposed for 6.6 h to 0.12 ppm O₃. Horstman et al. (1990) demonstrated significant decreases in the PD₁₀₀SRaw in 22 healthy subjects immediately after a 6.6-h exposure to concentrations of O₃ as low as 0.08 ppm. No relationship was found between O₃-induced changes in airway responsiveness and changes in FVC or FEV₁ (Folinsbee et al., 1988; Aris et al., 1995), suggesting that changes in airway responsiveness and spirometric volumes occur by different mechanisms.

Dimeo et al. (1981) were the first to investigate attenuation of the O₃-induced increases in nonspecific airway responsiveness after repeated O₃ exposure. Over 3 days of a 2 h/day exposure to 0.40 ppm O₃, they found progressive attenuation of the increases in airway responsiveness such that, after the third day of O₃ exposure, histamine airway responsiveness was no longer different from the sham exposure levels. Kulle et al. (1982) found that there was a significantly enhanced response to methacholine after the first 3 days of exposure, but this response slowly normalized by the end of the fifth day. Folinsbee et al. (1994) found a more persistent effect of O₃ on airway responsiveness which was only partially attenuated after 5 consecutive days of O₃ exposure.

The occurrence and duration of increased nonspecific airway responsiveness following O₃ exposure could have important clinical implications for asthmatics. Kreit et al. (1989) investigated changes in airway responsiveness to methacholine that occur after O₃ exposure in

TABLE AX6-11. Airway Responsiveness Following Ozone Exposures^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.125	245	3h IE (10 min rest, 15 min exercise on bicycle) $\dot{V}_E = 30$ L/min	27 °C	5 F, 6 M	Mild bronchial asthma	Mean early-phase FEV ₁ response and number of ≥20% reductions in FEV ₁ were significantly greater after 0.25 ppm O ₃ or 4 × 0.125 ppm O ₃ . Most of the ≥15% late-phase FEV ₁ responses occurred after exposure to 4 × 0.125 ppm O ₃ , as well as significant inflammatory effects, as indicated by increased sputum eosinophils (asthma and allergic rhinitis) and increased sputum lymphocytes, mast cell tryptase, histamine, and LDH (asthma only).	Holz et al. (2002)
0.250	490		50 % RH	20-53 years old 6 F, 16 M 19-48 years old	Allergic rhinitis		
0.125	245	3h IE × 4 days					
0.4	784	2 h IE $\dot{V}_E = 20$ L/min/m ² BSA	NA	6 F 1 M 19-26 years old	Stable mild asthma; no meds 8 h preexposure	Increased bronchial responsiveness to methacholine 16 h after exposure; inhaled apocynin treatment significantly reduced O ₃ -induced airway responsiveness.	Peters et al. (2001)
0.12	235	45 min IE exercise, rest, exercise $\dot{V}_E = 3 \times$ resting	60% RH	12 F 5 M 19-38 years old	Physician diagnosed asthma; SO ₂ -induced airway hyperreactivity	The authors concluded O ₃ exposure increases bronchial responsiveness to SO ₂ in asthmatics and that antioxidant supplementation has a protective effects against this responsiveness, especially in the “more-severe” responders.	Trenga et al. (2001)
0.2	392	4 h IE $\dot{V}_E = 25$ L/min/m ² BSA	20 °C 62% RH	4F 8M 23-47 years old	Healthy nonsmokers	Increased sputum total cells, % neutrophils, IL-6, and IL-8 at 18 h after exposure; increased airway responsiveness to methacholine 2 h after postexposure FEV ₁ returned to 5% of base-line; no anti-inflammatory effect of azithromycin.	Criqui et al. (2000)
0.4	784	2 h IE 40 min/h @ 50 W	NA	15 healthy subjects ; 9 F, 6 M; 31.1 ± 2.1 years old	Healthy; nonatopic	Decreased FEV ₁ and FVC; increased bronchial reactivity to methacholine 4 h postexposure; no protection from inhaled corticosteroid, budesonide.	Nightingale et al. (2000)
0.16	314	7.6 h IE 50 min/h $\dot{V}_E \approx 25$ l/min	22°C 40% RH	5 F 4 M	Mild atopic asthma, HMD sensitive, 20-35 years old	Mean 9.1% FEV ₁ decrease 18 h after O ₃ exposure; provocative dose of dust mite allergen decreased from 10.3 to 9.7 dose units.	Kehrl et al. (1999)

TABLE AX6-11 (cont'd). Airway Responsiveness Following Ozone Exposures^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.2	392	4 h IE 40 min/h @ 50 W	NA	10 asthmatic (6 F, 4 M), 26.6 ± 2.3 years old; 10 healthy (4 F, 6 M), 27.3 ± 1.4 years old	Mild atopic asthma; nonatopic healthy subjects; no meds 8 weeks pre-exposure	Decreased FEV ₁ in asthmatic (9.3%) and healthy (6.7%) subjects; increased sputum neutrophils in both groups (NS); no change in methacholine airway reactivity 24 h postexposure.	Nightingale et al. (1999)
0.12 Air-antigen	235	1 h rest	NA	6 F 9 M	Mild allergic asthma; 18 to 49 years if age	No effect of O ₃ on airway response to grass or ragweed allergen.	Hanania et al. (1998)
0.4	784	2 h IE $\dot{V}_E = 20$ L/min/m ² BSA	NA	5F 1M 18-27 years old	Stable mild asthma; no meds 8 h preexposure	Increased airway responsiveness to methacholine 16 h postexposure; no effect of proteinase inhibitor, rALP.	Hiltermann et al. (1998)
0.2	392	4 h IE 50 min/h $\dot{V}_E = 25$ L/min/m ² BSA	20 °C 50% RH	6 F 12 M 18-36 years old	Physician-diagnosed mild asthma; no meds prior to exposure	Decreased FEV ₁ and FVC, increased SRaw; lower respiratory Sx; increased % neutrophils, total protein, LDH, fibronectin, IL-8, GM-CSF, and MPO in BAL. Correlation between pre-exposure methacholine challenge and O ₃ -induced SRaw increase.	Balmes et al. (1997); Scannell et al. (1996)
0.4	784	3 h/d for 5 days; alternating 15 min of rest and exercise at $\dot{V}_E = 32$ L/min	31 °C 35% RH	2 F 8 M 19-48 years old	Mild asthma requiring only occasional bronchodilator therapy	Significant FEV ₁ and Sx response on 1st and 2nd O ₃ exposure days, then diminishing with continued exposure; tolerance partially lost 4 and 7 days postexposure; bronchial reactivity to methacholine peaked on 1st O ₃ exposure day, but remained elevated with continued exposure.	Gong et al. (1997b)
0.12	236	Rest	22 °C 40% RH	5 F 10 M	atopic asthma	No effect of O ₃ on airway response to grass allergen.	Ball et al. (1996)
0.25	490	3 h IE $\dot{V}_E = 30$ L/min 15 min ex/ 10 min rest/ 5 min no O ₃ ; every 30 min.	27 °C 54% RH mouthpiece exposure	24 mild asthmatics 11 F / 13 M 12 allergic rhinitics 6 M / 6 F 10 healthy 5 M/5 F	atopic mild asthmatic NS	Increased allergen responsiveness afer O ₃ exposure in subjects with allergic airway disease, with or without asthma.	Jörres et al. (1996)

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TABLE AX6-11 (cont'd). Airway Responsiveness Following Ozone Exposures^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.2	392	4h IE 50 min/10 min exercise/rest each hour	22 °C 50% RH	42 M/24 F	18-50 years NS healthy	FEV ₁ (-18.6%), FVC (-14.6%), decreased after O ₃ . Baseline PC ₁₀₀ for methacholine was not related to changes in FVC, FEV ₁ , a weak association was seen for PC ₁₀₀ and increased SRaw.	Aris et al. (1995)
0.12	235	1 h R	Ambient T & RH for exposure; 23 °C & 50% RH for exercise challenge	8 F 7 M 19-45 years old	Mild stable asthma	No significant difference in % fall FEV ₁ or V _{40p} ; no increase in bronchial responsiveness to exercise challenge.	Fernandes et al. (1994)
0.12	235	6.6 h, IE x 5 days 50 min exercise/10 min rest, 30 min lunch V _E = 38.8 L/min	18 °C 40% RH	17 M 25 ± 4 years old	Healthy nonsmokers	FEV ₁ responses were maximal on 1st day of exposure (-13%), less on second day (-9%), absent thereafter. Sx responses only the first 2 days. Methacholine airway responsiveness was at least doubled on all exposure days, but was highest on the second day of O ₃ .	Folinsbee et al. (1994)
0.10 0.25 0.40	196 490 785	1 h light IE 2 × 15 min on treadmill V _E = 27 L/min	21 °C 40% RH	9 F 12 M 19-40 years old	Stable mild asthmatics with FEV ₁ >70% and methacholine responsiveness	No significant differences in FEV ₁ or FVC were observed for 0.10 and 0.25 ppm O ₃ -FA exposures or postexposure exercise challenge; 12 subjects exposed to 0.40 ppm O ₃ showed significant reduction in FEV ₁ .	Weymer et al. (1994)
Air-antigen 0.12 ppm O ₃ -antigen		1 h at rest	NA	4 M, 3 F	Asthmatic, 21 to 64 years old	Increased bronchoconstrictor response to inhaled ragweed or grass after O ₃ exposure compared to air.	Molfino et al. (1991)
0.08 0.10 0.12	157 196 235	6.6 h IE at ≈39 L/min	18 °C 40% RH	22 M	Healthy NS, 18 to 32 years old	33, 47, and 55% decreases in cumulative dose of methacholine required to produce a 100% increase in SRaw after exposure to O ₃ at 0.08, 0.10, and 0.12 ppm, respectively.	Horstman et al. (1990)

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TABLE AX6-11 (cont'd). Airway Responsiveness Following Ozone Exposures^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.12 ppm O ₃ -100 ppb SO ₂ 0.12 ppm O ₃ -0.12 ppm O ₃ Air-100 ppb SO ₂		45 min in first atmosphere and 15 min in second IE	22 °C 75% RH	8 M, 5 F	Asthmatic, 12 to 18 years old	Greater declines in FEV ₁ and $\dot{V}_{max50\%}$ and greater increase in respiratory resistance after O ₃ -SO ₂ than after O ₃ -O ₃ or air-SO ₂ .	Koenig et al. (1990)
0.35	686	70 min with IE at 40 L/min	NA	18 F	Healthy NS, 19 to 28 years old	PD ₁₀₀ decreased from 59 CIU after air exposure to 41 CIU and 45 CIU, 1 and 18 h after O ₃ exposure, respectively.	Folinsbee and Hazucha (1989)
0.40	784	2 h with IE at $\dot{V}_E = 53$ to 55 L/min	22 °C 50% RH	8 M, 10 F	9 asthmatics (5 F, 4 M), 9 healthy (5 F, 4 M), 18 to 34 years old	Decreased PC ₁₀₀ SRaw from 33 mg/mL to 8.5 mg/mL in healthy subjects after O ₃ . PC ₁₀₀ SRaw fell from 0.52 mg/mL to 0.19 mg/mL in asthmatic subjects after exposure to O ₃ and from 0.48 mg/mL to 0.27 mg/mL after exposure to air.	Kreit et al. (1989)
0.12	235	6.6 h with IE at ≈25 L/min/m ² BSA	NA	10 M	Healthy NS, 18 to 33 years old	Approximate doubling of mean methacholine responsiveness after exposure. On an individual basis, no relationship between O ₃ -induced changes in airway responsiveness and FEV ₁ or FVC.	Folinsbee et al. (1988)
0.12 0.20	235 392	1 h at $\dot{V}_E = 89$ L/min followed by 3 to 4 min at ≈150 L/min	31 °C 35% RH	15 M, 2 F	Elite cyclists, 19 to 30 years old	Greater than 20% increase in histamine responsiveness in one subject at 0.12 ppm O ₃ and in nine subjects at 0.20 ppm O ₃ .	Gong et al. (1986)
0.40	784	3 h/day for 5 days in a row		13 M, 11 F	Healthy NS, 19 to 46 years old	Enhanced response to methacholine after first 3 days, but this response normalized by Day 5.	Kulle et al. (1982)
0.20 0.40 0.40	392 784 784	2 h with IE at 2 × resting 2 h with IE at 2 × resting 2 h/day for 3 days	22 °C 55% RH	12 M, 7 F	Healthy NS, 21 to 32 years old	110% increase in ΔSRaw to a 10-breath histamine (1.6%) aerosol challenge after exposure to O ₃ at 0.40 ppm, but no change at 0.20 ppm. Progressive adaptation of this effect over 3-day exposure.	Dimeo et al. (1981)

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TABLE AX6-11 (cont'd). Airway Responsiveness Following Ozone Exposures^a

Ozone Concentration ^b		Exposure Duration and Activity	Exposure Conditions	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³						
0.10	196	2 h	NA	14	Health NS, 24 ± 2 years old	Increased airway responsiveness to methacholine immediately after exposure at the two highest concentrations of O ₃ .	König et al. (1980)
0.32	627						
1.00	1,960						
0.60	1,176	2 h with IE at 2 × resting	22 °C 55% RH	11 M, 5 F	9 atopic, 7 nonatopic, NS, 21 to 35 years old	Ten-breath methacholine or histamine challenge increased SRaw ≥150% in 16 nonasthmatics after O ₃ . On average, the atopic subjects had greater responses than the nonatopic subjects. The increased responsiveness resolved after 24 h. Atropine premedication blocked the O ₃ -induced increase in airway responsiveness.	Holtzman et al. (1979)
0.6	1,176	2 h at rest	NA	5 M, 3 F	Healthy NS, 22 to 30 years old	300% increase in histamine-induced ΔRaw 5 min after O ₃ exposure; 84 and 50% increases 24 h and 1 week after exposure (p > 0.05), respectively. Two subjects had an increased response to histamine 1 week after exposure.	Golden et al. (1978)

^aSee Appendix A for abbreviations and acronyms.

^bListed from lowest to highest O₃ concentration.

mild asthmatics. They found that the baseline PC₁₀₀SRaw declined from 0.52 to 0.19 mg/mL after a 2-h exposure to 0.40 ppm O₃, as compared to a decline from 0.48 to 0.27 mg/mL after air exposure; however, because of the large variability in responses of the asthmatics, the percent decrease from baseline in mean PC₁₀₀SRaw was not statistically different between healthy and asthmatic subjects (74.2 and 63.5%, respectively).

Two studies examined the effects of preexposure to O₃ on exacerbation of exercise-induced bronchoconstriction (Fernandes et al., 1994; Weymer et al., 1994). Fernandes et al. (1994) preexposed subjects with stable mild asthma and a history of >15% decline in FEV₁ after exercise to 0.12 ppm O₃ for 1 h at rest followed by a 6-min exercise challenge test and found no significant effect on either the magnitude or time course of exercise-induced bronchoconstriction. Similarly, Weymer et al. (1994) observed that preexposure to either 0.10 or 0.25 ppm O₃ for 60 min while performing light IE did not enhance or produce exercise-induced bronchoconstriction in otherwise healthy adult subjects with stable mild asthma. Although the results suggested that preexposure to O₃ neither enhances nor produces exercise-induced asthma in asthmatic subjects, the relatively low total inhaled doses of O₃ used in these studies limit the ability to draw any definitive conclusions.

Gong et al. (1997b) found that subjects with asthma developed tolerance to repeated O₃ exposures in a manner similar to normal subjects; however, there were more persistent effects of O₃ on airway responsiveness, which only partially attenuated when compared to filtered air controls. Volunteer subjects with mild asthma requiring no more than bronchodilator therapy were exposed to filtered air or 0.4 ppm O₃, 3 h/d for 5 consecutive days, and follow-up exposures 4 and 7 days later. Symptom and FEV₁ responses were large on the 1st and 2nd exposure days, and diminished progressively toward filtered air responses by the 5th exposure day. A methacholine challenge was performed when postexposure FEV₁ returned to within 10% of preexposure baseline levels. The first O₃ exposure significantly decreased PD₂₀FEV₁ by an order of magnitude and subsequent exposures resulted in smaller decreases, but they were still significantly different from air control levels. Thus, the effects of consecutive O₃ exposures on bronchial reactivity differ somewhat from the effects on lung function. The same conclusion was drawn by Folinsbee et al. (1994) after consecutive 5-day O₃ exposures in healthy subjects, despite a much lower bronchial reactivity both before and after O₃ exposure.

A larger number of studies examined the effects of O₃ on exacerbation of antigen-induced asthma. Molfino et al. (1991) were the first to report the effects of a 1-h resting exposure to 0.12 ppm O₃ on the response of subjects with mild, stable atopic asthma to a ragweed or grass allergen inhalation challenge. Allergen challenges were performed 24 h after air and O₃ exposure. Their findings suggested that allergen-specific airway responsiveness of mild asthmatics is increased after O₃ exposure. However, Ball et al. (1996) and Hanania et al. (1998) were unable to confirm the findings of Molfino et al. (1991) in a group of grass-sensitive mild allergic asthmatics exposed to 0.12 ppm O₃ for 1 h. The differences between Hanania et al. (1998) and Molfino et al. (1991), both conducted in the same laboratory, were due to better, less variable control of the 1 h 0.12 ppm O₃ exposure and better study design by Hanania and colleagues. In the original, Molfino et al. (1991) study, the control (air) and experimental (O₃) exposures were not randomized after the second subject because of long-lasting (3 months), O₃-induced potentiation of airway reactivity in that subject. For safety reasons, therefore, the air exposures were performed prior to the O₃ exposures for the remaining 5 of 7 subjects being evaluated. It is possible that the first antigen challenge caused the significant increase in the second (post-O₃) antigen challenge.

Jörres et al. (1996) later confirmed that higher O₃ concentrations cause increased airway reactivity to specific antigens in subjects with mild allergic asthma, and to a lesser extent in subjects with allergic rhinitis, after exposure to 0.25 ppm O₃ for 3 h. The same laboratory repeated this study in separate groups of subjects with asthma and rhinitis and found similar enhancement of allergen responsiveness after O₃ exposure (Holz et al., 2002); however, the effects of a 3-h exposure to 0.25 ppm O₃ were more variable, most likely due to performing the allergen challenges 20 h after exposure, rather than the 3 h used in the first study.

The timing of allergen challenges in O₃-exposed subjects with allergic asthma is important. Bronchial provocation with allergen, and subsequent binding with IgE antibodies on mast cells in the lungs, triggers the release of histamine and leukotrienes and a prompt early-phase contraction of the smooth muscle cells of the bronchi, causing a narrowing of the lumen of the bronchi and a decrease in bronchial airflow (i.e., decreased FEV₁). In many asthma patients, however, the release of histamine and leukotrienes from the mast cells also attracts an accumulation of inflammatory cells, especially eosinophils, followed by the production of mucus and a late-phase decrease in bronchial airflow for 4 to 8 h.

A significant finding from the study by Holz et al. (2002) was that clinically relevant decreases in FEV₁ ($\geq 20\%$) occurred during the early-phase allergen response in subjects with rhinitis after a consecutive 4-day exposure to 0.125 ppm O₃. Kehrl et al. (1999) previously found an increased reactivity to house dust mite antigen in asthmatics 16 to 18 h after exposure to 0.16 ppm O₃ for 7.6 hours. These important observations indicate that O₃ not only causes immediate increases in airway-antigen reactivity, but that this effect may persist for at least 18 to 20 h. Ozone exposure, therefore, may be a clinically important co-factor in the response to airborne bronchoconstrictor substances in individuals with pre-existing allergic asthma. It is plausible that this phenomenon could contribute to increased symptom exacerbations and, even, consequent increased physician or ER visits, and possible hospital admissions (*see Chapter 7*).

A number of human studies, especially more recent ones, have been undertaken to determine various aspects of O₃-induced increases in nonspecific airway responsiveness, but most studies have been conducted in laboratory animals (*See the toxicology chapter, Section 5.3.4.4.*). In humans, increased airway permeability (Kehrl et al., 1987; Molfino et al., 1992) could play a role in increased airway responsiveness. Inflammatory cells and mediators also could affect changes in airway responsiveness. The results of a multiphase study (Scannell et al., 1996; Balmes et al., 1997) showed a correlation between preexposure methacholine responsiveness in healthy subjects and increased SRaw caused by a 4 h exposure to 0.2 ppm O₃, but not with O₃-induced decreases in FEV₁ and FVC. The O₃-induced increase in SRaw, in turn, was correlated with O₃-induced increases in neutrophils and total protein concentration in BAL fluid. Subjects with asthma had a significantly greater inflammatory response to the same O₃ exposures, but it was not correlated with increased SRaw, and nonspecific airway provocation was not measured. Therefore, it is difficult to determine from this series of studies if underlying airway inflammation plays a role in increased airway responsiveness to nonspecific bronchoconstrictors. The study, however, confirmed an earlier observation (e.g., Balmes et al., 1996) that O₃-induced changes in airway inflammation and lung volume measurements are not correlated.

Hiltermann et al. (1998) reported that neutrophil-derived serine proteinases associated with O₃-induced inflammation are not important mediators for O₃-induced nonspecific airway hyperresponsiveness. Subjects with mild asthma, prescreened for O₃-induced airway responsiveness to methacholine, were administered an aerosol of recombinant antileukoprotease

(rALP) or placebo at hourly intervals two times before and six times after exposure to filtered air or 0.4 ppm O₃ for 2 h. Methacholine challenges were performed 16 h after exposure. Treatment with rALP had no effect on the O₃-induced decrease in FEV₁ or PC₂₀FEV₁ in response to methacholine challenge. The authors speculated that proteinase-mediated tissue injury caused by O₃ may not be important in the development of airway hyperresponsiveness of asthmatics to O₃. In a subsequent study using a similar protocol (Peters et al., 2001), subjects with mild asthma were administered an aerosol of apocynin, an inhibitor of NADPH oxidase present in inflammatory cells such as eosinophils and neutrophils, or a placebo. In this study, methacholine challenge performed 16 h after O₃ exposure showed treatment-related effects on PC₂₀FEV₁, without an effect on FEV₁. The authors concluded that apocynin could prevent O₃-induced bronchial hyperresponsiveness in subjects with asthma, possibly by preventing superoxide formation by eosinophils and neutrophils in the larger airways.

Nightingale et al. (1999) reported that exposures of healthy subjects and subjects with mild atopic asthma to a lower O₃ concentration (0.2 ppm) for 4 h caused a similar neutrophilic lung inflammation in both groups but no changes in airway responsiveness to methacholine measured 24 h after O₃ exposure in either group. There were, however, significant decreases in FEV₁ of 6.7 and 9.3% immediately after O₃ exposure in both healthy and asthmatic subjects, respectively. In a subsequent study, a significant increase in bronchoresponsiveness to methacholine was reported 4 h after healthy subjects were exposed to 0.4 ppm O₃ for 2 h (Nightingale et al., 2000). In the latter study, preexposure treatment with inhaled budesonide (a corticosteroid) did not protect against O₃-induced effects on spirometry, methacholine challenge, or sputum neutrophils. These studies also confirm the earlier reported findings that O₃-induced increases in airway responsiveness usually resolve by 24 h after exposure.

Ozone-induced airway inflammation and hyperresponsiveness were used by Criqui et al. (2000) to evaluate anti-inflammatory properties of the macrolide antibiotic, azithromycin. In a double-blind, cross-over study, healthy volunteers were exposed to 0.2 ppm O₃ for 4 h after pretreatment with azithromycin or a placebo. Sputum induction 18 h postexposure resulted in significantly increased total cells, percent neutrophils, IL-6, and IL-8 in both azithromycin- and placebo-treated subjects. Significant pre- to postexposure decreases in FEV₁ and FVC also were found in both subject groups. Airway responsiveness to methacholine was not significantly different between azithromycin-treated and placebo-treated subjects when they were challenged

2 h after postexposure FEV₁ decrements returned to within 5 % of baseline. Thus, azithromycin did not have anti-inflammatory effects in this study.

The effects of dietary antioxidants on O₃-induced bronchial responsiveness to SO₂ provocation were evaluated in adult asthmatic subjects by Trenga et al. (2001). *This study and potential interpretative problems are discussed in detail in Section AX6.5.6.* Briefly, 17 adult asthmatic subjects sensitive to SO₂ provocation took vitamin supplements (400 IU vitamin E and 500 mg vitamin C) or placebo once a day for 5 weeks. After the fourth and fifth weeks of vitamin or placebo, subjects were randomly exposed to FA and 0.12 ppm O₃ for 45 min during IE ($\dot{V}_E \approx 3 \times$ resting rate) followed by two sequential 10 min exposures to 0.1 and 0.25 ppm SO₂. Vitamin treatment was not associated with decreased bronchial responsiveness following the 0.1 ppm SO₂ challenge. However, the change in spirometric responses (FEV₁, FVC, FEF₂₅₋₇₅, and PEF) between the 0.1 and 0.25 ppm SO₂ challenges were more severe for the placebo than the vitamin treatment regimen ($p = 0.009$). The authors concluded O₃ exposure increases bronchial responsiveness to SO₂ in asthmatics and that antioxidant supplementation has a protective effect against this responsiveness.

AX6.9 EFFECTS ON INFLAMMATION AND HOST DEFENSE

AX6.9.1 Introduction

In general, inflammation can be considered as the host response to injury, and the induction of inflammation can be accepted as evidence that injury has occurred. Several outcomes are possible: (1) inflammation can resolve entirely; (2) continued acute inflammation can evolve into a chronic inflammatory state; (3) continued inflammation can alter the structure or function of other pulmonary tissue, leading to diseases such as fibrosis or emphysema; (4) inflammation can alter the body's host defense response to inhaled microorganisms; and (5) inflammation can alter the lung's response to other agents such as allergens or toxins. At present, it is known that short-term exposure of humans to O₃ can cause acute inflammation and that long-term exposure of laboratory animals results in a chronic inflammatory state (see Chapter 5). However, the relationship between repetitive bouts of acute inflammation in humans caused by O₃ and the development of chronic respiratory disease is unknown.

Bronchoalveolar lavage (BAL) using fiberoptic bronchoscopy has been utilized to sample cells and fluids lining the respiratory tract primarily from the alveolar region, although the use of small volume lavages or balloon catheters permits sampling of the airways. Cells and fluid can be retrieved from the nasal passages using nasal lavage (NL) and brush or scrape biopsy.

Several studies have analyzed BAL and NL fluid and cells from O₃-exposed humans for markers of inflammation and lung damage (see Tables AX6-12 and AX6-13). The presence of neutrophils (PMNs) in the lung has long been accepted as a hallmark of inflammation and is an important indicator that O₃ causes inflammation in the lungs. It is apparent, however, that inflammation within airway tissues may persist beyond the point that inflammatory cells are found in BAL fluid. Soluble mediators of inflammation such as the cytokines (IL-6, IL-8) and arachidonic acid metabolites (e.g., PGE₂, PGF_{2α}, thromboxane, and leukotrienes [LTs] such as LTB₄) have been measured in the BAL fluid of humans exposed to O₃. In addition to their role in inflammation, many of these compounds have bronchoconstrictive properties and may be involved in increased airway responsiveness following O₃ exposure.

Some recent evidence suggests that changes in small airways function may provide a sensitive indicator of O₃ exposure and effect (*see Section AX6.2.5*), despite the fact that inherent variability in their measurement by standard spirometric approaches make their assessment difficult. Observations of increased functional responsiveness of these areas relative to the more central airways, and of persistent effects following repeated exposure, may indicate that further investigation of inflammatory processes in these regions is warranted.

Under normal circumstances, the epithelia lining the large and small airways develop tight junctions and restrict the penetration of exogenous particles and macromolecules from the airway lumen into the interstitium and blood, as well as restrict the flow of plasma components into the airway lumen. O₃ disrupts the integrity of the epithelial cell barrier in human airways, as measured by markers of plasma influx such as albumin, immunoglobulin, and other proteins into the airways. Markers of epithelial cell damage such as lactate dehydrogenase (LDH) also have been measured in the BAL fluid of humans exposed to O₃. Other soluble factors that have been studied include those involved with fibrin deposition and degradation (Tissue Factor, Factor VII, and plasminogen activator), potential markers of fibrogenesis (fibronectin, platelet derived growth factor), and components of the complement cascade (C3a).

Table AX6-12. Studies of Respiratory Tract Inflammatory Effects from Controlled Human Exposure to Ozone^a

Ozone Concentration ^b		Exposure Duration	Activity Level (\dot{V}_E)	Number and Gender of Subjects	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$					
<i>Upper Airway Studies</i>						
0.4	784	2 h	At rest	12 mild, asymptomatic dust mite-sensitive asthmatics; 18-35 years of age	Release of early-onset mast cell-derived mediators into NL in response to allergen not enhanced following O ₃ exposure. Neutrophil and eosinophil inflammatory mediators were not increased after O ₃ exposure or enhanced after allergen challenge. O ₃ increased eosinophil influx following allergen exposure.	Michelson et al. (1999)
0.2	392	2 h	IE (15 min/30 min); (\dot{V}_E) \approx 20 L/min/m ² BSA	8 M, 5 F healthy NS 20-31 years of age	No neutrophilia in NL samples by 1.5 h postexposure. Depletion of uric acid in NL fluid by 30% during h 2 of exposure with increase in plasma uric acid levels. No depletion of ascorbic acid, reduced glutathione, extracellular superoxide dismutase.	Mudway et al. (1999)
0.4	980	2 h	At rest	10 mild NS asthmatics 18-35 years old	Response to allergen increased (NS). PMN and eosinophils increased after O ₃ plus allergen challenge. Ozone alone increased inflammation in the nose.	Peden et al. (1995)
0.12 0.24	235 470	1.5 h	IE (20 L/min) at 15-min intervals	5 M, 5 F, asthmatic; 4 M, 4 F, nonasthmatic; 18 to 41 years old	NL done immediately and 24 h after exposure. Increased number of PMNs at both times in asthmatic subjects exposed to 0.24 ppm O ₃ ; no change in nonasthmatic subjects. No change in lung or nasal function.	McBride et al. (1994)
0.5	980	4 h	Resting	6 M, 6 F, allergic rhinitics, 31.4 \pm 2.0 (SD) years old	NL done immediately after exposure. Increased upper and lower respiratory symptoms and increased levels of PMNs, eosinophils, and albumin in NL fluid.	Bascom et al. (1990)
0.4	784	2 h	IE (70 L/min) at 15-min intervals	11 M, 18 to 35 years old	NL done immediately before, immediately after, and 22 h after exposure. Increased numbers of PMNs at both times after exposure; increased levels of tryptase, a marker of mast cell degranulation, immediately after exposure; increased levels of albumin 22 h after exposure.	Graham and Koren (1990) Koren et al. (1990)
0.5	980	4 h on 2 consecutive days	Resting	41 M (21 O ₃ -exposed, 20 air-exposed), 18 to 35 years old	NL done immediately before and after each exposure and 22 h after the second exposure. Increased levels of PMNs at all times after the first exposure, with peak values occurring immediately prior to the second exposure.	Graham et al. (1988)

Table AX6-12 (cont'd). Studies of Respiratory Tract Inflammatory Effects from Controlled Human Exposure to Ozone^a

Ozone Concentration ^b		Exposure Duration	Activity Level (\dot{V}_E)	Number and Gender of Subjects	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$					
<i>Lower Airway Studies</i>						
0.2	392	2 h	IE (15 min/30 min); (\dot{V}_E) \approx 20 L/min/m ² BSA	6M, 6F healthy, nonatopic and 9 M, 6F mild asthmatic subjects, 19-48 years of age	Significantly higher baseline expression of IL-4 and IL-5 in bronchial mucosal biopsies from asthmatic vs. healthy subjects 6 h postexposure. Following O ₃ exposure, epithelial expression of IL-5, GM-CSF, ENA-78, and IL-8 increased significantly in asthmatics, as compared to healthy subjects.	Bosson et al. (2003)
0.1	196	2 h	mild IE	12 M, 10 F healthy subjects mean age ~30 years	Markers of exposure in exhaled breath condensate, including increased 8-isoprostane, TBARS and LTB-4, and a marker of ROS-DNA interaction in peripheral blood leukocytes (8-OHdG), were increased in a sub-set of subjects bearing the wild genotype for NAD(P)H:quinone oxidoreductase and the null genotype for glutathione-S-transferase M1.	Corradi et al. (2002)
0.2	392	2 h	IE (15 min/30 min); (\dot{V}_E) \approx 20 L/min/m ² body surface area	6M, 9F healthy subjects and 9 M, 6F mild asthmatics	No evidence seen for increased responsiveness to the inflammatory effects of O ₃ in mild asthmatics versus healthy subjects at 6 h following exposure. Used neutrophil recruitment and exacerbation of pre-existing inflammation.	Stenfors et al. (2002)
0.27	529	2 h	IE (20 min/ 60 min); (\dot{V}_E) \approx 25 L/min/m ² BSA	12 subjects with intermittent-mild asthma exhibiting a dual response; 18-37 years of age	Exposure to O ₃ 24 h following allergen challenge resulted in a significant decrease in FEV1, FVC and VC and increase in symptom scores compared to air exposure. The percentage of eosinophils, but not neutrophils, in induced sputum was higher 6 h after O ₃ than after air.	Vagaggini et al. (2002)
0.22	431	4 h	IE (15 min/30 min); (\dot{V}_E) = 25 L/min/m ² BSA	12 nonsmoker, nonresponders; 13 nonsmoker, responders; 13 smokers; 18-40 years of age	Recovery of AM was approximately 3-fold higher in BAL from smokers versus nonsmokers. Unstimulated AM from smokers released ~2-fold greater amounts of superoxide anion than from nonsmokers at 30 min and 18 h postexposure, but release was not further enhanced by stimulation of the cells. ROS generation by AM from nonsmokers decreased following exposure at 18 h; markers of epithelial permeability increased. No relationship was found between measures of ROS production and lung function responsiveness to O ₃ .	Voter et al. (2001)

Table AX6-12 (cont'd). Studies of Respiratory Tract Inflammatory Effects from Controlled Human Exposure to Ozone^a

Ozone Concentration ^b		Exposure Duration	Activity Level (\dot{V}_E)	Number and Gender of Subjects	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$					
Lower Airway Studies (cont'd)						
0.2	392	2 h	IE (15 min/30 min); (\dot{V}_E) \approx 20 L/min/m ² BSA	8M, 5F healthy nonsmokers; 20-31 years of age	Early (1.5 h postexposure) increase in adhesion molecule expression, submucosal mast cell numbers and alterations in lining fluid redox status. No clear relationship between early markers of response and lung function deficits. 2.5-fold increase in % human leukocyte antigen (HLA)-DR+ alveolar macrophages in BAL.	Blomberg et al. (1999)
0.4	784	2 h	IE (15 min/30 min); (\dot{V}_E) \approx 20 L/min/m ² BSA	10M, 6F subjects with intermittent asthma; 19-35 years of age	In a cross-over study, levels of eosinophil cationic protein, IL-8 and percentage eosinophils were found to be highly correlated in induced sputum and BAL 16 h following O ₃ exposure.	Hiltermann et al. (1999)
0.4	784	2 h	At rest	12 mild, asymptomatic dust mite-sensitive asthmatics; 18-35 years of age	Release of early-onset mast cell-derived mediators into NL in response to allergen not enhanced following O ₃ exposure. Neutrophil and eosinophil inflammatory mediators were not increased after O ₃ exposure or enhanced after allergen challenge. O ₃ increased eosinophil influx following allergen exposure.	Michelson et al. (1999)
0.4	784	1 h	Continuous exercise; (\dot{V}_E) \approx 30 L/min/m ² BSA	4 healthy subjects	Apoptosis was observed in cells obtained by airway lavage 6 h following exposure. AM obtained by BAL showed the presence of a 4-hydroxynonenal (HNE) protein adduct and the stress proteins, 72-kD heat shock protein and ferritin. These effects were replicated by <i>in vitro</i> exposure of AM to HNE.	Hamilton et al. (1998)
0.2	392	2 h		15 healthy nonsmokers	Increased numbers of CD3+, CD4+, and CD8+ T lymphocyte subsets, in addition to neutrophils, in BAL 6 h postexposure.	Blomberg et al. (1997)
0.4	784	2 h/day for 5 days, 2 h either 10 or 20 days later	IE (40 L/min) at 15-min intervals	16 M; 18 to 35 years of age	BAL done immediately after fifth day of exposure and again after exposure 10 or 20 days later. Most markers of inflammation (PMNs, IL-6, PGE ₂ , fibronectin) showed partial to complete attenuation; markers of damage (LDH, IL-8, protein, α 1-antitrypsin, elastase,) did not. Reversal of attenuation was not complete for some markers, even after 20 days.	Devlin et al. (1997)

Table AX6-12 (cont'd). Studies of Respiratory Tract Inflammatory Effects from Controlled Human Exposure to Ozone^a

Ozone Concentration ^b		Exposure Duration	Activity Level (\dot{V}_E)	Number and Gender of Subjects	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$					
<i>Lower Airway Studies (cont'd)</i>						
0.22	431	4 h	IE 20 min ex/19 min rest (\dot{V}_E) \approx 39-45 l/min	31M, 7F smokers and nonsmokers	Post-O ₃ exposure FEV ₁ in 3 groups: Smokers (-13.9%); nonresponders (-1.4%) and responders (-28.5%). PMN's increased immediately and at 18 h in all groups. Eosinophils and lymphocytes increased after O ₃ . IL-6 increased more in nonsmokers. No relationship of symptoms with inflammation, lung function changes not related to inflammation. Nasal lavage indicators did not predict bronchial or alveolar inflammation.	Frampton et al. (1997a) Torres et al. (1997)
0.12	235	2 h	IE (15 min/30 min); (\dot{V}_E) \approx 20 L/min/m ² BSA	9M, 3F healthy nonsmokers; mean age ~28 years	Increase in the percentage of vessels expressing P-selectin in bronchial biopsies at 1.5 h postexposure. No changes in FEV ₁ , FVC, inflammatory cells or markers in BAL, or vessels expressing VCAM-1, E-selectin or ICAM-1 in biopsies.	Krishna et al. (1997b)
0.16	314	7.6 h	IE 50 min/hr (\dot{V}_E) = 25 L/min	8 asthmatics sensitive to dust mites	Increased numbers of eosinophils in BAL after O ₃ exposure.	Peden et al. (1997)
0.2	392	4 h T = 20 °C RH = 50%	IE (50 min/60 min); (\dot{V}_E) \approx 44 L/min	14 M, 6 F healthy NS	Ozone increased PMN, protein, IL-8, for all subjects. No relationship of inflammation with spirometric responses.	Balmes et al. (1996)
0.4	784	2 h T = 22 °C RH = 50%	15 min rest 15 min exercise cycle ergometer (\dot{V}_E) \approx 55 l/min	11 healthy nonsmokers; 18-35 years	Mean FEV ₁ , change = -10%. BAL occurred at 0, 2, or 4 h postexposure. Small n limits statistical inference. Trend for PMN's to be highest at 4 h. LTC ₄ increased at all time points. No change in PGE ₂ or thromboxane.	Coffey et al. (1996)
0.4	784	2 h 15 min, ex/15 min, rest	(\dot{V}_E) = 66 l/min	8 M healthy nonsmokers	Comparison of BAL at 1 h postexposure vs. 18 h postexposure. At 1 h, PMN's, total protein, LDH, α 1-antitrypsin, fibronectin, PGE ₂ , thromboxane B ₂ , C3 _a , tissue factor, and clotting factor VII were increased. IL-6 and PGE ₂ were higher after 1 h than 18 h. Fibronectin and tissue plasminogen activator higher after 18 h. No time differences for PMN and protein.	Devlin et al. (1996) (compare with Koren et al. (1989a)
0.2	392	4 h T = 20 °C RH = 50%	IE (50 min/60 min); (\dot{V}_E) \approx 44 L/min	17 M, 6F mild asthmatics	Increased PMN, protein, IL-8, LDH, in BAL. Inflammatory responses were greater than a group of nonasthmatics (Balmes et al., 1996)	Scannell et al. (1996)

Table AX6-12 (cont'd). Studies of Respiratory Tract Inflammatory Effects from Controlled Human Exposure to Ozone^a

Ozone Concentration ^b		Exposure Duration	Activity Level (\dot{V}_E)	Number and Gender of Subjects	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$					
Lower Airway Studies (cont'd)						
0.4	784	2 h mouthpiece exposure 20 °C 42% RH	15 min exercise 15 min rest (\dot{V}_E) \approx 40 l/min	5M, 5F healthy; age \approx 30	Sputum induction 4 h after O ₃ exposure 3-fold increase in neutrophils and a decrease in macrophages after O ₃ exposure. IL-6, IL-8, and myeloperoxidase increased after O ₃ . Possible relationship of IL-8 and PMN levels.	Fahy et al. (1995)
0.2	392	4 h	IE (50 min/60 min); (\dot{V}_E) = 40 L/min	15 M, 13 F, 21 to 39 years old	Bronchial lavage, bronchial biopsies, and BAL done 18 h after exposure. BAL shows changes similar to other studies. Airway lavage shows increased cells, LDH, IL-8. Biopsies show increased number of PMNs.	Aris et al. (1993)
0.08 0.10	157 196	6.6 h	IE (50 min/60 min) + 35 min lunch; (\dot{V}_E) = 40 L/min	18 M, 18 to 35 years of age	BAL fluid 18 h after exposure to 0.1 ppm O ₃ had significant increases in PMNs, protein, PGE ₂ , fibronectin, IL-6, lactate dehydrogenase, and α -1 antitrypsin compared with the same subjects exposed to FA. Similar but smaller increases in all mediators after exposure to 0.08 ppm O ₃ except for protein and fibronectin. Decreased phagocytosis of yeast by alveolar macrophages was noted at both concentrations.	Devlin et al. (1990, 1991) Koren et al. (1991)
0.4	784	2 h	IE (15 min/30 min); (\dot{V}_E) = 70 L/min	10 M, 18 to 35 years old	BAL fluid 1 h after exposure to 0.4 ppm O ₃ had significant increases in PMNs, protein, PGE ₂ , TXB ₂ , IL-6, LDH, α -1 antitrypsin, and tissue factor compared with the same subjects exposed to FA. Decreased phagocytosis of yeast by alveolar macrophages.	Koren et al. (1991)
0.3	588	1 h (mouth-piece)	CE (60 L/min)	5 M	Significantly elevated PMNs in the BAL fluid 1, 6, and 24 h after exposure, with peak increases at 6 h.	Schelegle et al. (1991)
0.40	784	2 h	IE (15 min/30 min); (\dot{V}_E) = 70 L/min	11 M, 18 to 35 years old	Macrophages removed 18 h after exposure had changes in the rate of synthesis of 123 different proteins as assayed by computerized densitometry of two-dimensional gel protein profiles.	Devlin and Koren (1990)
0.40	784	2 h	IE (15 min/30 min); (\dot{V}_E) = 70 L/min	11 M, 18 to 35 years old	BAL fluid 18 h after exposure contained increased levels of the coagulation factors, tissue factor, and factor VII. Macrophages in the BAL fluid had elevated tissue factor mRNA.	McGee et al. (1990)
0.4	784	2 h	IE (15 min/30 min); (\dot{V}_E) = 70 L/min	11 M, 18 to 35 years old	BAL fluid 18 h after exposure had significant increases in PMNs, protein, albumin, IgG, PGE ₂ , plasminogen activator, elastase, complement C3a, and fibronectin.	Koren et al. (1989a,b)

Table AX6-12 (cont'd). Studies of Respiratory Tract Inflammatory Effects from Controlled Human Exposure to Ozone^a

Ozone Concentration ^b		Exposure Duration	Activity Level (\dot{V}_E)	Number and Gender of Subjects	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$					
<i>Repeated Exposure Studies</i>						
0.125 0.25	245 490	3 h exposures to both O ₃ concs. and to FA; 3 h on four consecutive days to 0.125; study arms separated by >4 wks	IE (15 min/30 min)	5M, 6F allergic asthmatic and 16M, 6F allergic rhinitic subjects; 19-53 years of age	All subjects underwent 4 exposure arms and were challenged with allergen 20 h following the last exposure in each. Sputum was induced 6-7 h later. In rhinitics, but not asthmatics, the incidence and magnitude of early phase FEV ₁ decrements to Ag were greater after 0.25 and 4x 0.125 ppm O ₃ . Repeated exposure caused increases in neutrophil and eosinophil numbers in both subject groups, as well as increased percentage and number of lymphocytes in the asthmatics.	Holz et al. (2002)
0.25	490	2 h on four consecutive days; O ₃ and FA exposure study arms separated by ≥3 wks	IE (30 min/60 min); (\dot{V}_E) ≈ 8 times the FVC/min	5M, 3F healthy subjects; 25-31 years of age	Maximal mean reductions in FEV ₁ and FVC were observed on day 2, and became negligible by day 4. FEF ₂₅₋₇₅ , Vmax50, and Vmax75 were combined into a single value representing small airway function (SAWgrp). This variable was the only one to show persistent depression of the 24 h postexposure baseline from day 2 to day 5 measurements. Numbers of PMNs in BAL fluid on day 5 were significantly higher in subjects following O ₃ , compared to air, exposures.	Frank et al. (2001)
0.2	392	single, 4 h exposures to O ₃ and to FA; 4 h on four consecutive days to O ₃ ; study arms separated by >4 wks	IE (15 min/30 min); (Mean \dot{V}_E) = 14.8 L/min/m ² BSA	15M, 8F healthy subjects; 21-35 years of age	All subjects underwent 3 exposure arms with BAL and bronchial mucosal biopsies performed 20 h following the last exposure in each. After repeated exposure, functional and BAL cellular responses were not different from those after FA, whereas total protein, IL-6, IL-8, reduced glutathione and ortho-tyrosine remained elevated. Also at this time, macroscopic scores of inflammation and tissue neutrophils were increased in mucosal biopsies. IL-10 was detected only in BAL fluid following repeated O ₃ exposure.	Jörres et al. (2000)
0.2	392	single, 4 h exposure; 4 h exposures on four consecutive days; study arms separated by >4 wks	IE (30 min/60 min); (Mean \dot{V}_E) = 25 L/min/m ² BSA	9M, 6F healthy NS 23-37 years of age	Subjects were randomly assigned to each of the exposure regimens in a crossover design. Compared to single exposure, repeated exposure resulted in an initial progression followed by an attenuation of decrements in FEV ₁ , FVC and specific airways resistance by day 4. Bronchial and BAL washings showed decreases in the numbers of PMNs and fibronectin levels and IL-6 was decreased in BAL fluid on day 4.	Christian et al. (1998)

Table AX6-12 (cont'd). Studies of Respiratory Tract Inflammatory Effects from Controlled Human Exposure to Ozone^a

Ozone Concentration ^b		Exposure Duration	Activity Level (\dot{V}_E)	Number and Gender of Subjects	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$					
<i>Repeated Exposure Studies</i> (cont'd)						
0.4	784	2 h/day for 5 days, 2 h either 10 or 20 days later	IE (60 L/min) at 15-min intervals	16 M; 18 to 35 years of age	BAL done immediately after fifth day of exposure and again after exposure 10 or 20 days later. Most markers of inflammation (PMNs, IL-6, PGE ₂ , fibronectin) showed complete attenuation; markers of damage (LDH, IL-8, protein, α 1-antitrypsin, elastase) did not. Reversal of attenuation was not complete for some markers, even after 20 days.	Devlin et al. (1997)
0.40 0.60	784	2 h	IE (83 W for women, 100 W for men) at 15-min intervals	7M, 3F 23 to 41 years of age	BAL fluid 3 h after exposure had significant increases in PMNs, PGE ₂ , TXB ₂ , and PGF _{2α} at both O ₃ concentrations.	Seltzer et al. (1986)

^a See Appendix A for abbreviations and acronyms.

^b Listed from lowest to highest O₃ concentration.

Table AX6-13. Studies of Effects on Host Defense, on Drug Effects and Supportive In Vitro Studies Relating to Controlled Human Exposure to Ozone^a

Ozone Concentration ^b		Exposure Duration	Activity Level (\dot{V}_E)	Number and Gender of Subjects	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$					
Host Defense						
0.2	392	2 h	IE (15 min/30 min); (\dot{V}_E) \approx 20 L/min/m ² BSA	4M, 5F mild atopic asthmatics; 21-42 years of age	A significant decline in FEV ₁ and VC immediately following exposure. A 2-fold increase in percent PMNs, with no changes in other biomarkers, was observed at 6 h postexposure. By 24 h postexposure, PMNs had decreased, but albumin, total protein, myeloperoxidase and eosinophil cationic protein had increased.	Newson et al. (2000)
0.3	588	6 h/day for 5 consecutive days	IE (light treadmill)	24 M (12 O ₃ , 12 air)	Subjects inoculated with type 39 rhinovirus prior to exposure. NL was performed on the morning of Days 1 to 5, 8, 15, and 30. No difference in virus titers in NL fluid of air and O ₃ -exposed subjects at any time tested. No difference in PMNs or interferon gamma in NL fluid, or in blood lymphocyte proliferative response to viral antigen.	Henderson et al. (1988)
0.2	382	2 h	IE (15 min/30 min); (\dot{V}_E) \approx 30 L/min	10M, 2F healthy NS mean \sim 28 years of age	Subjects were exposed to O ₃ and FA in a cross-over design and underwent BAL 6 h postexposure. O ₃ exposure induced a 3-fold increase in % PMNs and epithelial cells, and increased IL-8, Gro- α , and total protein in BAL fluid. % PMNs correlated positively with chemokine levels. Exposure also resulted in a significant decrease in the CD4+/CD8+ ratio and the % of activated CD4+ and CD8+ T cells in BAL fluid.	Krishna et al. (1998)
Host Defense - Mucous Clearance						
0.4	784	1 h	CE (40 L/min)	15 healthy NS 18 to 35 years old	Subjects inhaled radiolabeled iron oxide particles 2 h after exposure. No significant O ₃ -induced effect on clearance of particles during the next 3 h or the following morning.	Gerrity et al. (1993)
0.20 0.40	392 784	2 h	IE (light treadmill)	7 M, 27.2 \pm 6.0 (SD) years old	Subjects inhaled radiolabeled iron oxide particles immediately before exposure. Concentration-dependent increase in rate of particle clearance 2 h after exposure, although clearance was confined primarily to the peripheral airways at the lower O ₃ concentration.	Foster et al. (1987)

Table AX6-13 (cont'd). Studies of Effects on Host Defense, on Drug Effects and Supportive *In Vitro* Studies Relating to Controlled Human Exposure to Ozone^a

Ozone Concentration ^b		Exposure Duration	Activity Level (\dot{V}_E)	Number and Gender of Subjects	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$					
<i>Host Defense - Epithelial Permeability</i>						
0.0	0	2 h	IE	10 M, 12 F	Clara cell protein (CC16) levels, a biomarker of epithelial permeability, were elevated by O ₃ exposure and remained high at 6 h postexposure. By 18 h postexposure, CC16 levels had returned to baseline. No correlation between CC16 and FEV ₁ decrements.	Blomberg et al. (2003)
0.2	392		4 × 15 min at $\dot{V}_E = 20$ L/min/m ² BSA	Healthy NS; mean 24 years of age		
0.15	294	130 min	IE	8M,1F	Subjects inhaled ^{99m} Tc-DTPA 19 h after exposure to O ₃ . Clearance was increased in the lung periphery. Clearance was not related to spirometry.	Foster and Stetkiewicz (1996)
0.35	686		10 exercise/ 10 rest (\dot{V}_E) ≈ 8×FVC	NS		
0.5	784	2.25 h	IE	16 M, 20 to 30 years old	Similar design and results as earlier study (Kehrl et al., 1987). For the combined studies the average rate of clearance was 60% faster in O ₃ -exposed subjects.	Kehrl et al. (1989)
0.4	784	2 h	IE	8 M, 20 to 30 years old	Subjects inhaled ^{99m} Tc-DTPA 75 min after exposure. Significantly increased clearance of ^{99m} Tc-DTPA from the lung in O ₃ -exposed subjects. Subjects had expected changes in FVC and SRaw.	Kehrl et al. (1987)
<i>Drug Effects on Inflammation</i>						
0.25	490	3 h IE 15-min intervals 4 O ₃ exposures: screening, placebo, and two treatments	27 °C 56 % RH (values from Holz et al. 1999)	14M, 4F Healthy NS ozone responders 31.4 ± 8.4 years old	On average, the screening and placebo O ₃ exposures caused greater than a 9-fold increase in sputum neutrophils relative to baseline levels. Relative to placebo, the inhaled or oral corticosteroids significantly reduced neutrophil levels by 62 and 64%, respectively. Post-O ₃ , spirometry not significantly different from baseline.	Holz et al. (2005)
0.4	784	2 h		23 healthy adults	Subjects were exposed to O ₃ following random selection for a 2 wk daily regimen of antioxidants, including vegetable juice high in the carotenoid, lycopene, or placebo. Concentrations of lycopene in the lungs of supplemented subjects increased by 12% following treatment. Supplemented subjects showed a 20% decrease in epithelial cell DNA damage as assessed by the Comet Assay. Effects attributable to lycopene could not be separated from those of other antioxidants.	Arab et al. (2002)

Table AX6-13 (cont'd). Studies of Effects on Host Defense, on Drug Effects and Supportive *In Vitro* Studies Relating to Controlled Human Exposure to Ozone^a

Oz one Concentration ^b		Exposure Duration	Activity Level (\dot{V}_E)	Number and Gender of Subjects	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$					
Drug Effects on Inflammation (cont'd)						
0.0 0.4	0 784	2 h IE 20 min mild-mod. exercise, 10 min rest	4 M, 5 F	Healthy NS 30 ± 3 years old	Subjects previously in Nightingale et al. (2000) study. Placebo-control: Immediately postexposure decrements in FVC (9%) and FEV ₁ (14%) relative to pre-exposure values. FEV ₁ decrement only 9% at 1 hr postexposure. By 3 h postexposure, recovery in FVC to 97% and FEV ₁ to 98% of preexposure values. Significant increases in 8-isoprostane at 4 h postexposure. Budesonide for 2 wk prior to exposure did not affect responses.	Montuschi et al. (2002)
0.2	392	2 h All exposures separated by at least 2 wks (mean ≈ 30d)	IE (15 min/30 min); (\dot{V}_E) ≈ 20 L/min/m ² BSA	Healthy (6 M, 9 F) and mild asthmatic (9 M, 6 F) subjects	Comparison was made of responses in healthy subjects, who had higher basal ascorbate (ASC) levels and lower glutathione disulfide (GSSG) levels than those of asthmatics. 6 h after exposure, ASC levels were decreased and GSSG levels were increased in BAL fluid of normals, but not asthmatics. Despite these differences in basal antioxidant levels and response to O ₃ , decrements in FEV ₁ and neutrophil influx did not differ in the two subject groups.	Mudway et al. (2001)
0.4	784	2 h	IE 15-min intervals; \dot{V}_E ≈ 20 L/min/m ² BSA	Placebo group 15 M, 1 F Antioxidant group 13 M, 2 F Mean age 27 years	All subjects were exposed to FA and then entered a 2 wk regimen of placebo or 250 mg Vit C, 50IU α -tocopherol, and 12 oz veg. cocktail/day prior to O ₃ exposure. O ₃ -induced decrements in FEV ₁ and FVC were 30% and 24% less, respectively, in supplemented subjects. Percent neutrophils and IL-6 levels in BAL fluid obtained 1 h postexposure were not different in the two treatment groups.	Samet et al. (2001) Stech-Scott et al. (2004)
0.27	529	2 h All exposures separated by at least 1 wk (mean ≈ 14 d)	Continuous exercise; (\dot{V}_E) ≈ 25 L/min/m ² BSA	7 M, F subjects with mild asthma; 20-50 years of age	Subjects were randomly exposed to FA and to O ₃ before and after 4 wks of treatment with 400 μg budesonide, b.i.d. Budesonide did not inhibit the decrement in FEV ₁ or increase in symptom scores, but significantly reduced the increase in % neutrophils and IL-8 in sputum induced 6 h postexposure.	Vagaggini et al. (2001)
0.4	784	2 h	IE 15-min intervals \dot{V}_E min ≈ 30 L/min	5 M, 4 F healthy 6 M, 7 F asthmatics	Subjects were pretreated for 3 days prior to exposure with indomethacin (75 mg/day) or placebo. Similar reductions in FEV ₁ and FVC were seen in both groups following placebo, whereas mid-flows showed greater decline in asthmatics than normals. Indomethacin attenuated decrements in FEV ₁ and FVC in normals, but not asthmatics. Attenuation of decrements was seen for FEF _{60p} in asthmatics and for FEF ₅₀ in normals.	Alexis et al. (2000)

Table AX6-13 (cont'd). Studies of Effects on Host Defense, on Drug Effects and Supportive *In Vitro* Studies Relating to Controlled Human Exposure to Ozone^a

Ozone Concentration ^b		Exposure Duration	Activity Level (\dot{V}_E)	Number and Gender of Subjects	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$					
<i>Drug Effects on Inflammation</i> (cont'd)						
0.4	784	2 h	IE (20 min/30 min); workload @ 50 watts	6 M, 9 F healthy NS mean ~31 years of age	Subjects were randomly exposed to FA and to O ₃ before and after 2 wks of treatment with 800 μg budesonide, b.i.d. O ₃ caused significant decrements in FEV ₁ and FVC immediately following exposure, and a small increase in MCh-reactivity and increases in neutrophils and myeloperoxidase in sputum induced at 4 h postexposure. No differences were detected between responses in the two treatment groups.	Nightingale et al. (2000)
0.0 0.4	784	2 h IE 4 × 15 min at $\dot{V}_E = 18$ L/min/m ² BSA 2 exposures: 25% subjects exposed to air-air, 75% to O ₃ -O ₃	21 °C 40% RH	Weak responders 7 M, 13F Strong responders 21 M, 21 F Healthy NS 20 to 59 years old	Significant O ₃ -induced decrements in spirometric lung function. Young adults (<35 years) were significantly more responsive than older individuals (>35 years). Sufentanil, a narcotic analgesic, largely abolished symptom responses and improved FEV ₁ in strong responders. Naloxone, an opioid antagonist, did not affect O ₃ effects in weak responders. <i>See Section AX6.2.5.1</i>	Passannante et al. (1998)
0.4	784	2 h	IE (60 L/min) at 15-min intervals	10 M	Subjects given 800 mg ibuprofen or placebo 90 min before exposure. Subjects given ibuprofen had less of a decrease in FEV ₁ after O ₃ exposure. BAL fluid 1 h after exposure contained similar levels of PMNs, protein, fibronectin, LDH, α -1 antitrypsin, LTB ₄ , and C3a in both ibuprofen and placebo groups. However, subjects given ibuprofen had decreased levels of IL-6, TXB ₂ , and PGE ₂ .	Hazucha et al. (1996)
0.4	784	2 h	IE (15 min/ 30 min); (\dot{V}_E) = 30 L/min/m ² BSA	13 healthy male subjects	Subjects received either placebo or 150 mg indomethacin/day four days prior to O ₃ exposure. Indomethacin treatment attenuated the O ₃ -induced decrease in FEV ₁ , but had no effect on the O ₃ -induced increase in MCh responsiveness.	Ying et al. (1990)
0.35	686	1 h	Continuous exercise; (\dot{V}_E) \approx 60 L/min	14 healthy college-age males	In a placebo- and air-controlled random design, subjects were treated with 75 mg indomethacin every 12 h for 5 days prior to exposure. Indomethacin significantly reduced O ₃ -induced decrements in FEV ₁ and FVC.	Schelegle et al. (1987)

Table AX6-13 (cont'd). Studies of Effects on Host Defense, on Drug Effects and Supportive *In Vitro* Studies Relating to Controlled Human Exposure to Ozone^a

Ozone Concentration ^b		Exposure Duration	Activity Level (\dot{V}_E)	Number and Gender of Subjects	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$					
<i>Supportive In Vitro Studies</i>						
0.01 to 0.10	19.6 to 196	6 h	bronchial epithelial cells	Nonatopic, nonasthmatic and atopic, mild asthmatic bronchial biopsy samples	Exposure to 0.01-0.10 ppm O ₃ significantly decreased the electrical resistance of cells from asthmatic sources, compared to nonasthmatic sources. This range of O ₃ concentrations also increased the movement of ¹⁴ C-BSA across the confluent cultures of "asthmatic" cells to an extent that was greater than that in "nonasthmatic" cells.	Bayram et al. (2002)
0.1	196	24 h	Nasal mucosa	Allergic and nonallergic patients	Increased concentrations of neurokinin A and substance P in medium following O ₃ exposure. Levels of release of both neuropeptides were higher from tissues derived from allergic compared to nonallergic patients.	Schierhorn et al. (2002)
0.2	392	3 h	Nasal epithelial cells and airway epithelial cell line		Synergistic effect of O ₃ exposure on rhinovirus-induced release of IL-8 at 24 h through mechanisms abrogated by antioxidant pretreatment. Additive enhancement of ICAM-1 expression.	Spannhake et al. (2002)
1	1,690	4 h	Macrophage-like THP-1 cells		THP-1 cells were treated with samples of human surfactant protein A (SP-A) genetic variants (SP-A1 and SP-A2) that had been previously exposed to O ₃ . O ₃ -exposed variants differed in their ability to stimulate the production of TNF- α and IL-8 by these cells.	Wang et al. (2002)
0.01 to 0.10	19.6 to 196	6 h	bronchial epithelial cells	Nonatopic, nonasthmatic and atopic, mild asthmatic bronchial biopsy samples	No difference in constitutive release of IL-8, GM-CSF, sICAM-1 and RANTES from cells from nonasthmatic and asthmatic sources, except for detection of RANTES in latter cells only. Increased release of all mediators 24 h after 0.05 to 0.10 ppm O ₃ in "asthmatic" cells, but only IL-8 and sICAM-1 in "nonasthmatic" cells.	Bayram et al. (2001)
0.12 0.24 0.50	235 470 980	3 h	Nasal epithelial cells		Small dose-response activation of NF- κ B coinciding with O ₃ -induced production of free radicals assessed by electron spin resonance. Increased TNF- α at two higher concentrations of O ₃ at 16 h postexposure.	Nichols et al. (2001)

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Table AX6-13 (cont'd). Studies of Effects on Host Defense, on Drug Effects and Supportive *In Vitro* Studies Relating to Controlled Human Exposure to Ozone^a

Ozone Concentration ^b		Exposure Duration	Activity Level (V _E)	Number and Gender of Subjects	Observed Effect(s)	Reference
ppm	µg/m ³					
<i>Supportive In Vitro Studies</i> (cont'd)						
0.06 to 0.20	118 to 392	24 h	Nasal mucosa	105 surgical samples from atopic and nonatopic patients	Increased histamine release correlated with mast cell degranulation. Increased release of IL-1, IL-6, IL-8 and TNF-α following O ₃ exposure at 0.10 ppm. Release of IL-4, IL-6, IL-8 and TNF-α at this concentration was significantly greater from tissues from atopic versus nonatopic patients.	Schierhorn et al. (1999)
0.5	980	1 h	Lung fibroblast cell line with an airway epithelial cell line		BEAS-2B cells in the presence or absence of HFL-1 cells were exposed and incubated for 11 or 23 h. Steady-state mRNA levels of alpha 1 procollagens type I and II, as well as TGFβ1, were increased in O ₃ -exposed co-cultured fibroblasts compared to air controls. Data support interactions between the cell types in the presence and the absence of O ₃ -exposure.	Lang et al. (1998)
0.5	980	1 h	tracheal epithelial cells		O ₃ exposure caused an increase in ROS formation and a decline in PGE ₂ production. No differences in mRNA and protein levels of prostaglandin endoperoxide G/H synthase 2 (PGHS-2) or the rate of its synthesis were detected, suggesting a direct effect of O ₃ -generated oxidants on PGHS-2 activity.	Alpert et al. (1997)
0.4	784	1 h	Lung fibroblasts; airway epithelial cell line		Cells incubated with O ₃ -exposed arachidonic acid (AA) were found to contain DNA single strand breaks. Pretreatment of the exposed AA solution with catalase eliminated the effect on DNA, indicating its dependence on H ₂ O ₂ production. The effect was potentiated by the non-carbonyl component of ozonized AA.	Kozumbo et al. (1996)
0.25 0.50	490 980	6 h	Human nasal epithelial cells		Increased in ICAM-1, IL-6, IL-1, and TNF expression at 0.5 ppm. No increase in IL-8 expression. No increases at 0.25 ppm.	Beck et al. (1994)
0.25 0.50 1.00	490 980 1,960	1 h	Airway epithelial cell line and alveolar macrophages		Increased secretion of IL-6, IL-8, and fibronectin by epithelial cells, even at lowest O ₃ concentration. No O ₃ -induced secretion of these compounds by macrophages.	Devlin et al. (1994)

Table AX6-13 (cont'd). Studies of Effects on Host Defense, on Drug Effects and Supportive *In Vitro* Studies Relating to Controlled Human Exposure to Ozone^a

Ozone Concentration ^b		Exposure Duration	Activity Level (\dot{V}_E)	Number and Gender of Subjects	Observed Effect(s)	Reference
ppm	$\mu\text{g}/\text{m}^3$					
<i>Supportive In Vitro Studies</i> (cont'd)						
0.20 to 1.0	392 to 1960	2 h or 4 h	Airway epithelial cell line		O ₃ caused a dose-related loss in cellular replicative activity at exposure levels that caused minimal cytotoxicity. DNA single strand breaks were not detected. These effects were different from those of H ₂ O ₂ and, thus, not likely related to production of this oxidant within the cells.	Gabrielson et al. (1994).
0.25 0.50 1.00	490 980 1,960	1 h	Airway epithelial cell line		Concentration-dependent increased secretion of PGE ₂ , TXB ₂ , PGF _{2α} , LTB ₄ , and LTD ₄ . More secretion basolaterally than apically.	McKinnon et al. (1993)
0.30 1.00	588 1,960	1 h	Alveolar macrophages		Concentration-dependent increases in PGE ₂ production, and decreases in phagocytosis of sheep erythrocytes. No O ₃ -induced secretion of IL-1, TNF, or IL-6.	Becker et al. (1991)

^aSee Appendix A for abbreviations and acronyms.

^bListed from lowest to highest O₃ concentration.

Inflammatory cells of the lung such as alveolar macrophages (AMs), monocytes, and PMNs also constitute an important component of the pulmonary host defense system. Upon activation, they are capable of generating free radicals and enzymes with microbicidal capabilities, but they also have the potential to damage nearby cells. More recently published studies since the last literature review (U.S. Environmental Protection Agency, 1996) observed changes in T lymphocyte subsets in the airways following exposure to O₃ that suggest components of the immune host defense also may be affected.

AX6.9.2 Inflammatory Responses in the Upper Respiratory Tract

The nasal passages constitute the primary portal for inspired air at rest and, therefore, the first region of the respiratory tract to come in contact with airborne pollutants. Nikasinovic et al. (2003) recently reviewed the literature of laboratory-based nasal inflammatory studies published since 1985. Nasal lavage (NL) has provided a useful tool for assessing O₃-induced inflammation in the nasopharynx. Nasal lavage is simple and rapid to perform, is noninvasive, and allows collection of multiple sequential samples. Graham et al. (1988) reported increased levels of PMNs in the NL fluid of humans exposed to 0.5 ppm O₃ at rest for 4 h on 2 consecutive days, with NL performed immediately before and after each exposure, as well as 22 h after the second exposure. Nasal lavage fluid contained elevated numbers of PMNs at all postexposure times tested, with peak values occurring immediately prior to the second day of exposure. Bascom et al. (1990) exposed subjects with allergic rhinitis to 0.5 ppm O₃ at rest for 4 h, and found increases in PMNs, eosinophils, and mononuclear cells following O₃ exposure. Graham and Koren (1990) compared inflammatory mediators present in both the NL and BAL fluids of humans exposed to 0.4 ppm O₃ for 2 h. Increases in NL and BAL PMNs were similar (6.6- and eightfold, respectively), suggesting a qualitative correlation between inflammatory changes in the lower airways (BAL) and the upper respiratory tract (NL), although the PMN increase in NL could not quantitatively predict the PMN increase in BAL. Torres et al. (1997) compared NL and BAL in smokers and nonsmokers exposed to 0.22 ppm O₃ for 4 h. In contrast to Graham and Koren (1990), they did not find a relationship between numbers or percentages of inflammatory cells (PMNs) in the nose and the lung, perhaps in part due to the variability observed in their NL recoveries. Albumin, a marker of epithelial cell permeability, was increased 18 h later, but not immediately after exposure, as seen by Bascom et al. (1990).

Tryptase, a constituent of mast cells, was also elevated after O₃ exposure at 0.4 ppm for 2 h (Koren et al., 1990). McBride et al. (1994) reported that asthmatic subjects were more sensitive than nonasthmatics to upper airway inflammation at an O₃ concentration (0.24 ppm for 1.5 h with light IE) that did not affect lung or nasal function or biochemical mediators. A significant increase in the number of PMNs in NL fluid was detected in the asthmatic subjects both immediately and 24 h after exposure. Peden et al. (1995) also found that O₃ at a concentration of 0.4 ppm had a direct nasal inflammatory effect, and reported a priming effect on the response to nasal allergen challenge, as well. A subsequent study in dust mite-sensitive asthmatic subjects indicated that O₃ at this concentration enhanced eosinophil influx in response to allergen, but did not promote early mediator release or enhance the nasal response to allergen (Michelson et al., 1999). Similar to observations made in the lower airways, the presence of O₃ molecular “targets” in nasal lining fluid is likely to provide some level of local protection against exposure. In a study of healthy subjects exposed to 0.2 ppm O₃ for 2 h, Mudway and colleagues (1999) observed a significant depletion of uric acid in NL fluid at 1.5 h following exposure.

An increasing number of studies have taken advantage of advances in cell and tissue culture techniques to examine the role of upper and lower airway epithelial cells and mucosa in transducing the effects of O₃ exposure. Many of these studies have provided important insight into the basis of observations made *in vivo*. One of the methods used enables the cells or tissue samples to be cultured at the air-liquid interface (ALI), allowing cells to establish apical and basal polarity, and both cells and tissue samples to undergo exposure to O₃ at the apical surfaces as would occur *in vivo*. Nichols and colleagues (2001) examined human nasal epithelial cells grown at the ALI for changes in free radical production, based on electron spin resonance, and activation of the NF-κB transcription factor following exposure to O₃ at 0.12 to 0.5 ppm for 3 h. They found a dose-related activation of NF-κB within the cells that coincided with O₃-induced free radical production and increased release of TNF-α at levels above 0.24 ppm. These data confirm the importance of this oxidant stress-associated pathway in transducing the O₃ signal within nasal epithelial cells and suggest its role in directing the inflammatory response. In a study of nasal mucosal biopsy plugs, Schierhorn et al. (1999) found that tissues exposed to O₃ at a concentration of 0.1 ppm induced release of IL-4, IL-6, IL-8, and TNF-α that was significantly greater from tissues from atopic patients compared to nonatopic controls. In a subsequent study, this same exposure regimen caused the release of significantly greater amounts of the

neuropeptides, neurokinin A and substance P, from allergic patients, compared to nonallergic controls, suggesting increased activation of sensory nerves by O₃ in the allergic tissues (Schierhorn et al., 2002).

AX6.9.3 Inflammatory Responses in the Lower Respiratory Tract

Seltzer et al. (1986) were the first to demonstrate that exposure of humans to O₃ resulted in inflammation in the lung. Bronchoalveolar lavage fluid (3 h postexposure) from subjects exposed to O₃ contained increased PMNs as well as increased levels of PGE₂, PGF_{2 α} , and TXB₂ compared to fluid from air-exposed subjects. Koren et al. (1989a,b) described inflammatory changes 18 h after O₃ exposure. In addition to an eightfold increase in PMNs, Koren et al. reported a two-fold increase in BAL fluid protein, albumin, and immunoglobulin G (IgG) levels, suggestive of increased epithelial cell permeability. There was a 12-fold increase in IL-6 levels, a two-fold increase in PGE₂, and a two-fold increase in the complement component, C3a. Evidence for stimulation of fibrogenic processes in the lung was shown by significant increases in coagulation components, Tissue Factor and Factor VII (McGee et al., 1990), urokinase plasminogen activator and fibronectin (Koren et al., 1989a). Subsequent studies by Lang et al. (1998), using co-cultures of cells of the BEAS-2B bronchial epithelial line and of the HFL-1 lung fibroblast line, provided additional information about O₃-induced fibrogenic processes. They demonstrated that steady-state mRNA levels of both alpha 1 and procollagens type I and III in the fibroblasts were increased following O₃ exposure and that this effect was mediated by the O₃-exposed epithelial cells. This group of studies demonstrated that exposure to O₃ results in an inflammatory reaction in the lung, as evidenced by increases in PMNs and proinflammatory compounds. Furthermore, they demonstrated that cells and mediators capable of damaging pulmonary tissue are increased after O₃ exposure and provided early suggestion of the potential importance of the epithelial cell-myofibroblast “axis” in modulating fibrotic and fibrinolytic processes in the airways.

Isolated lavage of the mainstream bronchus using balloon catheters or BAL using small volumes of saline have been used to assess O₃-induced changes in the large airways. Studies collecting lavage fluid from isolated airway segments after O₃ exposure indicate increased neutrophils in the airways (Aris et al., 1993; Balmes et al., 1996; Scannell et al., 1996). Other evidence of airway neutrophil increase comes from studies in which the initial lavage fraction

(“bronchial fraction”) showed increased levels of neutrophils (Schelegle et al., 1991; Peden et al., 1997; Balmes et al., 1996; Torres et al., 1997). Bronchial biopsies show increased PMNs in airway tissue (Aris et al., 1993) and, in sputum collected after O₃ exposure, neutrophil numbers are elevated (Fahy et al., 1995).

Increased BAL protein, suggesting O₃-induced changes in epithelial permeability (Koren et al., 1989a, 1991 and Devlin et al., 1991) supports earlier work in which increased epithelial permeability, as measured by increased clearance of radiolabeled diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) from the lungs of humans exposed to O₃, was demonstrated (Kehrl et al., 1987). In addition, Foster and Stetkiewicz (1996) have shown that increased permeability persists for at least 18-20 h and the effect is greater at the lung apices than at the base. In a study of mild atopic asthmatics exposed to 0.2 ppm O₃ for 2 h, Newson et al. (2000) observed a 2-fold increase in the percentage of PMNs present at 6 hours postexposure, with no change in markers of increased permeability as assessed by sputum induction. By 24 h, the neutrophilia was seen to subside while levels of albumin, total protein, myeloperoxidase, and eosinophil cationic protein increased significantly. It was concluded that the transient PMN influx induced by acute exposure of these asthmatic subjects was followed by plasma extravasation and the activation of both PMNs and eosinophils within the airway tissues. Such changes in permeability associated with acute inflammation may provide better access of inhaled antigens, particulates, and other substances to the submucosal region.

Devlin et al. (1991) reported an inflammatory response in subjects exposed to 0.08 and 0.10 ppm O₃ for 6.6 h. Increased numbers of PMNs and levels of IL-6 were found at both O₃ concentrations, suggesting that lung inflammation from O₃ can occur as a consequence of prolonged exposure to ambient levels while exercising. Interestingly, those individuals who had the largest increases in inflammatory mediators in this study did not necessarily have the largest decrements in pulmonary function, suggesting that separate mechanisms underlie these two responses. The absence of a relationship between spirometric responses and inflammatory cells and markers has been reported in several studies, including Balmes et al., 1996; Schelegle et al., 1991; Torres et al., 1997; Hazucha et al., 1996; Blomberg et al., 1999. These observations relate largely to disparities in the times of onset and duration following single exposures. The relationship between inflammatory and residual functional responses following repeated or chronic exposures may represent a somewhat different case (see Section AX6.9.4).

As indicated above, a variety of potent proinflammatory mediators have been reported to be released into the airway lumen following O₃ exposure. Studies of human alveolar macrophages (AM) and airway epithelial cells exposed to O₃ *in vitro* suggest that most mediators found in the BAL fluid of O₃-exposed humans are produced by epithelial cells. Macrophages exposed to O₃ *in vitro* showed only small increases in PGE₂ (Becker et al., 1991). In contrast, airway epithelial cells exposed *in vitro* to O₃ showed large concentration-dependent increases in PGE₂, TXB₂, LTB₄, LTC₄, and LTD₄ (McKinnon et al., 1993) and increases in IL-6, IL-8, and fibronectin at O₃ concentrations as low as 0.1 ppm (Devlin et al., 1994). Macrophages lavaged from subjects exposed to 0.4 ppm (Koren et al., 1989a) showed changes in the rate of synthesis of 123 different proteins, whereas AMs exposed to O₃ *in vitro* showed changes in only six proteins, suggesting that macrophage function was altered by mediators released from other cells. Furthermore, recent evidence suggests that the release of mediators from AMs may be modulated by the products of O₃-induced oxidation of airway lining fluid components, such as human surfactant protein A (Wang et al., 2002).

Although the release of mediators has been demonstrated to occur at exposure concentrations and times that are minimally cytotoxic to airway cells, potentially detrimental latent effects have been demonstrated in the absence of cytotoxicity. These include the generation of DNA single strand breaks (Kozumbo et al., 1996) and the loss of cellular replicative activity (Gabrielson et al., 1994) in bronchial epithelial cells exposed *in vitro*, and the formation of protein and DNA adducts. A highly toxic aldehyde formed during O₃-induced lipid peroxidation is 4-hydroxynonenal (HNE). Healthy human subjects exposed to 0.4 ppm O₃ for 1 h underwent BAL 6 h later. Analysis of lavaged alveolar macrophages by Western blot indicated increased levels of a 32-kDa HNE-protein adduct, as well as 72-kDa heat shock protein and ferritin, in O₃- versus air-exposed subjects (Hamilton et al., 1998). In a recent study of healthy subjects exposed to 0.1 ppm O₃ for 2 h (Corradi et al., 2002), formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a biomarker of reactive oxidant species (ROS)-DNA interaction, was measured in peripheral blood lymphocytes. At 18 h postexposure, 8-OHdG was significantly increased in cells compared to pre-exposure levels, presumably linked to concurrent increases in chemical markers of ROS. Of interest, the increase in 8-OHdG was only significant in a subgroup of subjects with the wild genotype for NAD(P)H:quinone oxidoreductase and the null genotype for glutathione-S-transferase M1, suggesting that polymorphisms in redox

enzymes may confer “susceptibility” to O₃ in some individuals. The generation of ROS following exposure to O₃ has been shown to be associated with a wide range of responses. In a recent study, ROS production by alveolar macrophages lavaged from subjects exposed to 0.22 ppm for 4 h was assessed by flow cytometry (Voter et al., 2001). Levels were found to be significantly elevated 18 h postexposure and associated with several markers of increased permeability. An *in vitro* study of human tracheal epithelial cells exposed to O₃ indicated that generation of ROS resulted in decrease in synthesis of the bronchodilatory prostaglandin, PGE₂, as a result of inactivation of prostaglandin endoperoxide G/H synthase 2 (Alpert et al., 1997). These and similar studies indicate that the responses to products of O₃ exposure in the airways encompass a broad range of both stimulatory and inhibitory activities, many of which may be modulated by susceptibility factors upstream in the exposure process, at the level of compensating for the imposed oxidant stress.

The inflammatory responses to O₃ exposure also have been studied in asthmatic subjects (Basha et al., 1994; Scannell et al., 1996; Peden et al., 1997). In these studies, asthmatics showed significantly more neutrophils in the BAL (18 h postexposure) than similarly exposed healthy individuals. In one of these studies (Peden et al., 1997), which included only allergic asthmatics who tested positive for *Dematophagoides farinae* antigen, there was an eosinophilic inflammation (2-fold increase), as well as neutrophilic inflammation (3-fold increase). In a study of subjects with intermittent asthma that utilized a 2-fold higher concentration of O₃ (0.4 ppm) for 2 h, increases in eosinophil cationic protein, neutrophil elastase and IL-8 were found to be significantly increased 16 h postexposure and comparable in induced sputum and BAL fluid (Hiltermann et al, 1999). Scannell et al. (1996) also reported that IL-8 tended to be higher in post-O₃ exposure BAL in asthmatics compared to nonasthmatics (36 vs. 12 pg/mL, respectively) suggesting a possible mediator for the significantly increased neutrophilic inflammation in asthmatics relative to healthy subjects (12 vs. 4.5%, respectively). In a recent study comparing the neutrophil response to O₃ at a concentration and exposure time similar to those of the latter three studies, Stenfors and colleagues (2002) were unable to detect a difference in the increased neutrophil numbers between 15 mild asthmatic and 15 healthy subjects by bronchial wash at the 6 h postexposure time point. These results suggest that, at least with regard to neutrophil influx, differences between healthy and asthmatic individuals develop gradually following exposure and may not become evident until later in the process.

In another study, mild asthmatics who exhibited a late phase underwent allergen challenge 24 hrs before a 2 h exposure to 0.27 ppm O₃ or filtered air in a cross-over design (Vagaggini et al., 2002). At 6 h postexposure, eosinophil numbers in induced sputum were found to be significantly greater after O₃ than after air. Studies such as these suggest that the time course of eosinophil and neutrophil influx following O₃ exposure can occur to levels detectable within the airway lumen by as early as 6 h. They also suggest that the previous or concurrent activation of proinflammatory pathways within the airway epithelium may enhance the inflammatory effects of O₃. For example, in an *in vitro* study of epithelial cells from the upper and lower respiratory tract, cytokine production induced by rhinovirus infection was enhanced synergistically by concurrent exposure to O₃ at 0.2 ppm for 3 h (Spannhake et al, 2002).

The use of bronchial mucosal biopsies has also provided important insight into the modulation by O₃ of existing inflammatory processes within asthmatics. In a study of healthy and allergic asthmatic subjects exposed to 0.2 ppm O₃ or filtered air for 2 h, biopsies were performed 6 hr following exposure (Bosson et al., 2003). Monoclonal antibodies were used to assess epithelial expression of a variety of cytokines and chemokines. At baseline (air exposure), asthmatic subjects showed significantly higher expression of interleukins (IL)-4 and -5. Following O₃ exposure, the epithelial expression of IL-5, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF) and epithelial cell-derived neutrophil-activating peptide 78 (ENA-78) was significantly greater in asthmatic subjects, as compared to healthy subjects. *In vitro* studies of bronchial epithelial cells derived by biopsy from nonatopic, nonasthmatic subjects and asthmatic subjects also demonstrated the preferential release of GM-CSF and also of regulated on activation, normal T cell-expressed and -secreted (RANTES) from asthmatic cells following O₃ exposure.

The time course of the inflammatory response to O₃ in humans has not been explored fully. Nevertheless, studies in which BAL was performed 1-3 h (Devlin et al., 1990; Koren et al., 1991; Seltzer et al., 1986) after exposure to 0.4 ppm O₃ demonstrated that the inflammatory response is quickly initiated, and other studies (Koren et al., 1989a,b; Torres et al., 1997; Scannell et al., 1996; Balmes et al., 1996) indicated that, even 18 h after exposure, inflammatory mediators such as IL-6 and PMNs were still elevated. However, different markers show peak responses at different times. Ozone-induced increases in IL-8, IL-6, and PGE₂ are greater immediately after O₃ exposure, whereas BAL levels of fibronectin and plasminogen activator are

greater after 18 h. PMNs and some products (protein, Tissue Factor) are similarly elevated both 1 and 18 h after O₃ exposure (Devlin et al., 1996; Torres et al., 1997). Schelegle et al. (1991) found increased PMNs in the “proximal airway” lavage at 1, 6, and 24 h after O₃ exposure, with a peak response at 6 h. In a typical BAL sample, PMNs were elevated only at the later time points. This is consistent with the greater increase 18 h after exposure seen by Torres et al. (1997). In addition to the influx of PMNs and (in allergic asthmatics) eosinophils, lymphocyte numbers in BAL were also seen to be elevated significantly at 6 h following exposure of healthy subjects to 0.2 ppm O₃ for 2 h (Blomberg et al., 1997). Analysis of these cells by flow cytometry indicated the increased presence of CD3+, CD4+ and CD8+ T cell subsets. This same laboratory later demonstrated that within 1.5 h following exposure of healthy subjects to the same O₃ regimen, expression of human leukocyte antigen (HLA)-DR on lavaged macrophages underwent a significant, 2.5-fold increase (Blomberg et al., 1999). The significance of these alterations in immune system components and those in IL-4 and IL-5 expression described above in the studies of Bosson et al. (2003) has not been fully explored and may suggest a role for O₃ in the modulation of immune inflammatory processes.

AX6.9.4 Adaptation of Inflammatory Responses

Residents of areas with high oxidant concentrations tend to have somewhat blunted pulmonary function responses and symptoms to O₃ exposure (Hackney et al., 1976, 1977b, 1989; Avol et al., 1988; Linn et al., 1988). Animal studies suggest that while inflammation may be diminished with repeated exposure, underlying damage to lung epithelial cells continues (Tepper et al., 1989). Devlin et al. (1997) examined the inflammatory responses of humans repeatedly exposed to 0.4 ppm O₃ for 5 consecutive days. Several indicators of inflammation (e.g., PMN influx, IL-6, PGE₂, fibronectin, macrophage phagocytosis) were attenuated after 5 days of exposure (i.e., values were not different from FA). Several markers (LDH, IL-8, total protein, epithelial cells) did not show attenuation, indicating that tissue damage probably continues to occur during repeated exposure. The recovery of the inflammatory response occurred for some markers after 10 days, but some responses were not normalized even after 20 days. The continued presence of markers of cellular injury indicates a persistent but not necessarily perceived response to O₃.

Christian et al. (1998) randomly subjected healthy subjects to a single exposure and to 4 consecutive days of exposure to 0.2 ppm O₃ for 4 h. As reported by others, they found an attenuation of FEV₁, FVC and specific airway resistance when comparing the single exposure with day 4 of the multiday exposure regimen. Similarly, both “bronchial” and “alveolar” fractions of the BAL showed decreased numbers of PMNs and fibronectin concentration at day 4 versus the single exposure, and a decrease in IL-6 levels in the alveolar fraction. Following a similar study design and exposure parameters, but with single day filtered air controls, Jörres et al. (2000) found a decrease in FEV₁ and increases in the percentages of neutrophils and lymphocytes, in concentrations of total protein, IL-6, IL-8, reduced glutathione, ortho-tyrosine and urate in BAL fluid, but no changes in bronchial biopsy histology following the single exposure. Twenty hours after the day 4 exposure, both functional and BAL cellular responses to O₃ were abolished. However, levels of total protein, IL-6, IL-8, reduced glutathione and ortho-tyrosine were still increased significantly. In addition, following the day 4 exposure, visual scores for bronchitis, erythema and the numbers of neutrophils in the mucosal biopsies were increased. Their results indicate that, despite reduction of some markers of inflammation in BAL and measures of large airway function, inflammation within the airways persists following repeated exposure to O₃.

In another study, Frank and colleagues (2001) exposed healthy subjects to filtered air and to O₃ (0.25 ppm, 2 h) on 4 consecutive days each, with pulmonary function measurements being made prior to and following each exposure. BAL was performed on day 5, 24 h following the last exposure. On day 5, PMN numbers remained significantly higher in the O₃ arm compared to air control. Of particular note in this study was the observation that small airway function, assessed by grouping values for isovolumetric FEF₂₅₋₇₅, $\dot{V}_{\max 50}$, and $\dot{V}_{\max 75}$ into a single value, showed persistent reduction from day 2 through day 5. These data suggest that methods to more effectively monitor function in the most peripheral airway regions, which are known to be the primary sites of O₃ deposition in the lung, may provide important information regarding the cumulative effects of O₃ exposure. Holz et al. (2002) made a comparison of early and late responses to allergen challenge following O₃ in subjects with allergic rhinitis or allergic asthma. With some variation, both early and late FEV₁ and cellular responses in the two subject groups were significantly enhanced by 4 consecutive days of exposure to 0.125 ppm O₃ for 3 h.

AX6.9.5 Effect of Anti-Inflammatory and Other Mitigating Agents

Studies have shown that indomethacin, a non-steroidal anti-inflammatory agent (NSAID) that inhibits the production of cyclooxygenase products of arachidonic acid metabolism, is capable of blunting the well-documented decrements in pulmonary function observed in humans exposed to O₃ (Schelegle et al., 1987; Ying et al., 1990). Indomethacin did not alter the O₃-induced increase in bronchial responsiveness to methacholine (Ying et al., 1990). Pretreatment of healthy subjects and asthmatics with indomethacin prior to exposure to 0.4 ppm for 2 h significantly attenuated decreases in FVC and FEV₁ in normals, but not asthmatics (Alexis et al., 2000). Subjects have also been given ibuprofen, another NSAID agent that blocks cyclooxygenase metabolism, prior to O₃ exposure. Ibuprofen blunted decrements in lung function following O₃ exposure (Hazucha et al., 1996). Subjects given ibuprofen also had reduced BAL levels of the cyclooxygenase product PGE₂ and thromboxane B₂, as well as IL-6, but no decreases were observed in PMNs, fibronectin, permeability, LDH activity, or macrophage phagocytic function. These studies suggest that NSAIDs can blunt O₃-induced decrements in FEV₁ with selective (perhaps drug-specific) effects on mediator release and other markers of inflammation.

At least two studies have looked at the effects of the inhaled corticosteroid, budesonide, on the effects of O₃, with differing outcome perhaps associated with the presence of preexistent disease. Nightingale and colleagues (2000) exposed healthy nonsmokers to 0.4 ppm O₃ for 2 h following 2 wk of treatment with budesonide (800 micrograms, twice daily) or placebo in a blinded, randomized cross-over study. This relatively high O₃ exposure resulted in significant decreases in spirometric measures and increases in methacholine reactivity and neutrophils and myeloperoxidase in induced sputum. No significant differences were observed in any of these endpoints following budesonide treatment versus placebo. In contrast, Vagaggini et al. (2001) compared the effects of treatment with budesonide (400 micrograms, twice daily) for 4 wk on the responses of mild asthmatic subjects to exposure to 0.27 ppm O₃ for 2 h. Prior to exposure, at the midpoint and end of exposure, and at 6 h postexposure, FEV₁ was measured and a symptom questionnaire was administered; at 6 h postexposure, sputum was induced. Budesonide treatment did not inhibit the decrement in FEV₁ or alter symptom score, but significantly blunted the increase in percent PMNs and concentration of IL-8 in the sputum. The difference in subject health status between the two studies (healthy versus mild asthmatic) may

suggest a basis for the differing outcomes; however, because of differences in the corticosteroid dosage and O₃ exposure levels, that basis remains unclear.

Holz et al. (2005) investigated the mitigation of O₃-induced inflammatory responses in subjects pretreated with single doses of inhaled fluticasone and oral prednisolone. Eighteen healthy ozone-responders (>10% increase in sputum neutrophils from O₃ exposure) received corticosteroid treatment or placebo 1-h before being exposed for 3-h with IE (15 min periods rest/exercise) to 0.25 ppm O₃. Sputum was collected 3-h post-O₃ exposure. The 18 ozone-responders were selected from 35 screened subjects. Twelve subjects were disqualified from the study (6 produced insufficient sputum and 6 had inadequate neutrophil responses to O₃), the remaining 5 subjects were [presumably] qualified but did not participate. The O₃ exposure caused small changes in FEV₁ (-3.6% ±6.8%) that were not significantly different from baseline or between treatment groups (i.e., prescreening, placebo, fluticasone, and prednisolone). On average, the prescreening and placebo O₃ exposures caused greater than a 9-fold increase in sputum neutrophils relative to baseline levels. Relative to placebo, the inhaled or oral corticosteroids significantly reduced neutrophil levels by 62 and 64%, respectively. Total protein levels were not altered by O₃ or corticosteroid treatment. Authors concluded that the pronounced anti-inflammatory effect of steroids in their study was due to administering the highest single doses shown to be safe and well tolerated. Furthermore, steroids were administered so that maximal plasma level would be reached at approximately the beginning of the O₃ exposure.

Because the O₃ exerts its actions in the respiratory tract by virtue of its strong oxidant activity, it is reasonable to assume that molecules that can act as surrogate targets in the airways, as constituents of either extracellular fluids or the intracellular milieu, could abrogate the effects of O₃. Some studies have examined the ability of dietary “antioxidant” supplements to reduce the risk of exposure of the lung to oxidant exposure. In a study of healthy, nonsmoking adults, Samet and colleagues (2001) restricted dietary ascorbate and randomly treated subjects for 2 weeks with a mixture of vitamin C, α-tocopherol and vegetable cocktail high in carrot and tomato juices or placebo. Responses to 0.4 ppm O₃ for 2 h were assessed in both groups at the end of treatment. O₃-induced decrements in FEV₁ and FVC were significantly reduced in the supplemented group, whereas the inflammatory response, as assessed by percentage neutrophils and levels of IL-6 in BAL fluid, were unaffected by antioxidant supplementation. In a study that

focused on supplementation with a commercial vegetable cocktail high in the carotenoid, lycopene, healthy subjects were exposed for 2 h to 0.4 ppm O₃ after 2 wk of antioxidant supplementation or placebo (Arab et al., 2002). These investigators observed that lung epithelial cell DNA damage, as measured by the Comet Assay, decreased by 20% in supplemented subjects. However, the relationships between the types and levels of antioxidants in airway lining fluid and responsiveness to O₃ exposure is likely to be complex. In another study where differences in ascorbate and glutathione concentrations between healthy and mild asthmatic subjects were exploited, no relationship between antioxidant levels and spirometric or cellular responses could be detected (Mudway et al., 2001).

AX6.9.6 Changes in Host Defense Capability Following Ozone Exposure

Concern about the effect of O₃ on human host defense capability derives from numerous animal studies demonstrating that acute exposure to as little as 0.08 ppm O₃ causes decrements in antibacterial host defenses (see Chapter 5). A study of experimental rhinovirus infection in susceptible human volunteers failed to show any effect of 5 consecutive days of O₃ exposure on the clinical evolution of, or host response to, a viral challenge (Henderson et al., 1988). Healthy men were nasally inoculated with type 39 rhinovirus (10³ TCID₅₀). There was no difference between the O₃-exposed and control groups in rhinovirus titers in nasal secretions, in levels of interferon gamma or PMNs in NL fluid, or in blood lymphocyte proliferative response to rhinovirus antigen. However, subsequent findings that rhinovirus can attach to the intracellular adhesion molecule (ICAM)-1 receptor on respiratory tract epithelial cells (Greve et al., 1989) and that O₃ can up-regulate the ICAM-1 receptor on nasal epithelial cells (Beck et al., 1994) suggest that more studies are needed to explore the possibility that prior O₃ exposure can enhance rhinovirus binding to, and infection of, the nasal epithelium.

In a single study, human AM host defense capacity was measured *in vitro* in AMs removed from subjects exposed to 0.08 and 0.10 ppm O₃ for 6.6 h while undergoing moderate exercise. Alveolar macrophages from O₃-exposed subjects had significant decrements in complement-receptor-mediated phagocytosis of *Candida albicans* (Devlin et al., 1991). The impairment of AM host defense capability could potentially result in decreased ability to phagocytose and kill inhaled microorganisms *in vivo*. A concentration-dependent decrease in phagocytosis of AMs exposed to 0.1 to 1.0 ppm O₃ *in vitro* has also been shown Becker et al. (1991). Although the

evidence is inconclusive at present, there is a concern that O₃ may render humans and animals more susceptible to a subsequent bacterial challenge.

Only two studies (Foster et al., 1987; Gerrity et al., 1993) have investigated the effect of O₃ exposure on mucociliary particle clearance in humans. Foster et al. (1987) had seven healthy subjects inhale radiolabeled particles (5 μm MMAD) and then exposed these subjects to FA or O₃ (0.2 and 0.4 ppm) during light IE for 2 h. Gerrity et al. (1993) exposed 15 healthy subjects to FA or 0.4 ppm O₃ during CE (40 L/min) for 1 h; at 2 h post-O₃ exposure, subjects then inhaled radiolabeled particles (5 μm MMAD). Subjects in both studies had similar pulmonary function responses (average FVC decrease of 11 to 12%) immediately postexposure to 0.4 ppm O₃. The Foster et al. (1987) study suggested there is a stimulatory affect of O₃ on mucociliary clearance; whereas, Gerrity et al. (1993) found that in the recovery period following O₃ exposure, mucus clearance is similar to control, i.e., following a FA exposure. The clearance findings in these studies are complementary not conflicting. Investigators in both studies suggested that O₃-induced increases in mucociliary clearance could be mediated by cholinergic receptors. Gerrity et al. (1993) further suggested that transient clearance increases might be coincident to pulmonary function responses; this supposition based on the return of sRaw to baseline and the recovery of FVC to within 5% of baseline (versus an 11% decrement immediately postexposure) prior to clearance measurements.

Insofar as the airway epithelial surface provides a barrier to entry of biological, chemical and particulate contaminants into the submucosal region, the maintenance of barrier integrity represents a component of host defense. Many of the studies of upper and lower respiratory responses to O₃ exposure previously cited above have reported increases in markers of airway permeability after both acute exposures and repeated exposures. These findings suggest that O₃ may increase access of airborne agents. In a study of bronchial epithelial cells obtained from nonatopic and mild atopic asthmatic subjects (Bayram et al., 2002), cells were grown to confluence and transferred to porous membranes. When the cultures again reached confluence, they were exposed to 0.01-0.1 ppm O₃ or air and their permeability was assessed by measuring the paracellular flux of ¹⁴C-BSA. The increase in permeability 24 h following O₃ exposure was observed to be significantly greater in cultures of cells derived from asthmatics, compared to healthy subjects. Thus, the late increase in airway permeability following exposure of asthmatic

subjects to O₃, of the sort described by Newson et al. (2000), may be related to an inherent susceptibility of ‘asthmatic’ cells to the barrier-reducing effects of O₃.

As referenced in Section 6.9.3, the O₃-induced increase in the numbers of CD8+ T lymphocytes in the airways of healthy subjects reported by Blomberg et al. (1997) poses several interesting questions regarding possible alterations in immune surveillance processes following exposure. In a subsequent study from the same group, Krishna et al. (1998) exposed healthy subjects to 0.2 ppm O₃ or filtered air for 2 h followed by BAL at 6 h. In addition to increased PMNs and other typical markers of inflammation, they found a significant decrease in the CD4+/CD8+ T lymphocyte ratio and in the proportion of activated CD4+ and CD8+ cells. Studies relating to the effects of low-level O₃ exposure on the influx and activity of immunocompetent cells in the upper and lower respiratory tracts may shed additional light on modulation of this important area of host defense.

AX6.10 EXTRAPULMONARY EFFECTS OF OZONE

Ozone reacts rapidly on contact with respiratory system tissue and is not absorbed or transported to extrapulmonary sites to any significant degree as such. Laboratory animal studies suggest that reaction products formed by the interaction of O₃ with respiratory system fluids or tissues may produce effects measured outside the respiratory tract—either in the blood, as changes in circulating blood lymphocytes, erythrocytes, and serum, or as changes in the structure or function of other organs, such as the parathyroid gland, the heart, the liver, and the central nervous system. Very little is known, however, about the mechanisms by which O₃ could cause these extrapulmonary effects. (*See Section 5.4 for a discussion of the systemic effects of O₃ observed in laboratory animals.*)

The results from human exposure studies discussed in the previous criteria documents (U.S. Environmental Protection Agency, 1986, 1996) failed to demonstrate any consistent extrapulmonary effects. Early studies on peripheral blood lymphocytes collected from human volunteers did not find any significant genotoxic or functional changes at O₃ exposures of 0.4 to 0.6 ppm for up to 4 h/day. Limited data on human subjects indicated that 0.5 ppm O₃ exposure for over 2 h caused transient changes in blood erythrocytes and sera (e.g., erythrocyte fragility and enzyme activities), but the physiological significance of these studies remains questionable.

The conclusions drawn from these early studies raise doubt that cellular damage or altered function is occurring to circulating cells at O₃ exposures under 0.5 ppm.

Other human exposure studies have attempted to identify specific markers of exposure to O₃ in blood. For example, Schelegle et al. (1989) showed that PGF_{2α} was elevated after O₃ exposure (0.35 ppm); however, no increase in α-1 protease inhibitor was observed by Johnson et al. (1986). Foster et al. (1996) found a reduction in the serum levels of the free radical scavenger α-tocopherol after O₃ exposure. Vender et al. (1994) failed to find any changes in indices of red blood cell antioxidant capacity (GSH, CAT) in healthy male subjects exposed to 0.16 ppm O₃ for 7.5 h while intermittently exercising. Liu et al. (1997, 1999) used a salicylate metabolite, 2,3-dihydroxybenzoic acid (DHBA), to indicate increased levels of hydroxyl radical which hydroxylates salicylate to DHBA. Increased DHBA levels after exposure to 0.12 and 0.40 ppm suggest that O₃ increases production of hydroxyl radical. The levels of DHBA were correlated with changes in spirometry.

Only a few experimental human studies have examined O₃ effects in other nonpulmonary organ systems besides blood. Early studies on the central nervous system (Gliner et al., 1979, 1980) were not able to find significant effects on motor activity or behavior (vigilance and psychomotor performance) from O₃ exposures at rest up to 0.75 ppm (U.S. Environmental Protection Agency, 1986). Drechsler-Parks et al. (1995) monitored ECG, HR, cardiac output, stroke volume, and systolic time intervals in healthy, older subjects (56 to 85 years of age) exposed to 0.45 ppm O₃ using a noninvasive impedance cardiographic method. No changes were found at this high O₃ concentration after 2 h of exposure while the subjects exercised intermittently at 25 L/min.

Gong et al. (1998) monitored ECG, HR, cardiac output, blood pressure, oxygen saturation, and chemistries, as well as calculating other hemodynamic variables (e.g., stroke volume, vascular resistance, rate-pressure products) in both healthy (n = 6) and hypertensive (n = 10) adult males (41-78 years old). Subjects were exposed for 3 h with IE ($\dot{V}_E \approx 30$ L/min) to FA and on the subsequent day to 0.3 ppm O₃. *See Section AX6.3 for more details about this study.* Statistically significant O₃ effects for both groups combined were increases in HR, rate-pressure product, and the alveolar-to-arterial PO₂ gradient. Gong et al. (1998) suggested that by impairing alveolar-arterial oxygen transfer, the O₃ exposure could potentially lead to adverse cardiac events by decreasing oxygen supply to the myocardium. The subjects in the Gong et al.

(1998) study had sufficient functional reserve so as to not experience significant ECG changes or myocardial ischemia and/or injury. However, Gong et al. (1998) concluded that O₃ exposure could pose a cardiopulmonary risk to persons with preexisting cardiovascular disease, with or without concomitant respiratory disease.

The mechanism for the decrease in arterial oxygen tension in the Gong et al. (1998) study could be due to an O₃ induced ventilation-perfusion mismatch. It is well recognized and accepted that ventilation and perfusion per unit lung volume increase with progression from the apex to the base of the lung in normal upright healthy humans (Inkley and MacIntyre, 1973; Kaneko et al., 1966). But, Foster et al. (1993) demonstrated that even in relatively young healthy adults (26.7 ± 7 years old), O₃ exposure can cause ventilation to shift away from the well perfused basal lung (*see Section AX6.2.3 for more details*). This effect of O₃ on ventilation distribution [and by association the small airways] may persist beyond 24-h postexposure (Foster et al., 1997). Hypoxic pulmonary artery vasoconstriction acts to shift perfusion away from areas of low ventilation and moderate ventilation-perfusion mismatches (Šantak et al., 1998). This arterial vasoconstriction is thought to be mediated by protein kinase C, (Barman, 2001; Tsai et al., 2004). A more generalized (i.e., not localized to poor ventilated areas) increase in pulmonary vascular resistance in response to O₃ exposure would presumably act against the ability of the hypoxic vasoconstriction in mediating ventilation-perfusion mismatches. Acute arterial vasoconstriction has been observed clinically in humans (15 M, 10 F; 34.9 ± 10 years old) exposed for 2-h to O₃ (0.12 ppm) in tandem with fine particulate ($\approx 150 \mu\text{g}/\text{m}^3$) (Brook et al., 2002). Delaunois et al. (1998) also found that O₃ exposure increases total (arterial, capillary, and venous segments) pulmonary vascular resistance in rabbits. Hence, vasoconstriction could potentially be induced by mechanisms other than regional hypoxia during O₃ exposure. This notion is consistent with the O₃-induced reduction in alveolar-arterial oxygen transfer observed by Gong et al. (1998).

Effects of O₃ 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 increased heterogeneity in both regional ventilation and perfusion (Kronenberg et al., 1973). King and Briscoe (1968) examined the distribution of ventilation and perfusion in a group of eight patients with severe COPD (mean FEV₁/FVC = 36%). In these patients, 68% of the lung by volume received 45% of the cardiac output, but only 10% of the total alveolar

ventilation. This distribution of ventilation and perfusion in the patients contributed to their low mean SaO₂ of only 82% (inspired oxygen, 20.93%). Thus, even prior to O₃ exposure, COPD patients may have reduced gas exchange and low SaO₂. Based on model predictions, increasing tidal volume increases the O₃ dose to the proximal alveolar region (Overton et al., 1996). Similarly, with 90% of the alveolar ventilation supplied to only 32% of lung's volume, the well ventilated regions of the COPD lung will be subjected to increased peripheral O₃ doses. Any inflammatory or edematous responses due to O₃ delivered to the well ventilated regions of the COPD lung will likely further inhibit gas exchange and reduce oxygen saturation.

In addition to reducing alveolar-arterial oxygen transfer, O₃ induced vasoconstriction could also acutely induce pulmonary hypertension. Individuals with COPD and coexisting pulmonary hypertension might be subpopulations sensitive to cardiac effects as a consequence of O₃ exposure. Acute pulmonary hypertension could potentially affect cardiac function by increasing right ventricular workloads. Oral or inhaled vasodilators are used in patients to reduce pulmonary artery pressure to improve right ventricular function (Šantak et al., 1998). Consequently, inducing pulmonary vasoconstriction in these patients would perhaps worsen their condition, especially if their right ventricular function was already compromised. There are reduced spirometric and symptom responses to O₃ exposure with age (*see Section AX6.5.1*). It is conceivable, therefore, that COPD patients and elderly individuals (due to their decreased symptomatic responses to ambient O₃) might further increase their risk of adverse cardiopulmonary responses by continuing their exposures beyond the point where young healthy adults might experience discomfort and cease exposure.

AX6.11 OZONE MIXED WITH OTHER POLLUTANTS

Controlled laboratory studies simulating conditions of ambient exposures have failed for the most part to demonstrate significant adverse effects either in healthy subjects, atopic individuals, or in young and middle-aged asthmatics.

AX6.11.1 Ozone and Sulfur Oxides

The difference in solubilities and other chemical properties of O₃ and SO_x seems to limit chemical interaction and formation of related species in the mixture of these pollutants either in

liquid or gaseous phase. Laboratory studies reviewed in the previous O₃ criteria document (Table AX6-14) reported, except for one study (Linn et al., 1994), no significant effects on healthy individuals exposed to mixtures of O₃ and SO₂ or H₂SO₄ aerosol. In the study of Linn et al. (1994), which was a repeated 6.5 h exposure protocol, O₃ alone and O₃ + H₂SO₄ induced significant spirometric decrements in healthy adults and asthmatics, but the magnitude of effects between exposure atmospheres was not significant. Asthmatic and atopic subjects showed somewhat enhanced or potentiated response to mixtures or sequential exposure, respectively; however, the observed effects were almost entirely attributable to O₃ (U.S. Environmental Protection Agency, 1996). Thus, in both healthy and asthmatic subjects, the interactive effects of O₃ and other pollutants were marginal and the response was dominated by O₃.

Since 1994, the only laboratory study that examined the health effects of a mixture of O₃ and sulfur oxides (SO₂ and H₂SO₄) has been that of Linn et al. (1997). In this study, the investigators closely simulated ambient summer haze air pollution conditions in Uniontown, PA as well as controlled the selection of study subjects with the objective to corroborate earlier reported findings of an epidemiologic study of Neas et al. (1995). The subjects were 41 children (22F/19M) 9 to 12 yrs old. Of these, 26 children had history of asthma or allergy. During a 14-day study period, children were exposed on the 4th and 11th day for 4 hrs (IE, 15 min @ avg. \dot{V}_E 22 L/min) in random order to air and a mixture of 0.10 ppm O₃, 0.10 ppm SO₂ and 42 to 198 mg/m³ H₂SO₄ (mean conc. 101 mg/m³, 0.6 mm MMAD). The effects of controlled exposures were assessed by spirometry. Except for exposure days, children used diaries to record activity, respiratory symptoms, location, and PEFR. Thus, every exposure day was bracketed by 3 days of monitoring. Spirometry, PEFR, and respiratory symptoms score showed no meaningful changes between any condition for a total study population. The symptoms score reported by a subset of asthmatic/allergic subjects was positively associated with the inhaled concentration of H₂SO₄ (p = 0.01). However, the reported symptoms were different from the ones reported in the Uniontown study (Neas et al., 1995). Although retrospective statistical power calculations using these study observations for the symptoms score, PEFR, and spirometric endpoints were sufficient to detect with >80% probability the same magnitude of changes as observed in Uniontown, the effects were minimal and not significant. The divergent observations of the two studies have been explained by the presence of an unidentified environmental factor in Uniontown, differences in physico-chemical properties of acid,

Table AX6-14. Ozone Mixed with Other Pollutants^a

Concentration ^b		Pollutant	Exposure Duration and Activity	Exposure Conditions ^c	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³							
<i>Sulfur-Containing Pollutants</i>								
0.0	0	Air	4 h	25 °C	8 M, 7 F	Healthy	Spirometry, PEFR and subjective symptoms score showed no meaningful changes between any condition for a total study population. The symptoms score reported by a subset of asthmatics/allergics were positively associated with inhaled concentration of H ₂ SO ₄ (p = 0.01).	Linn et al. (1997)
0.1 +	196 ^b +	O ₃ +	IE 15' ex/ 15' rest	50% RH	1 M, 4 F	Asthmatic		
0.1 +	262 ^b + 101 ^b	SO ₂ + H ₂ SO ₄	V _E = 22 L/min		10 M, 11 F	Allergic All NS, 9 to 12 yrs. old		
0.2	392	O ₃	90 min.	21 °C	24	Asthmatic NS,	H ₂ SO ₄ /O ₃ /NO ₂ , O ₃ /NO ₂ and clean air produced similar responses	Linn et al. (1995)
0.3	564	NO ₂ H ₂ SO ₄	V _E ≈ 32 L/min IE 3 × 15 min	50% RH	(17 M, 7 F)	11 to 18 years old		
0.12	235	O ₃	1.5 h with IE for	22 °C	22 completed	Asthmatic NS,	No significant pulmonary function changes following any exposure compared to response to clean air. Six additional subjects started the study, but dropped out due to uncomfortable symptoms.	Koenig et al. (1994)
0.30	564	NO ₂	2 consecutive days;	65% RH	study;	adolescents; NS, 12 to		
0.05	70	H ₂ SO ₄ HNO ₃	V _E ≈ 23.2 L/min		15 M, 7 F	19 years old		
0.12	235	O ₃	6.5 h	21 °C	8 M, 7 F	Nonasthmatic NS,	Exposure to O ₃ or O ₃ + H ₂ SO ₄ induced significant decrements in forced expiratory function. Differences between O ₃ and O ₃ + H ₂ SO ₄ were, at best, marginally significant. O ₃ is the more important pollutant for inducing respiratory effects. A few asthmatic and nonasthmatic subjects were more responsive to O ₃ + H ₂ SO ₄ than to O ₃ alone.	Linn et al. (1994)
	100	H ₂ SO ₄	2 consecutive days 50 min exercise/h V _E = 29 L/min	50% RH	13 M, 17 F	Asthmatic NS, 18 to 50 years old		
0.08	157	O ₃	3-h exposure to aerosol,	21 °C	16 M, 14 F	Nonasthmatic NS,	No significant changes in symptoms or lung function with any aerosol/O ₃ combination in the healthy group. In asthmatics, H ₂ SO ₄ preexposure enhanced the small decrements in FVC that occurred following exposure to 0.18 ppm O ₃ . Asthmatics had no significant changes on FEV ₁ with any O ₃ exposures, but symptoms were greater.	Utell et al. (1994) Frampton et al. (1995)
0.12	235	O ₃	followed 24 h later by a	≈40% RH		18 to 45 years old		
0.18	353	O ₃	3-h exposure to O ₃ . IE		10 M, 20 F	Asthmatic NS, 21 to 42 years old		
	100	NaCl	(10 min per half hour)					
	100	H ₂ SO ₄	V _E = 4 times resting (30 to 364 min)					

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Table AX6-14 (cont'd). Ozone Mixed with Other Pollutants^a

Concentration ^b		Pollutant	Exposure Duration and Activity	Exposure Conditions ^c	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³							
<i>Sulfur-Containing Pollutants (cont'd)</i>								
0.12	235	O ₃	1 h (mouthpiece)	22 °C	8 M, 5 F	Allergic asthmatics, 12 to 18 years old, medications withheld for at least 4 h before exposures	Prior exposure to O ₃ potentiated pulmonary function responses to SO ₂ ; decrements in FEV ₁ were -3, -2, and -8% for the air/O ₃ , O ₃ /O ₃ , and O ₃ /SO ₂ exposures, respectively.	Koenig et al. (1990)
0.10	262	SO ₂	IE $\dot{V}_E \approx 30$ L/min 45-min exposure to air or O ₃ , followed by 15-min exposure to O ₃ or SO ₂	75% RH				
0.25	490 1,200 to 1,600	O ₃ H ₂ SO ₄	2 h IE $\dot{V}_E = 30$ to 32 L/min	35 °C 83% RH	9 M	Healthy NS, 19 to 29 years old	No significant effects of exposure to O ₃ alone or combined with H ₂ SO ₄ aerosol.	Horvath et al. (1987)
<i>Nitrogen-Containing Pollutants</i>								
0.0	0	Air	3 h		9 M, 2 F	Atopic asthmatics 22 to 41 yrs. old	Exposure to NO ₂ alone had minimal effects on FEV ₁ . However, O ₃ alone or in combination elicited significantly greater decline in FEV ₁ in a short (3 h) exposure (higher concentrations) than a long (6 h) exposure where the effects were nonsignificant. Allergen challenge inhalation significantly reduced PD ₂₀ FEV ₁ in all short but not the long exposures. No additive or potentiating effects have been observed.	Jenkins et al. (1999)
0.2	392	O ₃	IE 10' ex/ 20' rest					
0.4	752	NO ₂	$\dot{V}_E = 32$ L/min					
0.2+0.4		O ₃ +NO ₂						
0.1	196	O ₃	6 h					
0.2	376	NO ₂	IE 10' ex/ 20' rest					
0.1+0.2		O ₃ +NO ₂	$\dot{V}_E = 32$ L/min T = 25 °C RH = 50%					
0.0	0	Air	2 h	Head only exposure	6 M, 6 F	Healthy NS 19 to 33 yrs. old	For NO ₂ and SO ₂ the absorbed fraction of O ₃ increased relative (to baseline) whereas after O ₃ exposure it decreased. The differences explained by an increased production of O ₃ -reactive substrate in ELF due to inflammation.	Rigas et al. (1997)
0.36	706	O ₃	rest					
0.36	677	NO ₂						
0.75	1,411	NO ₂						
0.36	943	SO ₂						
0.45	883	O ₃	2-h random exposures to	23.6 °C	6 M 2 F	Healthy, NS, 56 to 85 years old	Exercise-induced cardiac output was smaller with O ₃ + NO ₂ exposure compared to FA or O ₃ alone.	Drechsler-Parks et al. (1995)
0.60	1,129	NO ₂	FA, O ₃ , NO ₂ , and O ₃ + NO ₂ ; IE; $\dot{V}_E = 26$ -29 L/min	62% RH				

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Table AX6-14 (cont'd). Ozone Mixed with Other Pollutants^a

Concentration ^b		Pollutant	Exposure Duration and Activity	Exposure Conditions ^c	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³							
<i>Nitrogen-Containing Pollutants (cont'd)</i>								
0.30 0.60	589 1,129	O ₃ NO ₂	2-h exposure to NO ₂ or FA, followed 3 h later by 2-h exposure to O ₃ , IE V _E = 20 L/min/m ² BSA	21 °C 40% RH	21 F	Healthy NS, 18 to 34 years old	No significant effect of NO ₂ exposures on any measured parameter. Sequential exposure of NO ₂ followed by O ₃ induced small but significantly larger decrements in FEV ₁ and FEF ₂₅₋₇₅ than FA/O ₃ sequence. Subjects had increased airway responsiveness to methacholine after both exposures, with significantly greater responsiveness after the NO ₂ /O ₃ sequences than after the FA/O ₃ sequence.	Hazucha et al. (1994)
0.2	392 500	O ₃ HNO ₃ H ₂ O	5 h IE (50 min/h exercise) V _E ≈ 40 L/min 2 h HNO ₃ or H ₂ O fog or air, followed by 1-h break, followed by 3 h O ₃	20 °C 5% RH	6 M, 4 F	Healthy NS, minimum of 10% decrement in FEV ₁ after 3 h exposure to 0.20 ppm O ₃ with 50 min exercise/h	Exposure to HNO ₃ or H ₂ O fog followed by O ₃ induced smaller pulmonary function decrements than air followed by O ₃ .	Aris et al. (1991)
0.0 0.12 0.30 0.12+0.30	0 235 564	Air O ₃ NO ₂ O ₃ + NO ₂	1 h (mouthpiece) IE V _E = 33 L/min V _E = 35 L/min	22 °C 75% RH	5 M, 7 F 9 M, 3 F	Healthy NS, 12 to 17 years old Asthmatic 13 to 18 years old	Findings inconsistent across cohorts and atmospheres. No significant differences in FEV ₁ and R _T between asthmatics and healthy, or between atmospheres and cohorts.	Koenig et al. (1988)
0.30 0.60	589 1,129	O ₃ NO ₂	1 h (mouthpiece) CE V _E ≈ 70 L/min for men V _E ≈ 50 L/min for women		20 M, 20 F	Healthy NS, 21.4 ± 1.5 (SD) years old for F, 22.7 ± 3.3 (SD) years old for M	No differences between responses to O ₃ and NO ₂ + O ₃ for spirometric parameters. Increase in SRaw with NO ₂ + O ₃ was significantly less than for O ₃ alone.	Adams et al. (1987)
0.30 0.30	589 564 200	O ₃ NO ₂ H ₂ SO ₄	2 h CE for 20 min V ≈ 25 L/min	28 to 29 °C 50 to 60% RH	6 M	Healthy subjects, some smokers	Possible small decrease in SG _{aw}	Kagawa (1986)
0.15 0.15	294 284 200	O ₃ NO ₂ H ₂ SO ₄	2 h, 60 min total exercise V ≈ 25 L/min		6 M		Possible small decrease in SG _{aw}	
0.15 0.15 0.15	294 282 393 200	O ₃ NO ₂ SO ₂ H ₂ SO ₄	2 h, 60 min total exercise V ≈ 25 L/min		3 M		Possible small decrease in FEV ₁	

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Table AX6-14 (cont'd). Ozone Mixed With Other Pollutants^a

Concentration ^b			Exposure Duration and Activity	Exposure Conditions ^c	Number and Gender of Subjects	Subject Characteristics	Observed Effect(s)	Reference
ppm	µg/m ³	Pollutant						
<i>Peroxyacetyl Nitrate</i>								
0.45	883	O ₃	2 h	24 °C	8 M, 8 F	Healthy NS; 19 to 26 years old; 51 to 76 years old	No differences between responses to O ₃ alone, O ₃ + NO ₂ , O ₃ + PAN, or O ₃ + NO ₂ + PAN.	Drechsler-Parks et al. (1989)
0.60	1,129	NO ₂	IE	55 to 58% RH	8 M, 8 F			
0.13	644	PAN	$\dot{V}_E \approx 25$ L/min					
0.45	883	O ₃	2 h	22 °C	3 M, 5 F	Healthy NS, mean age = 24 years	No differences between responses to exposure to O ₃ alone and O ₃ + PAN.	Drechsler-Parks et al. (1987b)
0.30	1,485	PAN	IE $\dot{V}_E \approx 27$ L/min	60% RH				
0.485	952	O ₃	2 h	21 °C	10 F	Healthy NS, 19 to 36 years old	Exposure to the mixture of PAN + O ₃ induced decrements in FVC and FEV ₁ averaging 10% greater than observed following exposure to O ₃ alone.	Horvath et al. (1986)
0.27	1,337	PAN	IE $\dot{V}_E \approx 25$ L/min	WBGT				
<i>Particle-Containing Pollutants</i>								
0.0	0	Air	2-2.5 h	22 °C	15 M, 10 F	Healthy NS 18 to 50 yrs. old	Neither systolic nor diastolic pressure has been affected by pollutants exposure despite a significant brachial artery constriction and a reduction in arterial diameter when compared to filtered air (p = 0.03). Absence of flow- and nitroglycerin-mediated brachial artery dilatation.	Brook et al. (2002)
0.12	235 ^b + 153 ^b	O ₃ + PM _{2.5}	rest	30% RH				

^aSee Appendix A for abbreviations and acronyms.

^bGrouped by pollutant mixture.

^cWBGT = 0.7 T_{wet bulb} + 0.3 T_{dry bulb or globe}

differences in time course of exposure and history of previous exposure of children to pollutants, psychological and physiological factors related to chamber exposures, and by other conjectures.

AX6.11.2 Ozone and Nitrogen-Containing Pollutants

Nitrogen dioxide is a key component of the photooxidation cycle and formation of O₃. Both gases are almost invariably present in ambient atmosphere. Compared to O₃, NO_x species have limited solubility and moderate oxidizing capability. Both O₃ and NO₂ are irritants and tissue oxidants and exert their toxic actions through many common mechanisms. The regional dosimetry and the primary sites of action of O₃ and NO₂ overlap but are not the same. Since these gases are relatively insoluble in water, they will likely penetrate into the peripheral airways that are more sensitive to damage than better protected conducting airways. The controlled studies reviewed in the previous O₃ criteria document (Table AX6-14) generally reported only small pulmonary function changes after combined exposures of NO₂ or nitric acid (HNO₃) with O₃, regardless if the interactive effects were potentiating or additive. In two of these studies, the effects reached statistical significance, but they were not coherent. Preexposure with NO₂ potentiated both spirometric and nonspecific airway reactivity response following subsequent O₃ exposure (Hazucha et al., 1994); however, exposure to NO₂ + O₃ mixture blunted SRaw increase as compared to O₃ alone (Adams et al., 1987). As with O₃ and SO_x mixtures, the effects have been dominated by O₃ (U.S. Environmental Protection Agency, 1996).

Combined exposure to O₃ and NO₂ also blunted the exercise-induced increase in cardiac output found with FA and O₃ exposures alone (Drechsler-Parks, 1995). Eight healthy older subjects (56 to 85 years of age) were exposed for 2 h to FA, 0.60 ppm NO₂, 0.45 ppm O₃, and to 0.60 ppm NO₂ + 0.45 ppm O₃ while alternating 20-min periods of rest and exercise. Cardiac output, HR, stroke volume, and systolic time intervals were measured by noninvasive impedance cardiography at the beginning of each exposure, while the subjects were at rest, and again during the last 5 min of exercise. Metabolic exercise data (\dot{V}_E , $\dot{V}O_2$, f_B) also were measured. There were no statistically significant differences between exposures for HR, \dot{V}_E , $\dot{V}O_2$, f_B , stroke volume, or systolic time intervals. Exercise increased cardiac output after all exposures; however, the incremental increase over rest was significantly smaller for the combined O₃ and NO₂ exposures. The authors speculated that nitrate and nitrite reaction products from the interaction of O₃ and NO₂ cross the air/blood interface in the lungs, causing peripheral

vasodilation and a subsequent drop in cardiac output. No major cardiovascular effects of O₃ only exposures have been reported in human subjects (*see Section AX6.10*).

Despite suggested potentiation of O₃ response by NO₂ in healthy subjects, it is unclear what response, and at what dose, either sequential or combined gas exposures will induce in asthmatics. Jenkins et al. (1999) exposed 11 atopic asthmatics in random order to air, 0.1 ppm O₃, 0.2 ppm NO₂, and 0.1 ppm O₃ + 0.2 ppm NO₂ for 6 h (IE for 10 min @ 32 L/min every 40 min). Two weeks later, 10 of these subjects were exposed for 3 h to doubled concentrations of these gases (i.e., 0.2 ppm O₃, 0.4 ppm NO₂, and 0.2 ppm O₃ + 0.4 ppm NO₂) employing the same exercise regimen. Immediately following each exposure, subjects were challenged with allergen (*D. pteronyssinus*) and PD₂₀ FEV₁ was determined. Exposure to NO₂ alone had minimal effects on FEV₁ or airway responsiveness. However, O₃ alone or in combination with NO₂ elicited a significantly ($p < 0.05$) greater decline in FEV₁ in a short (3 h) exposure (higher concentrations) than the long (6 h) exposure, where the effects were not significant. Allergen challenge inhalation significantly ($p = 0.018$ to 0.002) reduced PD₂₀ FEV₁ in all short, but not the long, exposures. No associations were observed between pollutant concentrations and physiologic endpoints. The statistical analyses of these data suggest that the combined effect (O₃ + NO₂) on lung function (FVC, FEV₁) was not significantly greater than the effect of individual gases for 6-h exposures, thus no additive or potentiating effects have been observed. Shorter 3-h exposures using twice as high NO₂ concentrations, however, showed significant FEV₁ decrements following exposures to atmospheres containing O₃. The analysis also suggests that it is the inhaled concentration, rather than total dose, that determines lung airway responsiveness to allergen.

The potential for interaction between O₃ and other gas mixtures was studied by Rigas et al. (1997). They used an O₃ bolus absorption technique to determine how exposures to O₃, NO₂, and SO₂ will affect distribution of O₃ adsorption by airway mucosa. The selected O₃ bolus volume was set to reach lower conducting airways. Healthy young nonsmokers (6F/6M) were exposed on separate days at rest in a head dome to 0.36 ppm O₃, 0.36 ppm NO₂, 0.75 ppm NO₂ and 0.75 ppm SO₂ for 2 h. The rationale for the selection of these gases was their differential absorption. Because O₃ and NO₂ are much less soluble in liquid (i.e., ELF) than SO₂, they are expected to penetrate deeper into the lung than SO₂ which is absorbed more quickly in the epithelial lining fluid of the upper airways. The actual experimental measurements have shown

that during continuous NO₂ and SO₂ exposure the absorbed fraction of an O₃ bolus in lower conducting airways increased relative to baseline, whereas during continuous O₃ exposure the O₃ bolus fraction in lower conducting airways decreased. The authors attempted to explain the differences by suggesting that there may be increased production of an O₃-reactive substrate in epithelial lining fluid due to airway inflammation. As interpreted by the investigators, during NO₂ and SO₂ exposures the substrate was not depleted by these gases and so could react with the O₃ bolus, whereas during O₃ exposure the substrate was depleted, causing the fractional absorption of the O₃ bolus to decrease. Greater absorption in males than females for all gases was attributed to anatomical differences in the bronchial tree.

AX6.11.3 Ozone and Other Pollutant Mixtures Including Particulate Matter

Almost all of the studies published over the last twenty years investigating the health effects of mixtures of O₃ with other air pollutants involved peroxyacetyl nitrate (PAN). These studies on healthy individuals exposed under laboratory conditions came from the Horvath laboratory at UC Santa Barbara (Table AX6-13). In the last of this series of studies, Drechsler-Parks and colleagues (1989) found the same equivocal interaction of O₃ and PAN as in previous studies, which is attributable to O₃ exposure alone (U.S. Environmental Protection Agency, 1996). Subsequently, only a couple of studies have investigated the effects of more complex air pollutant mixtures on human pathophysiology under controlled conditions.

It is not only the interaction between air pollutants in ambient air, but, as Rigas et al. (1997) has found, an uneven distribution of O₃, SO₂, and NO₂ absorption in the lower conducting airways of young healthy subjects may modulate pathophysiologic response as well. Exposure to SO₂ and NO₂ increased, while exposure to O₃ decreased, the absorbing capacity of the airways for O₃. The authors have suggested that SO₂ or NO₂-inflamed airways release additional substrates into the epithelial lining fluid that react with O₃, thus progressively removing O₃ from the airway lumen. This mechanism may explain findings of antagonistic response (e.g., Adams et al., 1987; Dreschler-Parks, 1995) when the two gases are combined in an exposure atmosphere.

The mechanisms by which inhalation exposure to other complex ambient atmospheres containing particulate matter (PM) and O₃ induce cardiac events frequently reported in epidemiologic studies are rarely studied in human subjects under laboratory conditions.

Recently, Brook et al. (2002) have reported changes in brachial artery tone and reactivity in healthy nonsmokers following 2-h exposures to a mixture of 0.12 ppm O₃ and 153 µg/m³ of concentrated ambient PM_{2.5}, and a control atmosphere of filtered air with a trace of O₃, administered in random order. Neither systolic nor diastolic pressure was affected by pollutant exposure despite a significant brachial artery constriction and a reduction in arterial diameter when compared to filtered air (p = 0.03). The authors postulate that changes in arterial tone may be a plausible mechanism of air pollution-induced cardiac events. However, the observations of no changes in blood pressure, and an absence of flow- and nitroglycerin- mediated brachial artery dilatation, cast some doubt on the plausibility of this mechanism. A number of other proposed mechanisms advanced to establish a link between cardiac events due to pollution and changes in vasomotor tone based on the findings of this study are purely speculative.

AX6.12 CONTROLLED STUDIES OF AMBIENT AIR EXPOSURES

A large amount of informative O₃ exposure-effects data has been obtained in controlled laboratory exposure studies under a variety of different experimental conditions. However, laboratory simulation of the variable pollutant mixtures present in ambient air is not practical. Thus, the exposure effects of one or several artificially generated pollutants (i.e., a simple mixture) on pulmonary function and symptoms may not explain responses to ambient air where complex pollutant mixtures exist. Epidemiologic studies, which do investigate ambient air exposures, do not typically provide the level of control and monitoring necessary to adequately characterize short term responses. Thus, controlled exposures to ambient air using limited numbers of volunteers have been used to try and bridge the gap between laboratory and community exposures.

AX6.12.1 Mobile Laboratory Studies

As presented in previous criteria documents (U.S. Environmental Protection Agency, 1986; 1996), quantitatively useful information on the effects of acute exposure to photochemical oxidants on pulmonary function and symptoms responses originated from field studies using a mobile laboratory. These field studies involved subjects exposed to ambient air, FA without pollutants, or FA containing artificially generated concentrations of O₃ that are comparable to

those measured in the ambient environment. As a result, measured pulmonary responses in ambient air can be directly compared to those found in more artificial or controlled conditions. However, the mobile laboratory shares some of the same limitations of stationary exposure laboratories (e.g., limited number of both subjects and artificially generated pollutants for testing). Further, mobile laboratory ambient air studies are dependent on ambient outdoor conditions which can be unpredictable, uncontrollable, and not completely characterizable.

As summarized in Table AX6-15, investigators in California used a mobile laboratory and demonstrated that pulmonary effects of ambient air in Los Angeles residents are related to O₃ concentration and level of exercise (Avol et al., 1983, 1984, 1985a,b,c, 1987; Linn et al., 1980, 1983). Avol et al. (1987) observed no significant pulmonary function or symptoms responses in children (8 to 11 years) engaged in moderate continuous exercise for 1 h while breathing ambient air with an O₃ concentration of 0.113 ppm. However, significant pulmonary function decrements and increased symptoms of breathing discomfort were observed in healthy exercising (1 h continuous) adolescents (Avol et al., 1985a,b), athletes, (Avol et al., 1984, 1985c) and lightly exercising asthmatic subjects (Linn et al., 1980, 1983) at O₃ concentrations averaging from 0.144 to 0.174 ppm. Many of the healthy subjects with a history of allergy appeared to be more responsive to O₃ than “nonallergic” subjects (Linn et al., 1980, 1983), although a standardized evaluation of atopic status was not performed. Comparative studies of exercising athletes (Avol et al., 1984, 1985c) with chamber exposures to oxidant-polluted ambient air (mean O₃ concentration of 0.153 ppm) and purified air containing a controlled concentration of generated O₃ at 0.16 ppm showed similar pulmonary function responses and symptoms, suggesting that acute exposures to coexisting ambient pollutants had minimal contribution to these responses under the typical summer ambient conditions in Southern California. This contention is similar to, but extends, the laboratory finding of no significant difference in pulmonary function effects between O₃ and O₃ plus PAN exposures (Drechsler-Parks, 1987b). *Additional supporting evidence is provided in Section AX6.11.*

AX6.12.2 Aircraft Cabin Studies

Respiratory symptoms and pulmonary function effects resulting from exposure to O₃ in commercial aircraft flying at high altitudes, and in altitude-simulation studies, have been reviewed elsewhere (U.S. Environmental Protection Agency, 1986, 1996). Flight attendants,

Table AX6-15. Acute Effects of Ozone in Ambient Air in Field Studies with a Mobile Laboratory^a

Mean Ozone Concentration ^b		Ambient Temperature ^c (°C)	Exposure Duration	Activity Level (V _E)	Number of Subjects	Observed Effect(s)	Reference
ppm	µg/m ³						
0.113 ± .033	221 ± 65	33 ± 1	1 h	CE (22 L/min)	66 healthy children, 8 to 11 years old	No significant changes in forced expiratory function and symptoms of breathing discomfort after exposure to 0.113 ppm O ₃ in ambient air.	Avol et al. (1987)
0.144 ± .043	282 ± 84	32 ± 1	1 h	CE (32 L/min)	59 healthy adolescents, 12 to 15 years old	Small significant decreases in FVC (-2.1%), FEV _{0.75} (-4.0%), FEV ₁ (-4.2%), and PEFR (-4.4%) relative to control with no recovery during a 1-h postexposure rest; no significant increases in symptoms.	Avol et al. (1985a,b)
0.153 ± .025	300 ± 49	32 ± 2	1 h	CE (53 L/min)	50 healthy adults (competitive bicyclists)	Mild increases in symptoms scores and significant decreases in FEV ₁ (-5.3%) and FVC; mean changes in ambient air were not statistically different from those in purified air containing 0.16 ppm O ₃ .	Avol et al. (1984, 1985c)
0.156 ± .055	306 ± 107	33 ± 4	1 h	CE (38 L/min)	48 healthy adults, 50 asthmatic adults	No significant changes for total symptom score or forced expiratory performance in normals or asthmatics; however, FEV ₁ remained low or decreased further (-3%) 3 h after ambient air exposure in asthmatics.	Linn et al. (1983) Avol et al. (1983)
0.165 ± .059	323 ± 115	33 ± 3	1 h	CE (42 L/min)	60 "healthy" adults (7 were asthmatic)	Small significant decreases in FEV ₁ (-3.3%) and FVC with no recovery during a 1-h postexposure rest; TLC decreased and ΔN ₂ increased slightly.	Linn et al. (1983) Avol et al. (1983)
0.174 ± .068	341 ± 133	33 ± 2	2 h	IE (2 times resting) at 15-min intervals	34 "healthy" adults, 30 asthmatic adults	Increased symptom scores and small significant decreases in FEV ₁ (-2.4%), FVC, PEFR, and TLC in both asthmatic and healthy subjects; however, 25/34 healthy subjects were allergic and "atypically" reactive to polluted ambient air.	Linn et al. (1980, 1983)

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^aSee Appendix A for abbreviations and acronyms.

^bRanked by lowest level of O₃ in ambient air, presented as the mean ± SD.

^cMean ± SD.

because of their physical activities at altitude, tend to receive higher exposures. In a series of hypobaric chamber studies of nonsmoking subjects exposed to 1,829 m (6,000 ft) and O₃ at concentrations of 0.2 and 0.3 ppm for 3 or 4 h (Lategola et al., 1980a,b), increased symptoms and pulmonary function decrements occurred at 0.3 ppm but not at 0.2 ppm.

Commercial aircraft cabin O₃ levels were reported to be very low (average concentration 0.01 to 0.02 ppm) during 92 randomly selected smoking and nonsmoking flights in 1989 (Nagda et al., 1989). None of these flights recorded O₃ concentrations exceeding the 3-h time-weighted average (TWA) standard of 0.10 ppm promulgated by the Federal Aviation Administration (FAA, 1980), probably due to the use of O₃-scrubbing catalytic filters (Melton, 1990). However, in-flight O₃ exposure can still occur because catalytic filters are not necessarily in continuous use during flight. Other factors to consider in aircraft cabins, however, are erratic temperature changes, lower barometric pressure and oxygen pressure, and lower humidity, often reaching levels between 4 and 17% (Rayman, 2002).

Ozone contamination aboard high-altitude aircraft also has been an interest to the U.S. Air Force because of complaints by crew members of frequent symptoms of dryness and irritation of the eyes, nose, and throat and an occasional cough (Hetrick et al., 2000). Despite the lack of ventilation system modifications as used in commercial aircraft, the O₃ concentrations never exceeded the FAA ceiling limit of 0.25 ppm and exceeded the 3-h TWA of 0.10 ppm only 7% of the total monitored flight time (43 h). The authors concluded that extremely low average relative humidity (12%) during flight operations was most likely responsible for the reported symptoms.

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**ANNEX AX7. EPIDEMIOLOGIC STUDIES OF HUMAN
HEALTH EFFECTS ASSOCIATED WITH AMBIENT
OZONE EXPOSURE**

**AX7.1 TABLES OF EPIDEMIOLOGIC STUDIES OF HUMAN HEALTH
EFFECTS ASSOCIATED WITH AMBIENT OZONE EXPOSURE**

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Table AX7-1. Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
United States					
Mortimer et al. (2002) Eight urban areas in the U.S.: St. Louis, MO; Chicago, IL; Detroit, MI; Cleveland, OH; Washington, DC; Baltimore, MD; East Harlem, NY; Bronx, NY Jun-Aug 1993	National Cooperative Inner-City Asthma Study (NCICAS) cohort. This panel study examined 846 asthmatic children aged 4-9 years for O ₃ exposure effects on PEF and morning symptoms using linear mixed effects models and GEE.	8-h avg O ₃ (10 a.m.-6 p.m.): 48 ppb SD not provided. Range of medians across cities shown in a figure: Approximately 34 to 58 ppb. <5% of days exceeded 80 ppb.	PM ₁₀ , NO ₂ , SO ₂	No associations were seen between single or multiday O ₃ measures and any evening outcome measure. The effects of O ₃ on morning outcomes increased over several days with the strongest associations seen for multiday lags. Joint modeling of O ₃ with NO ₂ or SO ₂ resulted in slightly reduced estimates for each pollutant. Closed cohort. Approximately 60% of NCICAS cohort returned diary, characterizations similar to entire cohort.	8-h avg O ₃ (per 15 ppb): % change in morning PEF: Lag 1-5: All areas: -0.59% (-1.05, -0.13) St. Louis: -0.86% (-2.10, 0.38) Chicago: -0.62% (-2.41, 1.16) Detroit: -0.75% (-2.36, 0.86) Cleveland: -0.62% (-2.23, 0.99) Washington: -0.54% (-2.02, 0.93) Baltimore: 0.24% (-0.95, 1.43) East Harlem: -0.73% (-1.63, 0.17) Bronx: -0.69% (-1.54, 0.15) Odds ratios: Morning symptoms: Lag 1-4: All areas: 1.16 (1.02, 1.30) St. Louis: 0.82 (0.59, 1.14) Chicago: 1.09 (0.69, 1.72) Detroit: 1.72 (1.12, 2.64) Cleveland: 1.20 (0.81, 1.79) Washington: 1.11 (0.72, 1.72) Baltimore: 1.19 (0.89, 1.60) East Harlem: 1.22 (0.97, 1.53) Bronx: 1.23 (0.98, 1.54)

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
United States (cont'd)					
Mortimer et al. (2000) Eight urban areas in the U.S.: St. Louis, MO; Chicago, IL; Detroit, MI; Cleveland, OH; Washington, DC; Baltimore, MD; East Harlem, NY; Bronx, NY Jun-Aug 1993	A cohort of 846 asthmatic children aged 4-9 years examined for effects of summer O ₃ exposure on PEF and morning symptoms. Two subgroups were compared: (1) low birth weight or premature and (2) normal birth weight or full-term. Analysis using GEE and linear mixed effects models. Panel study.	8-h avg O ₃ (10 a.m.-6 p.m.): 48 ppb SD not provided. See Mortimer et al. (2002).	None	Low birth weight and premature asthmatic children had greater declines in PEF and higher incidence of morning symptoms than normal birth weight and full-term asthmatic children.	8-h avg O ₃ (per 15 ppb): % change in morning PEF: Low birth weight: Lag 1-5: -1.83% (-2.65, -1.01) Normal birth weight: Lag 1-5: -0.30% (-0.79, 0.19) Interaction term for birth weight, p < 0.05 Odds ratios: Morning symptoms: Low birth weight: Lag 1-4: 1.42 (1.10, 1.82) Normal birth weight: Lag 1-4: 1.09 (0.95, 1.24) Interaction term for birth weight, p < 0.05
Avol et al. (1998) Southern California communities Spring-summer 1994	Three panels of children (age 10-12 years): (1) asthmatic (n = 53); (2) wheezy (n = 54); and (3) healthy (n = 103). Examined for symptoms, medication use, outdoor time, physical activity, and pulmonary function measures in relation to O ₃ exposure, via logistic regression and GLM.	Stratified analysis of low and high O ₃ : Fixed site 1-h max O ₃ : Low: <100 ppb High: >100 ppb Personal 24-h avg O ₃ : Low: ≤15.6 ppb High: ≥32.4 ppb	None	The three groups responded similarly. Few pulmonary function or symptom associations. Asthmatic children had the most trouble breathing, the most wheezing, and the most inhaler use on high O ₃ days in the spring. Ozone levels were considered too low during the period of the study. Noncompliance by subjects may have been a problem. Other analysis methods may have been more appropriate.	Multiple endpoints analyzed. Few consistent or statistically significant responses to O ₃ exposure reported.

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
United States (cont'd)					
Gilliland et al. (2001) 12 Southern California communities Jan-Jun 1996	Time-series study of 1,933 4th grade children (age 9-10 years) followed for school absences. Each absence classified as illness-related or not. Among former, classified into respiratory or gastrointestinal. Respiratory absences further classified into upper or lower. Pollution measured in central site in each town. Analysis of distributed lag effects controlling for time, day of week, and temperature in a Poisson model.	8-h avg O ₃ (10 a.m.-6 p.m.): Levels not reported. Figure depicts mean range of approximately 35 to 55 ppb across the 12 communities.	PM ₁₀ , NO ₂	Ozone strongly associated with illness-related and respiratory absences. PM ₁₀ only associated with upper respiratory absences. Long distributed lag effects for O ₃ raise questions about adequacy of control for seasonal changes.	8-h avg O ₃ (per 20 ppb): % change in school absences: All illness: 62.9% (18.4, 124.1) Nonrespiratory illnesses: 37.3% (5.7, 78.3) Respiratory illnesses: 82.9% (3.9, 222.0) Upper respiratory: 45.1% (21.3, 73.7) Lower respiratory with wet cough: 173.9% (91.3, 292.3)
Linn et al. (1996) Three towns in California: Rubidoux, Upland, Torrance Fall-spring 1992-1993 and 1993-1994	Panel study of 269 school children, each followed for morning/afternoon lung function and symptoms for 1 week in fall, winter, and spring during their 4th and 5th grade school years. Personal exposure monitoring in a subset. Analyzed afternoon symptoms vs. same day pollution and morning symptoms vs. 1-day lag pollution.	24-h avg O ₃ : Personal: 5 ppb SD 3 Range 1-16 Central site: 23 ppb SD 12 Range 3-53	PM _{2.5} , NO ₂	Central site O ₃ correlated with personal exposures, r = 0.61. Ozone effects observed on lung function but only significant for FEV ₁ in one analysis. No effects on symptoms. Ozone effects were not robust to NO ₂ or PM _{2.5} . Power may have been limited by short followup within seasons (limiting both person-days and variability in exposures).	Change in lung function (per ppb): FEV ₁ next morning: -0.26 mL (SE 0.25), p = 0.30 FEV ₁ afternoon: -0.18 mL (SE 0.26), p = 0.49 FEV ₁ crossday difference: -0.58 mL (SE 0.23), p = 0.01 FVC next morning: -0.21 mL (SE 0.22), p = 0.34 FVC afternoon: -0.20 mL (SE 0.29), p = 0.48 FVC crossday difference: -0.25 mL (SE 0.25), p = 0.32

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
United States (cont'd)					
Ostro et al. (2001) Central Los Angeles and Pasadena, CA Aug-Oct 1993	Panel study of 138 African-American children aged 8-13 years with doctor diagnosed asthma requiring medication in past year followed for daily respiratory symptoms and medication use. Lags of 0 to 3 days examined.	1-h max O ₃ : Los Angeles: 59.5 ppb SD 31.4 Pasadena: 95.8 ppb SD 49.0	PM ₁₀ , NO ₂ , pollen, mold	Correlation between PM ₁₀ and O ₃ was r = 0.35. Significant O ₃ effect seen for extra medication use (above normal use). No O ₃ effect on symptoms in expected direction observed. Inverse association seen for cough. PM ₁₀ effects seen at a lag of 3 days. Time factors not explicitly controlled in analysis; may have led to confounding of O ₃ effects.	1-h max O ₃ (per 40 ppb): Odds ratios: Extra medication use: Lag 1: 1.15 (1.12, 1.19) Respiratory symptoms: Shortness of breath: Lag 3: 1.01 (0.92, 1.10) Wheeze: Lag 3: 0.94 (0.88, 1.00) Cough: Lag 3: 0.93 (0.87, 0.99)
Delfino et al. (2003) Los Angeles, CA Nov 1999-Jan 2000	A panel study of 22 Hispanic children with asthma aged 10-16 years. Filled out symptom diaries in relation to pollutant levels. Analysis using GEE model.	1-h max O ₃ : 25.4 ppb SD 9.6	NO ₂ , SO ₂ , CO, volatile organic compounds, PM ₁₀	Support the view that air toxics in the pollutant mix from traffic may have adverse effects on asthma in children.	1-h max O ₃ (per 14.0 ppb): Odds ratio: Symptoms interfering with daily activities: Lag 0: 1.99 (1.06, 3.72)
Delfino et al. (1997a) Alpine, CA May-Aug1994	Panel study of 22 asthmatics aged 9-46 years followed for respiratory symptoms, morning-afternoon PEF, and β ₂ agonist inhaler use. Personal O ₃ measured for 12 h/day using passive monitors. GLM mixed model.	Ambient: 12-h avg O ₃ (8 a.m.-8 p.m.): 64 ppb SD 17 Personal: 12-h avg O ₃ : (8 a.m.-8 p.m.) 18 ppb SD 14	PM ₁₀ , pollen, fungi	No O ₃ effects observed.	No quantitative results for O ₃ .

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
United States (cont'd)					
Delfino et al. (1998a) Alpine, CA Aug-Oct 1995	A panel of 24 asthmatics aged 9-17 years followed for daily symptoms. Analysis using GEE model.	1-h max O ₃ : 90 ppb SD 18	PM ₁₀	Asthma symptoms were significantly associated with both ambient O ₃ and PM ₁₀ in single-pollutant models. Ozone effects generally robust to PM ₁₀ . Current day O ₃ effects strongest in asthmatics not on anti-inflammatory medication. Effects of O ₃ and PM ₁₀ were largely independent. The largest effects for PM ₁₀ were seen for a 5-day distributed lag. For O ₃ effects, there were no lag day effects; current day results showed the greatest effect.	1-h max O ₃ (per 58 ppb): Odds ratios: O ₃ only model: Lag 0: 1.54 (1.02, 2.33) O ₃ with PM ₁₀ model: Lag 0: 1.46 (0.93, 2.29)
Delfino et al. (2004) Alpine, CA Aug-Oct 1999, Apr-Jun 2000	Panel study of 19 asthmatic children (age 9-17 years) followed daily for 2 weeks to determine relationship between air pollutants, namely PM, and FEV ₁ . Linear mixed model used for analysis.	8-h max O ₃ : 62.8 ppb SD 15.1 IQR 22.0	PM _{2.5} , PM ₁₀ , NO ₂	Significant declines in FEV ₁ associated with various PM indices (personal, indoor home, etc.), but not ambient O ₃ levels.	No quantitative results for O ₃ .
Delfino et al. (1996) San Diego, CA Sep-Oct 1993	Panel study of 12 well-characterized moderate asthmatics aged 9-16 years (7 males, 5 females) followed over 6 weeks for medication use and respiratory symptoms. Allergy measured at baseline with skin prick tests. Personal O ₃ measured with passive badge. Analysis with GLM mixed model.	Ambient: 1-h max O ₃ : 68 ppb SD 30 Ambient: 12-h avg O ₃ : 43 ppb SD 17 Personal: 12-h avg O ₃ : 11.6 ppb SD 11.2	PM _{2.5} , SO ₄ ²⁻ , H ⁺ , HNO ₃ , pollen, fungal spores	No effect of ambient O ₃ on symptom score. Personal O ₃ significant for symptoms, but effect disappeared when confounding day-of-week effect was controlled with weekend dummy variable. β ₂ inhaler used among 7 subjects was significantly related to personal O ₃ . Results of this small study suggest the value of personal exposure data in providing more accurate estimates of exposures. However, nearly 50% of personal O ₃ measurements were below limits of detection, diminishing value of these data. Pollen and fine particulate (low levels) were not associated with any of the outcomes.	Change in β ₂ -agonist inhaler use (per ppb personal O ₃): 0.0152 puffs/day (SE 0.0075), p = 0.04

AX7-13

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
United States (cont'd)					
Chen et al. (2000) Washoe County, NV 1996-1998	Time-series study of school absenteeism examined among 27,793 students (kindergarten to 6th grade) from 57 elementary schools. First-order autoregression models used to assess relationship between O ₃ and school absenteeism after adjusting for weather, day of week, month, holidays, and time trends. Ozone levels from the current day, and cumulative lags of 1-14 days, 1-21 days, and 1-28 days examined.	1-h max O ₃ : 37.45 ppb SD 13.37	PM ₁₀ , CO	Multipollutant models were examined. Ozone concentrations in the preceding 14 days were significantly associated with school absenteeism for students in grades 1 through 6, but not those in kindergarten. Both PM ₁₀ and CO concentrations on the concurrent day were associated with school absenteeism, but the estimate for PM ₁₀ was a negative value.	1-h max O ₃ (per 50 ppb): Total absence rate: O ₃ with PM ₁₀ and CO model: Lag 1-14: 3.79% (1.04, 6.55)
Newhouse et al. (2004) Tulsa, OK Sep-Oct 2000	Panel study of 24 subjects aged 9-64 years with physician diagnosis of asthma. Performed PEF twice daily (morning and afternoon), and reported daily respiratory symptoms and medication use. Forward stepwise multiple regression models and Pearson correlation analyses.	24-h avg O ₃ : 30 ppb Range 10-70	PM _{2.5} , CO, SO ₂ , pollen, fungal spores	Among ambient air pollutants, O ₃ seemed to be most significant factor. Morning PEF values significantly associated with average and maximum O ₃ levels on the previous day. Individual symptoms, including wheezing, headache, and fatigue, also significantly related to average and maximum daily O ₃ . Multiple regression analyses produced complex models with different predictor variables for each symptom.	Pearson correlation coefficient: Morning PEF: Mean O ₃ levels: Lag 1: -0.274, p < 0.05 Maximum O ₃ levels: Lag 1: -0.289, p < 0.05

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
United States (cont'd)					
Ross et al. (2002) East Moline, IL and nearby communities May-Oct 1994	Panel study of 59 asthmatics aged 5-49 years recruited. 19 lost to follow-up, yielding study population of 40. Assessment of PEF and respiratory symptoms. Analytical methods unclear in terms of control for time factors.	8-h max O ₃ : 41.5 ppb SD 14.2 IQR 20	PM ₁₀ , SO ₂ , NO ₂ , pollen, fungi	Saw significant associations between O ₃ and both PEF declines and symptom increases. Most but not all effects remained after controlling for temperature, pollen and fungi. Ozone effect on morning PEF disappeared after adjusting for temperature. No PM ₁₀ effects observed.	8-h max O ₃ (per 20 ppb): Change in PEF (L/min): Morning: Lag 0-1: -2.29 (-4.26, -0.33) Afternoon: Lag 0: -2.58 (-4.26, -0.89) Symptom score (on scale of 0-3): Morning: Lag 1-3: 0.08 (0.03, 0.13) Afternoon: Lag 1-3: 0.08 (0.04, 0.12)
Neas et al. (1995) Uniontown, PA Summer 1990	Panel study of 83 4th and 5th grade children reported twice daily PEF and the presence of cold, cough, or wheeze. Relationship to pollutants was analyzed by an autoregressive linear regression model/GEE. The number of hours each child spent outdoors during the preceding 12-h period was evaluated.	12-h avg O ₃ : Daytime (8 a.m.-8 p.m.): 50.0 ppb Overnight (8 p.m.-8 a.m.): 24.5 ppb	SO ₂ , PM ₁₀ , H ⁺	Evening cough was associated with O ₃ levels weighted by hours spent outdoors during the prior 12 h. A decrease in PEF was associated with O ₃ levels weighted by hours spent outdoors. When particle-strong acidity was added to the model, the decrement was decreased and no longer significant.	12-h avg O ₃ (per 30 ppb): Evening PEF: -2.24 L/min (-4.43, -0.05) Odds ratio: Evening cough: 1.36 (0.86, 2.13) Concentration weighted by proportion of time spent outdoors during prior 12 h: Evening PEF: -2.79 L/min (-6.69, -1.12) Odds ratio: Evening cough: 2.20 (1.02, 4.75)

AX7-15

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
United States (cont'd)					
Neas et al. (1999) Philadelphia, PA Jul-Sep 1993	Panel study of 156 children aged 6-11 years at two summer camps followed for twice-daily PEF. Analysis using mixed effects models adjusting for autocorrelated errors.	Daytime 12-h avg O ₃ (9 a.m-9 p.m.): SW camp: 57.5 ppb IQR 19.8 NE camp: 55.9 ppb IQR 21.9	H ⁺ , SO ₄ ²⁻ , PM _{2.5} , PM ₁₀ , PM _{10-2.5}	Some O ₃ effects detected as well as PM effects. Similar O ₃ -related decrements observed in both morning and afternoon PEF. Ozone effects not robust to SO ₄ ²⁻ in two-pollutant models, whereas SO ₄ ²⁻ effects relatively robust to O ₃ .	12-h avg O ₃ (per 20 ppb): Morning and evening PEF: O ₃ only models: Lag 0: -1.38 L/min (-2.81, 0.04) Lag 1-5: -2.58 L/min (-4.81, -0.35) O ₃ with SO ₄ ²⁻ model: Lag not specified: -0.04 L/min
Gent et al. (2003) Southern New England Apr-Sep 2001	Panel study of 271 children (age <12 years) with active, doctor-diagnosed asthma followed over 183 days for respiratory symptoms. For analysis, cohort split into two groups: 130 who used maintenance medication during follow-up and 141 who did not, on assumption that medication users had more severe asthma. Logistic regression analyses performed.	1-h max O ₃ : 58.6 ppb SD 19.0 8-h max O ₃ : 51.3 ppb SD 15.5	PM _{2.5}	Correlation between 1-h max O ₃ and daily PM _{2.5} was 0.77 during this warm-season study. Large numbers of statistical tests performed. Significant associations between symptoms and O ₃ seen only in medication users, a subgroup considered to be more sensitive. PM _{2.5} significant for some symptoms, but not in two-pollutant models. Ozone effects generally robust to PM _{2.5} . Study limitations include limited control for meteorological factors and the post-hoc nature of the population stratification by medication use.	1-h max O ₃ (per 50 ppb): Odds ratios: Regular medication users (n = 130): Chest tightness: O ₃ only model: Lag 1: 1.26 (1.00, 1.48) O ₃ with PM _{2.5} model: Lag 1: 1.42 (1.14, 1.78) Shortness of breath: O ₃ only model: Lag 1: 1.22 (1.02, 1.45)

AX7-16

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
United States (cont'd)					
Korrick et al. (1998) Mount Washington, NH Summers 1991, 1992	Cross-sectional study evaluating the acute effects of ambient O ₃ on pulmonary function of exercising adults. 530 hikers (age 15-64 years) monitored before and after their hike. Analysis using a general linear regression model.	Avg of hourly O ₃ during each hike: 40 ppb SD 12 Range 21-74	PM _{2.5} , smoke, acidity	With prolonged outdoor exercise low-level exposures to O ₃ were associated with significant effects on pulmonary function. Hikers with asthma had a 4-fold greater responsiveness to exposure to O ₃ .	% change in lung function (per 50 ppb O ₃): FEV ₁ : -2.6% (-4.7, -0.4) FVC: -2.2% (-3.5, -0.8)
Thurston et al. (1997) Connecticut River Valley, CT June 1991, 1992, 1993	Panel study of children (age 7-13 years) with moderate-to-severe asthma followed for medication use, lung function, and medical symptoms at a summer asthma camp for 1 week in 1991 (n = 52), 1992 (n = 58), and 1993 (n = 56). Analysis was conducted using both Poisson modeling and GLM.	1-h max O ₃ : 1991: 114.0 ppb 1992: 52.2 ppb 1993: 84.6 ppb 1991-1993: 83.6 ppb	H ⁺ , SO ₄ ²⁻	Ozone was most consistently associated with acute asthma exacerbation, chest symptoms, and lung function decrements. Pollen was poorly associated with any adverse effect. Consistent results were obtained between the aggregate and individual analyses.	1-h max O ₃ (per 83.6 ppb): Relative risks: β ₂ -agonist use: 1.46 (t = 3.57) Chest symptoms: 1.50 (t = 4.77) Change in PEF (per ppb): -0.096 L/min (t = 1.92)
Naeher et al. (1999) Vinton, VA Summers 1995, 1996	Panel study evaluated the relationship between O ₃ and daily change in PEF studied in a sample of 473 nonsmoking women aged 19-43 years who recently delivered babies. PEF performed twice daily for a 2-week period. Mixed linear random coefficient model.	8-h max O ₃ : 53.69 ppb Range 17.00-87.63 24-h avg O ₃ : 34.87 ppb Range 8.74-56.63	PM _{2.5} , PM ₁₀ , SO ₄ ²⁻ , H ⁺	Ozone was the only exposure related to evening PEF with 5-day cumulative lag exposure showing the greatest effect.	24-h avg O ₃ (per 30 ppb): Morning PEF: Lag 1: -2.13 L/min (-4.72, 0.46) Lag 1-3: -3.60 L/min (-7.66, 0.46) Evening PEF: Lag 0: -2.49 L/min (-5.02, 0.04) Lag 1-5: -7.65 L/min (-13.0, -2.25)

AX7-17

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Canada					
Brauer et al. (1996) Fraser Valley, British Columbia, Canada Jun-Aug 1993	Panel study of 58 berry pickers aged 10-69 years had lung function measured before and after a series of outdoor work shifts (average duration = 11 h) over 59 days. Analysis using pooled regression with subject-specific intercepts, with and without temperature control.	1-h max O ₃ : 40.3 ppb SD 15.2 Work shift O ₃ : 26.0 ppb SD 11.8	PM _{2.5} , SO ₄ ²⁻ , NO ₃ ⁻ , NH ₄ ⁺ , H ⁺	End shift FEV ₁ and FVC significantly diminished in relation to O ₃ levels. PM _{2.5} also related to lung function declines, but O ₃ remained significant in two-pollutant models. Next morning lung function remained diminished following high O ₃ days. Ozone effects still evident at or below 40 ppb. There was an overall decline of lung function of roughly 10% over course of study, suggesting subchronic effect. Levels of other pollutants low during study.	Change in lung function (per ppb 1-h max O ₃): Endshift lung function: FEV ₁ : -3.8 mL (SE 0.4) FVC: -5.4 mL (SE 0.6) Next morning function: FEV ₁ : -4.5 mL (SE 0.6) FVC: -5.2 mL (SE 0.7)
Brauer and Brook (1997) Fraser Valley, British Columbia, Canada Jun-Aug 1993	Additional analysis of Brauer et al. (1996) with personal exposure presented for three groups, stratified by time spent outdoors. Group 1: 25 individuals who spent most of the day indoors. Group 2: 25 individuals who spent much of the day indoors, but still spent several daylight hours outdoors. Group 3: 15 individuals who spent the entire work day outdoors.	1-h max O ₃ : Ambient: 40 ppb SD 15 Range 13-84	PM _{2.5} , SO ₄ ²⁻ , NO ₃ ⁻ , NH ₄ ⁺ , H ⁺	Group 1: 9.0% sampling time (24-h) outdoors. Personal to ambient O ₃ ratio was 0.28. Group 2: 25.8% sampling time (24-h) outdoors. Personal to ambient O ₃ ratio was 0.48. Group 3: 100% sampling time (11-h work shift) outdoors. Personal to ambient O ₃ ratio was 0.96. One of the first direct demonstrations that magnitude of personal exposure to O ₃ is related to amount of time spent outdoors. Further showed that, on average, outdoor fixed O ₃ monitors were representative of day-to-day changes in O ₃ exposure experienced by the study population.	Same outcomes as reported in Brauer et al. (1996).

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Europe					
Scarlett et al. (1996) Surrey, England Jun-Jul 1994	Panel study examined 154 children aged 7 years in a primary school next to a major motorway for O ₃ exposure effects on PEF _{0.75} , FVC, and FEV ₁ using autoregression for % change in function.	8-h max O ₃ : 50.7 ppb SD 24.48	PM ₁₀ , NO ₂ , pollen	No significant association was seen between pulmonary function measures and O ₃ levels. No pollen effects.	Change in lung function (per ppb O ₃ weighted by inverse of variance): FEV _{0.75} : Lag 1: 0.01 mL (-0.12, 0.13) FVC: Lag 1: 0.07 mL (-0.09, 0.23) FEV _{0.75} /FVC: Lag 1: -0.1% (-5.1, 4.8)
Ward et al. (2002) Birmingham and Sandwell, England Jan-Mar 1997 May-Jul 1997	A panel study of 162 children (age 9 years at time of enrollment in Sept 1996). 39 of 162 children (24%) reported wheezing in the past 12 months. Examined association of ambient acid species with PEF and symptoms. Single-day lags of 0 to 3 days and a 7-day cumulative lag were investigated. Linear regression used for PEF and logistic regression used for symptoms.	24 h-avg O ₃ : Winter: Median 13.0 ppb Range 2-33 Summer: Median 22.0 ppb Range 10-41	PM ₁₀ , PM _{2.5} , SO ₂ , H ⁺ , Cl ⁻ , HCl, HNO ₃ , NH ₃ , NH ₄ ⁺ , NO ₃ ⁻ , SO ₄ ²⁻	Pollutants levels were generally low, even in the summer. Significant associations were noted between respiratory health outcomes and air pollutants, but no consistent patterns were identified. The association between O ₃ and PEF was generally negative in the summer and positive in the winter. More associations between O ₃ and symptoms were observed in the winter. Ozone was associated with a significant increase in cough, shortness of breath, and wheeze during the winter. Results did not indicate that children with atopy or a history of recent wheezing were more susceptible to short-term effects of air pollutants.	24-h avg O ₃ (per 21.5 ppb for winter; per 10.2 ppb for summer): Change in PEF (L/min): Morning (lag 0-6): Winter: 17.53 (6.56, 28.52) Summer: -5.66 (-11.21, -0.09) Afternoon (lag 0-6): Winter: 0.28 (-9.03, 9.79) Summer: -0.14 (-5.34, 5.04) Odds ratios: Symptoms: Cough (lag 0-6): Winter: 0.88 (0.42, 1.81) Summer: 0.95 (0.76, 1.19) Shortness of breath (lag 0-6): Winter: 2.79 (1.56, 4.95) Summer: 1.35 (0.95, 1.94) Wheeze (lag 0-6): Winter: 1.59 (0.77, 3.31) Summer: 0.88 (1.38, 0.57)

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Europe (cont'd)					
Taggart et al. (1996) Runcorn and Widnes in NW England Jul-Sep 1993	Panel study investigated the relationship of asthmatic bronchial hyperresponsiveness and pulmonary function with summertime ambient air pollution among 38 adult nonsmoking asthmatics (age 18-70 years) using log-linear models. Analysis limited to investigation of within subject variance of the dependent variables.	1-h avg O ₃ : Maximum 61 µg/m ³ 24-h avg O ₃ : Maximum 24.5 µg/m ³	SO ₂ , NO ₂ , smoke	No association found for O ₃ . Changes in bronchial hyperresponsiveness were found to correlate significantly with change in the levels of 24-h mean SO ₂ , NO ₂ , and smoke.	24-h avg O ₃ (per 10 µg/m ³): % change in bronchial hyperresponsiveness: Lag 1: 0.3% (-16.6, 20.6) Lag 2: 2.6% (-22.1, 34.9)
Desqueyroux et al. (2002a) Paris, France Nov 1995-Nov 1996	Panel study of 60 severe asthmatics (mean age 55 years) were monitored by their physicians for asthma attacks. Asthma attacks were based on medical data collected by a pulmonary physician at time of clinical examination. Analysis using GEE.	8-h avg O ₃ (10 a.m.-6 p.m.): Summer: 41 µg/m ³ SD 18 Winter: 11 µg/m ³ SD 10	PM ₁₀	Significant associations between PM ₁₀ , O ₃ , and incident asthma attacks were found. Low O ₃ levels raise plausibility concerns.	8-h avg O ₃ (per 10 µg/m ³): Odds ratio: Lag 2: 1.20 (1.03, 1.41)
Desqueyroux et al. (2002b) Paris, France Oct 1995-Nov 1996	Panel study of 39 adult patients with severe COPD (mean age 67 years) followed over 14 months by physicians for exacerbations. Logistic regression with GEE, examining exposure lags of 0 to 5 days.	8-h avg O ₃ (10 a.m.-6 p.m.): Summer: 41 µg/m ³ SD 18 Winter: 11 µg/m ³ SD 10	PM ₁₀ , SO ₂ , NO ₂	50 COPD exacerbations observed over follow-up period. 1-, 2-, and 3-day lag O ₃ significantly related to exacerbations. No other pollutants significant. Low O ₃ levels raise plausibility and confounding concerns.	8-h avg O ₃ (per 10 µg/m ³): Odds ratio: Lag 1: 1.56 (1.05, 2.32) Effects appeared larger among smokers and those with worse gas exchange lung function.

AX7-20

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Europe (cont'd)					
Just et al. (2002) Paris, France Apr-Jun 1996	Panel study of 82 medically diagnosed asthmatic children (mean age 10.9 years) followed for O ₃ exposure and PEF, asthmatic attacks, cough, supplementary use of β ₂ -agonists, and symptoms of airway irritation. Analysis by GEE.	24-h avg O ₃ : 58.9 μg/m ³ SD 24.5 Range 10.0-121.0	PM ₁₀ , NO ₂	In asthmatic children, O ₃ exposure was related to the occurrence of asthma attacks and additional bronchodilator use. O ₃ was the only pollutant associated with changes in lung function, as shown by an increase in PEF variability and decrease in PEF.	24-h avg O ₃ (per 10 μg/m ³): % change in daily PEF variability: Lag 0-2: 2.6%, p = 0.05 Odds ratio: Supplementary use of β ₂ -agonist on days on which no steroids were used: Lag 0: 1.41 (1.05, 1.89)
Lagerkvist et al. (2004) Brussels, Belgium May 2002	Panel study of 57 children (mean age 10.8 years) stratified by swimming pool attendance. Pulmonary function test performed and Clara cell protein levels measured in blood before and after light exercise outdoors for 2 h. Analysis using Student's t test and Pearson correlation test. For dose calculations, O ₃ levels indoors assumed to be 50% of the mean outdoor O ₃ concentration.	Daytime outdoor O ₃ : Range 77-116 μg/m ³ Exposure dose: Range 352-914 μg/m ³ ·h	None	Ozone levels did not have any adverse effect on FEV ₁ after 2 h of outdoor exercise. In addition, no significant differences were observed between Clara cell protein levels before and after exercise. A marginally significant positive correlation between ambient O ₃ dose and Clara cell protein levels observed among the nonswimmers, indicating increased antioxidant activity following O ₃ exposure in this group. The lack of a clear relationship between Clara cell protein levels and O ₃ dose may be attributable to the short period of time between measurements and diurnal variability of the protein levels.	Pearson correlation: O ₃ exposure dose and Clara cell protein levels in serum: All subjects (n = 54): r = 0.17, p = 0.21 Nonswimmers (n = 33): r = 0.34, p = 0.06 Swimmers (n = 21): r = -0.08, p = 0.74

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Europe (cont'd)					
Schindler et al. (2001) Eight communities of Switzerland May-Sep 1991	A random sample of 3,912 adult never-smokers, aged 18-60 years, examined for short-term O ₃ -related changes in lung function. Natural logarithms of FVC, FEV ₁ , and FEF ₂₅₋₇₅ were regressed against the individual predictor variables and O ₃ . Spline functions were used to control potential trends. Sensitivity analyses for grass and pollens, and NO ₂ and TSP involved linear time-trend variables.	8 h-avg O ₃ (10 a.m.-6 p.m.): 90.3 µg/m ³ Range 2.9-247.1	NO ₂ , TSP	Daily average concentrations of O ₃ were associated with daily sample means of FEV ₁ and FEF ₂₅₋₇₅ in this random adult cross-sectional sample. The associations between daily O ₃ levels and daily means of lung function were smaller in magnitude than the association between annual O ₃ levels in the previous analyses (Ackermann and Liebrich et al., 1997). This analytic approach was designed to filter out long-term components. Sensitive analyses indicated that major confounding by uncontrolled effects of pollen, NO ₂ , and TSP was unlikely.	8-h avg O ₃ (per 10 µg/m ³): % change in lung function: FEV ₁ : -0.51% (-0.88, -0.13) FVC: -0.24% (-0.59, 0.11) FEF ₂₅₋₇₅ : -1.04% (-1.85, -0.22)
Frischer et al. (1993) Umkirch, Germany May-Oct 1991	Panel study of nasal lavage repeatedly performed on 44 school children (age 9-11 years) according to protocol published by Koren et al. (1990). Samples collected morning after "low" and "high" O ₃ days. Nasal lavage samples analyzed for polymorphonuclear leukocyte counts, albumin, tryptase, eosinophil cationic protein, and myeloperoxidase. Analysis using individual regression methods.	Stratified analysis of ½-h avg O ₃ at 3 p.m.: Low: <140 µg/m ³ High: >180 µg/m ³	None	Significant higher polymorphonuclear leukocyte counts after high O ₃ days. In children without symptoms of rhinitis, significantly elevated myeloperoxidase and eosinophil cationic protein concentrations detected. Results suggest that ambient O ₃ produces an inflammatory response in the upper airways of healthy children.	Children without symptoms of rhinitis (n = 30): Myeloperoxidase: Low O ₃ : median 77.39 µg/L High O ₃ : median 138.60 µg/L p < 0.05; Wilcoxon sign rank test Eosinophilic cationic protein: Low O ₃ : median 3.49 µg/L High O ₃ : median 5.39 µg/L p < 0.05; Wilcoxon sign rank test

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Europe (cont'd)					
Frischer et al. (1997) Umkirch, Germany May-Oct 1991	Panel study examined 44 school children aged 9-11 years for ratio of <i>ortho</i> -tyrosine to <i>para</i> -tyrosine in nasal lavage as a marker of hydroxyl radical attack. Nasal lavage performed according to protocol published by Koren et al. (1990). Concomitant lung function tests performed. Analysis using individual regression methods.	Stratified analysis of ½-h avg O ₃ at 3 p.m.: Low: <140 µg/m ³ High: >180 µg/m ³	None	Ambient O ₃ was associated with the generation of hydroxyl radicals in the upper airways of healthy children and significant lung function decrements. However, the <i>ortho/para</i> ratio was not related to polymorphonuclear leukocyte counts. Passive smoking was not related to outcomes.	FEV ₁ (% predicted): Low: 105.4 (SD 15.6) High: 103.9 (SD 15.0) Δ: 1.5, p = 0.031 <i>Ortho/para</i> ratio: Low: 0.02 (SD 0.07) High: 0.18 (SD 0.16) Δ: 0.17, p = 0.0001
Höppe et al. (1995a,b) Munich, Germany Apr-Sep 1992-1994	Panel study of five study groups (age 12-95 years): (1) senior citizens (n = 41); (2) juvenile asthmatics (n = 43); (3) forestry workers (n = 41); (4) athletes (n = 43); and (5) clerks (n = 40) as a control group. Examined for lung function (FVC, FEV ₁ , PEF) and questions on irritated airways. Each subject tested 8 days, 4 days with elevated or high O ₃ and 4 days with low O ₃ . Analysis using Wilcoxon matched pairs signed rank test and linear regression.	½-h max O ₃ (1 p.m.-4 p.m.): Seniors: High: 70 ppb Low: 31 ppb Asthmatics: High: 74 ppb Low: 34 ppb Forestry workers: High: 64 ppb Low: 32 ppb Athletes: High: 71 ppb Low: 28 ppb Clerks: High: 68 ppb Low: 15 ppb	None	No indication that senior citizens represent a risk group in this study. Senior citizens had the lowest ventilation rate (mean 10 L/min). Athletes and clerks experienced significant decrements in lung function parameters. Well-medicated juvenile asthmatics have a trend toward large pulmonary decrements. Forestry workers were exposed to motor tool exhaust, which might be a potential promoting factor.	½-h max O ₃ (per 100 ppb): Change in lung function: Seniors: FEV ₁ : 0.034 L (SD 0.101) PEF: 0.006 L/s (SD 0.578) Asthmatics: FEV ₁ : -0.210 L (SD 0.281) PEF: -0.712 L/s (SD 0.134)* Forestry workers: FEV ₁ : -0.140 L (SD 0.156) PEF: -1.154 L/s (SD 0.885)* Athletes: FEV ₁ : -0.152 L (SD 0.136)* PEF: -0.622 L/s (SD 0.589)* Clerks: FEV ₁ : -0.158 L (SD 0.114)* PEF: -0.520 L/s (SD 0.486)* *p < 0.05

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Europe (cont'd)					
Höppe et al. (2003) Munich, Germany Apr-Sep 1992-1995	Three of the same study groups examined in Höppe et al. (1995a,b): asthmatics (n = 43), athletes (n = 43), and elderly = 41). One additional risk group, children (n = 44), was examined. Over 80% of the elderly and asthmatic groups took medications on a daily basis. Eye and airway symptoms were assessed, as were pulmonary function test. GLM analyses was conducted.	½-h max O ₃ (1 p.m.-4 p.m.): Asthmatics: High: 66.9 ppb Low: 32.5 ppb Athletes: High: 65.9 ppb Low: 27.2 ppb Children: High: 70.4 ppb Low: 29.8 ppb Elderly: High: 66.1 ppb Low: 30.6 ppb	NO ₂	Stratified analyses by group did not show consistent O ₃ effects at the concentration level of this study; lack of power may have made it difficult to detect small O ₃ effects. Analyses on an individual basis show clearly different patterns of O ₃ sensitivity. Ozone responders are defined as individuals with relevant lung function changes of at least 10% for FEV ₁ , FVC, and PEF, and 20% for sRaw. Most of the responders were found in the asthmatic and children groups. In these responders, a significant O ₃ concentration-response relationship was observed in individual regressions (results not presented). The sample size may limit quantitative extrapolation to larger populations, but may allow cautious first estimates.	½-h max O ₃ (per 50 ppb): % change in lung function, lag 0: Asthmatics: FEV ₁ : 4.26% (-3.13, 11.66) PEF: 6.67% (-1.55, 14.89) Athletes: FEV ₁ : 0.01% (-0.13, 0.11) PEF: -0.13% (-0.29, 0.03) Children: FEV ₁ : -1.81% (-5.34, 1.73) PEF: -11.88% (-18.98, -4.78) Elderly: FEV ₁ : 2.10% (-4.65, 8.84) PEF: 7.29% (-2.84, 17.43) Ozone responders: Asthmatics: 21% Athletes: 5% Children: 18% Elderly: 5%
Kopp et al. (1999) Two towns in Black Forest, Germany Mar-Oct 1994	Panel study of 170 school children (median age 9.1 years) followed over 11 time points with nasal lavage sampling. Subjects were not sensitive to inhaled allergens. Nasal lavage samples analyzed for eosinophil cationic protein, albumen, and leukocytes. Analysis using GEE.	½-h max O ₃ : Villingen: 64 µg/m ³ 5th %-95th % 1-140 Freudenstadt: 105 µg/m ³ 5th %-95th % 45-179	PM ₁₀ , NO ₂ , SO ₂ , TSP	Eosinophil cationic protein and leukocyte levels peaked soon after first major O ₃ episode of summer, but did not show response to later, even higher, O ₃ episodes. These observations are consistent with an adaptive response in terms of nasal inflammation.	Change in log eosinophil cationic protein concentration (per µg/m ³ O ₃): Early summer: 0.97 (0.03, 1.92) Late summer: -0.43 (-1.34, 0.47)

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Europe (cont'd)					
Ulmer et al. (1997) Freudenstadt and Villingen, Germany Mar-Oct 1994	Panel study of 135 children aged 8-11 years in two towns were evaluated. Pulmonary function was associated with the highest O ₃ concentration in the previous 24 h. An initial cross-sectional analysis was followed by a longitudinal analysis using GEE with the data at four time periods (Apr, Jun, Aug, Sep).	½-h max O ₃ : Freudenstadt: Median 50.6 ppb 10th %-90th % 22.5-89.7 Villingen: Median 32.1 ppb 10th %-90th % 0.5-70.1	None	In the cross-sectional analysis, a significant negative association between O ₃ exposure and FVC was only shown at the June testing. For FEV ₁ , no significant associations were detected. In contrast, the longitudinal analysis obtained a statistically significant negative correlation between O ₃ exposure, and FVC and FEV ₁ for the subpopulation living in the town with higher O ₃ levels, Freudenstadt. The associations were more pronounced in males than females.	Change in lung function (per µg/m ³ ½-h max O ₃): FEV ₁ : Freudenstadt: -1.13 mL, p = 0.002 Villingen: -0.19 mL, p = 0.62 FVC: Freudenstadt: -1.23 mL, p = 0.002 Villingen: 0.02 mL, p = 0.96
Cuijpers et al. (1994) Maastricht, the Netherlands Nov-Dec 1990 (baseline), Aug 8-16, 1991 (smog episode)	During episode, 212 children (age unspecified) randomly chosen from 535 reexamined for lung function and symptoms. Corrected baseline lung function compared by paired t test. Difference in prevalence of respiratory symptoms examined.	Baseline: 8-h avg O ₃ : Range 2-56 µg/m ³ Smog episode: 1-h max O ₃ : Exceeded 160 µg/m ³ on 11 days	PM ₁₀ , SO ₂ , NO ₂	Small decrements in FEV ₁ and FEF ₂₅₋₇₅ were found in the 212 children. However, significant decreases in resistance parameters also were noted. Each day a different group of 30 children were measured. The results of the lung function are contradictory in that spirometry suggest airflow obstruction while impedance measurement suggest otherwise. Respiratory symptoms impacted by low response rate of 122 of 212 children due to summer holidays. No increase was observed.	Change in lung function and impedance between baseline and smog episode: FEV ₁ : -0.032 L (SD 0.226), p ≤ 0.05 FEF ₂₅₋₇₅ : -0.086 L/s (SD 0.415), p ≤ 0.01 Resistance at 8 Hz: -0.47 cmH ₂ O/(L/s) (SD 1.17), p ≤ 0.05
Gielen et al. (1997) Amsterdam, the Netherlands Apr-Jul 1995	Panel study of 61 children aged 7-13 years from two special schools for chronically ill children, followed for twice-daily PEF, symptoms, and medication usage. 77% of cohort had doctor-diagnosed asthma.	1-h max O ₃ : 77.3 µg/m ³ SD 15.7 8-h max O ₃ : 67.0 µg/m ³ SD 14.9	PM ₁₀ , BS, pollen	Morning PEF significantly associated with 8-h max O ₃ at a lag of 2 days. BS also associated with PEF. Among 14 symptom models tested, only one yielded a significant O ₃ finding (for upper respiratory symptoms). PM ₁₀ and BS, but not O ₃ , were related to β ₂ -agonist inhaler use.	8-h max O ₃ (per 83.2 µg/m ³): % change in PEF: Morning: Lag 2: -1.86% (-3.58, -0.14) Afternoon: Lag 2: -1.88% (-3.94, 0.18)

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Europe (cont'd)					
Hiltermann et al. (1998) Bilthoven, the Netherlands Jul-Oct 1995	Panel study of 60 adult nonsmoking intermittent to severe asthmatics (age 18-55 years) followed over 96 days. Measured morning and afternoon PEF, respiratory symptoms, and medication use. Analysis controlled for time trends, aeroallergens, environmental tobacco smoke exposures, day of week, temperature. Lags of 0 to 2 days examined.	8-h max O ₃ : 80.1 µg/m ³ Range 6-94	PM ₁₀ , NO ₂ , SO ₂ , BS	Ozone had strongest association with symptoms of any pollutant analyzed. PEF lower with O ₃ but not statistically significant. No effect on medication use. No effect modification by steroid use or hyperresponsiveness.	8-h max O ₃ (per 100 µg/m ³): Odds ratios: Respiratory symptoms: Shortness of breath: Lag 0: 1.18 (1.02, 1.36) Sleep disturbed by breathing: Lag 0: 1.14 (0.90, 1.45) Pain on deep inspiration: Lag 0: 1.44 (1.10, 1.88) Cough of phlegm: Lag 0: 0.94 (0.83, 1.07) Bronchodilator use: Lag 0: 1.05 (0.94, 1.19)
Hoek and Brunekreef (1995) Deurne and Enkhuizen, the Netherlands Mar-Jul 1989	The occurrence of acute respiratory symptoms investigated in children aged 7-11 years (Deurne n = 241; Enkhuizen n = 59). Symptoms included cough, shortness of breath, upper and lower respiratory symptoms, throat and eye irritation, headache and nausea. Ozone-related symptom prevalence and incidence were examined. Lags of 0 and 1 day, and mean O ₃ concentration from previous week were investigated. Analyses using 1st-order autoregressive models and logistic regression models.	1-h max O ₃ : Deurne: 57 ppb SD 20 Range 22-107 Enkhuizen: 59 ppb SD 14 Range 14-114	PM ₁₀ , NO ₂ , SO ₂	No consistent association between ambient O ₃ concentrations and the prevalence or incidence of symptoms in either city. The one significant positive coefficient in Enkhuizen for prevalence of upper respiratory symptoms was not confirmed by the Deurne results. No associations of daily symptom prevalence or incidence found with any of the other copollutants examined.	1-h max O ₃ (per 50 ppb): Prevalence of symptoms: Deurne: Any respiratory symptom: Lag 0: -0.06 (SE 0.04) Cough: Lag 0: -0.07 (SE 0.07) Upper respiratory symptoms: Lag 0: -0.06 (SE 0.05) Enkhuizen: Any respiratory symptom: Lag 0: 0.12 (SE 0.07) Cough: Lag 0: -0.07 (SE 0.18) Upper respiratory symptoms: Lag 0: 0.18 (SE 0.09)*
					*p < 0.05

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Latin America					
Castillejos et al. (1995) SW Mexico City Aug 1990-Oct 1991	Panel study of children aged 7½-11 years (22 males, 18 females) tested up to 8 times for FEV ₁ and FVC, before and after exercise. Target minute ventilation was 35 L/min/m ² . Analysis using GEE models.	1-h max O ₃ : 112.3 ppb Range 0-365 5th quintile mean 229.1 ppb	PM ₁₀	The mean % decrements in lung function were significantly greater than zero only in the fifth quintile of O ₃ exposure (183-365 ppb).	% change with exercise in 5th quintile of O ₃ exposure (183-365 ppb): FEV ₁ : -2.85% (-4.40, -1.31) FVC: -1.43% (-2.81, -0.06)
Gold et al. (1999) SW Mexico City 1991	Panel study of 40 school children aged 8-11 years in polluted community followed for twice-daily PEF and respiratory symptoms. PEF deviations in morning/afternoon from child-specific means analyzed in relation to pollution, temperature, season, and time trend. Morning symptoms analyzed by Poission regression.	24-h avg O ₃ : 52.0 ppb IQR 25	PM _{2.5} , PM ₁₀	Reported significant declines in PEF in relation to 24-h avg O ₃ levels. Effects did not vary by baseline symptom history. Lags chosen to maximize effects and varied by outcome. Ozone generally robust to PM _{2.5} . Morning phlegm significantly related to 24-h avg O ₃ at a 1-day lag.	24-h avg O ₃ (per 25 ppb): % change in PEF: Morning: Lag 1-10: -3.8% (-5.8, -1.8) Afternoon: Lag 0-9: -4.6% (-7.0, -2.1) % change in phlegm: Morning: Lag 1: 1.1% (1.0, 1.3)

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Latin America (cont'd)					
Romieu et al. (1996) N Mexico City Apr-Jul 1991, Nov 1991-Feb 1992	Panel study of 71 mildly asthmatic children aged 5-13 years followed for PEF and respiratory symptoms. Lower respiratory symptoms included cough, phlegm, wheeze and/or difficulty breathing.	1-h max O ₃ : 190 ppb SD 80	PM _{2.5} , PM ₁₀ , NO ₂ , SO ₂	Ozone effects observed on both PEF and symptoms. Symptom, but not PEF, effects robust to PM ₁₀ in two-pollutant models. Symptoms related to O ₃ included cough and difficulty breathing.	1-h max O ₃ (per 50 ppb): Change in PEF (L/min): Morning: Lag 0: -2.44 (-4.40, -0.49) Lag 1: -0.23 (-0.41, 1.62) Lag 2: -1.49 (-3.80, 0.80) Afternoon: Lag 0: -0.56 (-2.70, 1.60) Lag 1: -1.27 (-3.20, 0.62) Lag 2: -1.92 (-4.50, 0.66) Odds ratios: Lower respiratory symptoms: Lag 0: 1.09 (1.03, 1.15) Lag 1: 1.10 (1.04, 1.17) Lag 2: 1.04 (0.97, 1.12)
Romieu et al. (1997) SW Mexico City Apr-Jul 1991, Nov 1991-Feb 1992	Same period as Romieu et al., 1996, but in different section of city. 65 mildly asthmatic children aged 5-13 years followed for twice-daily PEF, and respiratory symptoms. Up to 2 months follow-up per child. Analysis included temperature and looked at 0- to 2-day lags. No time controls. Lower respiratory symptoms included cough, phlegm, wheeze and/or difficulty breathing. Panel study.	1-h max O ₃ : 196 ppb SD 78	PM ₁₀	Ozone had significant effects on PEF and symptoms, with largest effects at lags 0 and 1 day. Symptoms related to O ₃ included cough and phlegm. Ozone effects stronger than those for PM ₁₀ .	1-h max O ₃ (per 50 ppb): Change in PEF (L/min): Morning: Lag 0: -1.32 (-3.21, 0.57) Lag 1: -0.39 (-2.24, 1.47) Lag 2: -0.97 (-2.94, 0.99) Afternoon: Lag 0: -1.81 (-3.60, -0.01) Lag 1: -2.32 (-4.17, -0.47) Lag 2: -0.21 (-2.44, 2.02) Odds ratios: Lower respiratory symptoms: Lag 0: 1.11 (1.05, 1.19) Lag 1: 1.08 (1.01, 1.15) Lag 2: 1.07 (1.02, 1.13)

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Latin America (cont'd)					
Romieu et al. (1998) Mexico City Mar-May 1996 (1st phase) Jun-Aug 1996 (2nd phase)	Panel study of 47 street workers aged 18-58 years randomly selected to take a daily supplement (vitamin C, vitamin E, and beta carotene) or placebo during 1st phase of study. Following washout period, the use of supplements and placebos was reversed during 2nd phase. Pulmonary function test performed twice a week at end of workday. Plasma concentrations of beta carotene and α -tocopherol measured. Analysis using GEE models.	1-h max O ₃ : 123 ppb SD 40 55% of days >110 ppb. Workday hourly average during workday prior to pulmonary function test: 67.3 ppb SD 24	PM ₁₀ , NO ₂	During the 1st phase, O ₃ levels were significantly associated with declines in lung function parameters. No associations were observed in the daily supplement group. A significant supplement effect was observed. Ozone-related decrements also were observed during the 2nd phase, however the associations were not significant. Supplementation with antioxidants during the 1st phase may have had a residual protective effect on the lung.	1-h max O ₃ (per 10 ppb): Placebo group: 1st phase: FEV ₁ : Lag 0: -17.9 mL (SE 5.4)* FVC: Lag 0: -14.8 mL (SE 7.1)* 2nd phase: FEV ₁ : Lag 0: -3.3 mL (SE 6.5) FVC: Lag 0: -0.27 mL (SE 7.8) No significant associations with O ₃ observed when taking supplements.
Romieu et al. (2002) Mexico City Oct 1998-Apr 2000	Panel study of 158 asthmatic children aged 6-16 years randomly given a vitamin (C and E) supplement or placebo followed for 12 weeks. Peak flow was measured twice a day and spirometry was performed twice per week in the morning. Double blind study. Plasma concentration of vitamin E levels measured. Analysis using GEE models.	1-h max O ₃ : 102 ppb SD 47	PM ₁₀ , NO ₂	Ozone levels were significantly correlated with decrements in FEF ₂₅₋₇₅ in the placebo group, but not in the supplement group. When analysis was restricted to children with moderate-to-severe asthma, amplitudes of decrements were larger and significant for FEV ₁ , FEF ₂₅₋₇₅ , and PEF in the placebo group. Supplementation with antioxidants may modulate the impact of O ₃ exposure on the small airways of children with moderate to severe asthma.	1-h max O ₃ (per 10 ppb): Children with moderate to severe asthma: Placebo group: O ₃ with PM ₁₀ and NO ₂ models: FEV ₁ : Lag 1: -4.59 mL, p = 0.04 FEF _{2.5-75} : Lag 1: -13.32 mL/s, p ≤ 0.01 PEF: Lag 1: -15.01 mL/s, p = 0.04 No association observed in the vitamin supplement group.

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Latin America (cont'd)					
Romieu et al. (2004) Mexico City Oct 1998-Apr 2000	Additional analysis of Romieu et al., 2002 with data on glutathion S-transferase M1 polymorphism (GSTM1 null genotype) in 158 asthmatic children. Analysis performed using GEE models, stratified by GSTM1 genotype (null vs. positive) within the two treatment groups (placebo and antioxidant supplemented). Panel study.	1-h max O ₃ : 102 ppb SD 47	None	In the placebo group, O ₃ exposure was significantly and inversely associated with FEF _{2.5-75} in children who had the GSTM1 null genotype, with larger effects seen in children with moderate-to-severe asthma. No significant decrements were seen in the GSTM1 positive children. These results provide preliminary evidence that asthmatic children who may be genetically impaired to handle oxidative stress are most susceptible to the effect of O ₃ on small airways function.	1-h max O ₃ (per 50 ppb): FEF _{2.5-75} in children with moderate to severe asthma: Placebo group: GSTM1 null: Lag 1: -80.8 mL/s, p = 0.002 GSTM1 positive: Lag 1: -34.4 mL/s, p > 0.10 Supplement group: GSTM1 null: Lag 1: -7.3 mL/s, p > 0.10 GSTM1 positive: Lag 1: 2.0 mL/s, p > 0.10
Australia					
Jalaludin et al. (2000) Sydney, Australia Feb-Dec 1994	Panel study of three groups of children (mean age 9.6 years): (1) n = 45 with history of wheeze 12 months, positive histamine challenge, and doctor-diagnosed asthma; (2) n = 60 with history of wheeze and doctor-diagnosed asthma; (3) n = 20 with only history of wheeze. Examined for evening PEF and daily O ₃ using GEE model and population regression models.	Mean daytime O ₃ (6 a.m.-9 p.m.): 12 ppb SD 6.8 Maximum daytime O ₃ (6 a.m.-9 p.m.): 26 ppb SD 14.4	PM ₁₀ , NO ₂	A significant negative association was found between daily mean deviation in PEF and same-day mean daytime O ₃ concentration after adjusting for copollutants, time trend, meteorological variables, pollen count, and <i>Alternaria</i> count. The association was stronger in a subgroup of children with bronchial hyper-reactivity and doctor-diagnosed asthma. In contrast, the same-day maximum O ₃ concentration was not statistically associated.	Change in PEF (per 10 ppb mean daytime O ₃): All children (n = 125): O ₃ only model: -0.9178 (SE 0.4192), p = 0.03 O ₃ with PM ₁₀ model: -0.9195 (SE 0.4199), p = 0.03 O ₃ with PM ₁₀ and NO ₂ model: -0.8823 (SE 0.4225), p = 0.04

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Australia (cont'd)					
Jalaludin et al. (2004) Sydney, Australia Feb-Dec 1994	Same three groups of children as studied in Jalaludin et al., 2000. Examined relationship between O ₃ and evening respiratory symptoms (wheeze, dry cough, and wet cough), evening asthma medication use (inhaled β ₂ -agonist and inhaled corticosteroids), and doctor visits for asthma. Analysis using GEE logistic regression models. Panel study.	Mean daytime O ₃ (6 a.m.-9 p.m.): 12 ppb SD 6.8 Maximum daytime O ₃ (6 a.m.-9 p.m.): 26 ppb SD 14.4	PM ₁₀ , NO ₂	No significant O ₃ effects observed on evening symptoms, evening asthma medication use, and doctors visits. Also, no differences in the response of children in the three groups. A potential limitation is that the use of evening outcome measures rather than morning values may have obscured the effect of ambient air pollutants. Only consistent relationship was found between mean daytime PM ₁₀ concentrations and doctor visits for asthma.	Mean daytime O ₃ (per 8.3 ppb): Odds ratios: All children (n = 125): Wheeze: Lag 1: 1.00 (0.93, 1.08) Dry cough: Lag 1: 1.03 (0.96, 1.11) Wet cough: Lag 1: 0.97 (0.92, 1.03) Inhaled β ₂ -agonist use: Lag 1: 1.02 (0.97, 1.07) Inhaled corticosteroid use: Lag 1: 1.02 (0.99, 1.04) Doctor visit for asthma: Lag 1: 1.05 (0.77, 1.43)
Chen et al. (1998) Six communities in Taiwan 1994-1995	4,697 school children (age unspecified) from a rural area (Taihsi), urban areas (Keelung and Sanchung), and petrochemical industrial areas (Jenwu, Linyuan, and Toufen) cross-sectionally examined for respiratory symptoms and diseases using parent-completed questionnaires. Multiple logistic regression models used to compare odds of symptoms and diseases in urban or petrochemical areas to the rural area after controlling for potential confounding factors. Cross-sectional panel study.	24-h avg O ₃ : Rural area: 52.56 ppb Urban area: Mean range 38.34-41.90 ppb Petrochemical industrial area: Mean range 52.12-60.64 ppb	SO ₂ , CO, PM ₁₀ , NO ₂	School children in urban communities, but not in petrochemical industrial areas, had significantly more respiratory symptoms and diseases vs. those living in the rural community. However, mean O ₃ levels in the urban communities were lower than that of the rural community. No causal relationship could be derived between O ₃ and respiratory symptoms and diseases in this cross-sectional study.	Urban areas vs. rural area: Odds ratios: Respiratory symptoms: Morning cough: 1.33 (0.98, 1.80) Day or night cough: 1.67 (1.21, 2.29) Shortness of breath: 1.40 (1.04, 1.91) Wheezing or asthma: 1.68 (1.11, 2.54)

Table AX7-1 (cont'd). Effects of Acute O₃ Exposure on Lung Function and Respiratory Symptoms in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Asia					
Chen et al. (1999) Three towns in Taiwan: Sanchun, Taihsi, Linyuan May 1995-Jan 1996	Valid lung function data obtained once on each of 895 children (age 8-13 years) in three towns. Examined relation between lung function and pollution concentrations on same day and over previous 1, 2, and 7 days. Multipollutant models examined. Cross-sectional panel study.	1-h max O ₃ : Range 19.7-110.3 ppb SD not provided.	SO ₂ , CO, PM ₁₀ , NO ₂	FEV ₁ and FVC significantly associated with day 1-day lag O ₃ . FVC also related to NO ₂ , SO ₂ , and CO. No PM ₁₀ effects observed. Only O ₃ remained significant in multipollutant models. No PM ₁₀ effects. A significant O ₃ effect was not evident at O ₃ levels below 60 ppb.	Change in lung function: O ₃ only models: Lag 1: FEV ₁ : -0.64 mL/ppb (SE 0.34)* FVC: -0.79 mL/ppb (SE 0.32)* O ₃ with NO ₂ models: Lag 1: FEV ₁ : -0.85 mL/ppb (SE 0.34)* FVC: -0.91 mL/ppb (SE 0.37)* *p < 0.05
Chan and Wu (2005) Taichung City, Taiwan Sep 2001 (Questionnaire survey) Nov-Dec 2001 (Field study)	A cohort of mail carriers (mean age 39 years) examined for effects of O ₃ exposure on PEF. Their exposure periods were between 9 a.m. and 5 p.m. every working day. PEF measurements taken twice daily. Single-day lags from 0 to 3 days examined. A two-step statistical model was used, a multiple linear regression without air pollutants followed by a linear mixed effects model to estimate pollution effects.	8-h avg O ₃ (9 a.m.-5 p.m.): 35.6 ppb SD 12.1 Range 7.6-65.1	PM ₁₀ , NO ₂	Significant associations observed between evening PEF and O ₃ concentrations at lags of 0, 1 and 2 days. Largest effect observed at a day 1-day lag. Similar O ₃ effects on morning PEF also noted (data not presented). Neither PM ₁₀ nor NO ₂ showed consistent associations with PEF. Ozone results were robust to adjustment for PM ₁₀ and NO ₂ .	8-h avg O ₃ (per 10 ppb): % change in evening PEF: Lag 0: 0.54%, p < 0.05 Lag 1: 0.69%, p < 0.05 Lag 2: 0.52%, p < 0.05

Table AX7-2. Effects of Acute O₃ Exposure on Cardiovascular Outcomes in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
United States					
Liao et al. (2004) Three locations in U.S.: Minneapolis, MN; Jackson, MS; Forsyth County, NC 1996-1998	Cross-sectional study of 5,431 cohort members of the Atherosclerosis Risk in Communities study, men and women aged 45-64 years at entry in 1987. Association between O ₃ and cardiac autonomic control assessed using 5-min heart rate variability indices collected over a 4-h period. Analysis using multivariable linear regression models, adjusting for individual cardiovascular disease risk factors and meteorological factors.	8-h avg O ₃ (10 a.m.-6 p.m.): 41 ppb SD 16	PM ₁₀ , CO, SO ₂ , NO ₂	Significant interaction between O ₃ and ethnicity in relation to high-frequency power (p < 0.05). Ambient O ₃ significantly associated with high- frequency power among whites, but not blacks. No significant O ₃ effect on other heart rate variability indices, including low-frequency power and SD of normal R-R intervals. More consistent relationships observed between PM ₁₀ and heart rate variability indices.	8-h avg O ₃ (per 16 ppb): Log-transformed high-frequency power: White race: Lag 1: -0.069 (SE 0.019)* Black race: Lag 1: 0.047 (SE 0.034) Log-transformed high-frequency power: Lag 1: -0.010 (SE 0.016) SD of normal R-R intervals: Lag 1: -0.336 (SE 0.290) *p < 0.05
Peters et al. (2000a) Eastern Massachusetts 1995-1997	Records of detected arrhythmias and therapeutic interventions were downloaded from defibrillators implanted in cardiac clinic patients aged 22-85 years (n = 100). Analysis was restricted to defibrillator discharges precipitated by ventricular tachycardias or fibrillation. Data were analyzed by logistic regression models using fixed effect models with individual intercepts.	24-h avg O ₃ : 18.6 ppb IQR 14.0	PM _{2.5} , PM ₁₀ , BC, CO, NO ₂ , SO ₂	No significant O ₃ effects observed for defibrillator discharge interventions. For patients with 10 or more interventions, increased arrhythmias were associated significantly with PM _{2.5} , CO, and NO ₂ at various lag periods, but not O ₃ .	24-h avg O ₃ (per 32 ppb): Odds ratios: Defibrillator discharges: Patients with at least one event: Lag 0: 0.96 (0.47, 1.98) Patients with at least 10 events: Lag 0: 1.23 (0.53, 2.87)

Table AX7-2 (cont'd). Effects of Acute O₃ Exposure on Cardiovascular Outcomes in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
United States (cont'd)					
Peters et al. (2001) Greater Boston area, MA Jan 1995-May 1996	Case-crossover study design used to investigate association between air pollution and triggering of myocardial infarction in 772 patients (mean age 61.6 years). For each subject, one case period was matched to three control periods 24 h apart. Conditional logistic regression used for analysis.	1-h max O ₃ : 19.8 ppb SD 148 5th%-95th% 1-46 24-h avg O ₃ : 19.9 ppb SD 10.0 5th%-95th% 6-36	PM _{2.5} , PM ₁₀ , PM _{10-2.5} , BC, CO, NO ₂ , SO ₂	None of the gaseous pollutants, including O ₃ , were significantly associated with the triggering of myocardial infarctions. Significant associations reported for PM _{2.5} and PM ₁₀ . Note that the use of unidirectional referent sampling may lead to time trend bias and overlap bias (i.e., biased conditional logistic regression estimating equations), which can result in overestimated effects of exposure.	Odds ratios: Myocardial infarctions: 2-h avg O ₃ (per 45 ppb): Lag 1 h: 1.31 (0.85, 2.03) 24-h avg O ₃ (per 30 ppb): Lag 24 h: 0.94 (0.60, 1.49)
Park et al. (2005) Greater Boston area, MA Nov 2000-Oct 2003	Cross-sectional study examining the effect of O ₃ on heart rate variability in 497 adult males (mean age 72.7 years). Subjects were monitored during a 4-min rest period between 8 a.m. and 1 p.m. Ozone levels measured at central site 1 km from study site. Exposure averaging times of 4, 24, and 48 h investigated. Modifying effects of hypertension, ischemic heart disease, diabetes, and use of cardiac/antihypertensive medications also examined. Linear regression analyses.	24-h avg O ₃ : 23.0 ppb SD 13.0	PM _{2.5} , particle number concentration, BC, NO ₂ , SO ₂ , CO	Of the pollutants examined, only PM _{2.5} and O ₃ showed significant associations with heart rate variability outcomes. The 4-h averaging period was most strongly associated with heart rate variability indices. The O ₃ effect was robust in models including PM _{2.5} . The associations between O ₃ and heart rate variability indices were stronger in subjects with hypertension (n = 335) and ischemic heart disease (n = 142). In addition, calcium-channel blockers significantly influenced the effect of O ₃ on low frequency power. Major limitations of this study are the use of a short 4-min period to monitor heart rate variability and the lack of repeated measurements for each subject.	4-h avg O ₃ (per 13 ppb): Change in low frequency power: All subjects: -11.5% (-21.3, -0.4) Subjects with hypertension: -12.6% (-25.0, 1.9) Subjects without hypertension: -5.4% (-21.6, 14.1) Subjects with ischemic heart disease: -25.8% (-41.9, -5.3) Subjects without ischemic heart disease: -4.8% (-16.7, 8.8)

Table AX7-2 (cont'd). Effects of Acute O₃ Exposure on Cardiovascular Outcomes in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
United States (cont'd)					
Gold et al. (2000; reanalysis Gold et al., 2003) Boston, MA Jun-Sep 1997	Panel study of repeated measurements of heart rate variability in subjects aged 53-87 years (n = 21, 163 observations). Twenty-five minute protocol included 5 min each of rest, standing, exercise outdoors, recovery, and 20 cycles of slow breathing. Ozone levels measured at central site 4.8 miles from study site. Analyses using random effects models and GAM with stringent convergence criteria.	1-h avg O ₃ during HRV measurement: 25.7 ppb IQR 23.0	PM _{2.5} , NO ₂ , SO ₂	Increased levels of O ₃ were associated with reduced r-MSSD (square root of the mean of the squared differences between adjacent normal RR intervals) during the slow breathing period after exercise outdoors. The estimated O ₃ effects were similar to those of PM _{2.5} . Results suggest that O ₃ exposure may decrease vagal tone, leading to reduced heart rate variability.	1-h avg O ₃ (per 23.0 ppb): Change in r-MSSD: During first rest period: O ₃ only model: -3.0 ms (SE 1.9), p = 0.12 During slow breathing period: O ₃ only model: -5.8 ms (SE 2.4), p = 0.02 O ₃ with PM _{2.5} model: -5.4 ms (SE 2.5), p = 0.03
Schwartz et al. (2005) Boston, MA 12 weeks during the summer of 1999	A panel study of 28 elderly subjects (age 61-89 years). Various HRV parameters were measured for 30 min once a week. Analysis using linear mixed models with log-transformed HRV measurements. To examine heterogeneity of effects, hierarchical model was used.	1-h avg O ₃ during HRV measurement: Median 34 ppb IQR 26	BC, PM _{2.5} , CO, SO ₂ , NO ₂	HRV parameters examined included: standard deviation of normal RR intervals (SDNN), root mean squared differences between adjacent R-R intervals (r-MSSD), proportion of adjacent NN intervals differing by more than 50 ms (PNN ₅₀), and low frequency/high frequency ratio (LFHFR). Ozone was weakly associated with HRV parameters. Strongest association seen for BC, an indicator of traffic particles. The random effects model indicated that the negative effect of BC on HRV was not restricted to a few subjects. Subjects with MI experienced greater BC-related decrements in HRV parameters. Authors noted that in this study ambient O ₃ might represent a secondary particle effect and not a true O ₃ effect, and suggested that personal exposure measurements might be necessary to assess the effect of O ₃ on cardiovascular outcomes.	1-h avg O ₃ (per 26 ppb): Change in HRV parameters: SDNN: -3.1 ms (-7.0, 0.9) r-MSSD: -8.5 ms (-16.6, 0.3) PNN ₅₀ : -6.5% (-18.9, 7.8)

Table AX7-2 (cont'd). Effects of Acute O₃ Exposure on Cardiovascular Outcomes in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
United States (cont'd)					
Dockery et al. (2005) Boston, MA Jul 1995-Jul 2002	Effect of air pollution on incidence of ventricular arrhythmias was examined in 203 patients with implantable cardioverter defibrillators using time-series methods. Mean follow-up period was 3.1 year/subject. All subjects located <40 km of air pollution monitoring site. Two-day mean air pollution level used in analysis. Results analyzed by logistic regression using GEE with random effects. Modifying effects of previous arrhythmia within 3 days also examined.	48-h avg O ₃ : Median 22.9 ppb IQR 15.4	PM _{2.5} , BC, SO ₄ ²⁻ , particle number, CO, NO ₂ , SO ₂	No associations were observed between air pollutants and ventricular arrhythmias when all events were considered. When only examining ventricular arrhythmias within 3 days of a prior event, positive associations were found for most pollutants except for O ₃ . Suggestive evidence of a concentration-response relationship between ventricular arrhythmias and increasing quintiles of O ₃ .	48-h avg O ₃ (per 15.4 ppb): Odds ratios: All events: 1.09 (0.93, 1.29) Prior arrhythmia event <3 days: 1.01 (0.76, 1.35) Prior arrhythmia event >3 days: 1.14 (0.92, 1.40)

Table AX7-2 (cont'd). Effects of Acute O₃ Exposure on Cardiovascular Outcomes in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
United States (cont'd)					
Rich et al. (2005) Boston, MA Jul 1995-Jul 2002	Same study population as Dockery et al. (2005). Case-crossover study design used to examine association between air pollution and ventricular arrhythmias. For each case period, 3-4 control periods were selected. Various moving average concentrations of exposure considered – lags 0-2, 0-6, 0-23, and 0-47 h. Analysis using conditional logistic regression models.	1-h avg O ₃ : Median 22.2 ppb IQR 21.7 24-h avg O ₃ : Median 22.6 ppb IQR 15.7	PM _{2.5} , BC, CO, NO ₂ , SO ₂	Associations observed for PM _{2.5} and O ₃ with a 24-h moving average, and for NO ₂ and SO ₂ with a 48-h moving average. In two-pollutant analyses, only PM _{2.5} and O ₃ appeared to act independently. In contrast to results from other pollutants, stratified analyses indicated that O ₃ was associated with increased risk among subjects without a recent event, but not those with recent events. The odds ratio for the 24-h moving average concentration was larger than that for the same-calendar day concentration. This suggested that using calendar day concentrations might result in greater exposure misclassification which could lead to underestimation of risk. Findings of an association with 24-h moving average concentrations but not with shorter time periods could imply a cumulative effect across the previous 24 h.	Odds ratios: 24-h moving average O ₃ (per 15.9 ppb): O ₃ only model: All events: 1.21 (1.00, 1.45) Prior arrhythmia event <3 days: 1.04 (0.78, 1.37) Prior arrhythmia event >3 days: 1.28 (1.05, 1.58) O ₃ with PM _{2.5} model: All events: 1.18 (0.94, 1.49) 24-h calendar day O ₃ (per 15.7 ppb): O ₃ only model: All events: 0.96 (0.80, 1.15)
Canada					
Rich et al. (2004) Vancouver, British Columbia, Canada Feb-Dec 2000	Case-crossover study design used to investigate association between air pollution and cardiac arrhythmia in patients aged 15-85 years (n = 34) with implantable cardioverter defibrillators. Controls periods were selected 7 days before and after each case day. Analysis using conditional logistic regression.	1-h max O ₃ : 27.5 ppb SD 9.7 IQR 13.4	PM _{2.5} , PM ₁₀ , EC, OC, SO ₄ ²⁻ , CO, NO ₂ , SO ₂	No consistent association between any of the air pollutants, including O ₃ , and implantable cardioverter defibrillators discharges. No significant association observed in all-year data, however, significant relationship found in winter months at a 3-day lag. Overall, little evidence that air pollutants affect risk of cardiac arrhythmias, however, power was limited to study subtle effects.	No quantitative results for O ₃ .

Table AX7-2 (cont'd). Effects of Acute O₃ Exposure on Cardiovascular Outcomes in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Canada (cont'd)					
Vedal et al. (2004) Vancouver, British Columbia, Canada 1997-2000	Retrospective, longitudinal panel study of 50 patients (age 12-77 years) with implantable cardioverter defibrillators. Occurrence of cardiac arrhythmia was associated with air pollutants over 4-year period. GEE used for analysis.	1-h max O ₃ : 28.2 ppb SD 10.2 IQR 13.8	PM ₁₀ , CO, NO ₂ , SO ₂	No consistent association between any of the air pollutants and % change in arrhythmia. Among patients with at least 2 arrhythmia event-days per year, a significant negative relationship between O ₃ and arrhythmias was observed at lag 3-day during the summer, but no associations were found during the winter. These results do not provide evidence for an O ₃ effect on cardiac arrhythmias in susceptible patients.	No quantitative results for O ₃ .
Europe					
Ruidavets et al. (2005) Toulouse, France Jan 1997 - Jun 1999	MONICA Project. Examined short-term effects of pollution on acute MI using case-crossover study design. The study population included 395,744 inhabitants aged 35 to 64 years. Acute MI was examined using clinical, electrocardiograms, and enzymatic data. Four case definitions were used; there were a total of 635 cases for the most inclusive definition. Deaths were validated. Age, gender, history of ischemic heart disease, and survival status evaluated. Analyses using fixed-effects method with conditional logistic regression.	8-h max O ₃ : 74.8 µg/m ³ SD 28.1 Range 3.8-160.2	NO ₂ , SO ₂	After adjustment for temperature, relative humidity, and influenza epidemics, an association between O ₃ and acute MI was found for 0- and 1-day lags, but not for longer lags. Older age was an important risk factor. Subjects with no personal history of ischemic heart disease yielded a stronger association. Moderate levels of NO ₂ and SO ₂ were observed. NO ₂ and SO ₂ were not associated with acute MI. No PM data was reported.	8-h max O ₃ (per 5 µg/m ³): Relative risk: All cases (n = 635): Lag 0: 1.05 (1.01, 1.08) Lag 1: 1.05 (1.01, 1.09) Age group: Age 35-54 years (n = 281): Lag 0: 1.04 (0.99, 1.09) Age 55-64 years (n = 283): Lag 0: 1.06 (1.01, 1.12) History of ischemic heart disease: Yes (n = 127): Lag 0: 1.03 (0.96, 1.12) No (n = 437): Lag 0: 1.05 (1.01, 1.09) Age 55-64 years with no history of ischemic heart disease (n = 225): Lag 0: 1.07 (1.01, 1.13) Lag 1: 1.11 (1.04, 1.19)

Table AX7-2 (cont'd). Effects of Acute O₃ Exposure on Cardiovascular Outcomes in Field Studies

Reference, Study Location and Period	Outcomes and Methods	Mean O ₃ Levels	Copollutants Considered	Findings, Interpretation	Effects
Latin America					
Holguín et al. (2003) Mexico City Feb-Apr 2000	Panel study of the association between O ₃ and heart rate variability examined in 34 elderly subjects (mean age 79 years) in a nursing home. Subjects were monitored during a 5-min rest period between 8 a.m. and 1 p.m. every other day for a 3-mo period. A total of 595 observations were collected. Ambient O ₃ levels obtained from central site 3 km upwind from study site. Analysis performed using GEE models adjusting for potential confounding factors including age and average heart rate.	1-h max O ₃ : 149 ppb SD 40	PM _{2.5} (indoor, outdoor, total), NO ₂ , SO ₂ , CO	Only PM _{2.5} and O ₃ were significantly associated with heart rate variability outcomes. A significant effect of O ₃ on heart rate variability was limited to subjects with hypertension (n = 21). In two-pollutant models, the magnitude of the PM _{2.5} effect decreased slightly but remained significant, whereas O ₃ was no longer associated with heart rate variability indices.	1-h max O ₃ (per 10 ppb): Log ₁₀ high frequency power/100,000 ms ² : All subjects: -0.010 (-0.022, 0.001) Subjects with hypertension: -0.031 (-0.051, -0.012) Subjects without hypertension: 0.002 (-0.012, 0.016) Log ₁₀ low frequency power/100,000 ms ² : All subjects: -0.010 (-0.021, 0.001) Subjects with hypertension: -0.029 (-0.046, -0.011) Subjects without hypertension: 0.001 (-0.012, 0.015)

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Table AX7-3. Effects of O₃ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
United States						
Jaffe et al. (2003) Cincinnati, Cleveland, and Columbus, OH Jun-Aug 1991-1996	Daily time-series study of emergency department visits for asthma among Medicaid recipients aged 5-34 years.	8-h max O ₃ : Cincinnati: 60 ppb SD 20 Cleveland: 50 ppb SD 17 Columbus: 57 ppb SD 16	PM ₁₀ , NO ₂ , SO ₂	1, 2, 3	Poisson regression with control for city, day of week, week, year, minimum temperature, overall trend, and a dispersion parameter. No specific effort to control cycles, but regression residuals were uncorrelated, presumably due to seasonal restriction. Results shown for individual cities and overall. PM ₁₀ available only every 6th day. Positive relationships between emergency department visits for asthma and 8-h max O ₃ levels lagged 2 to 3 days. Results of borderline statistical significance. Other pollutants also related to asthma emergency department visits in single-pollutant models.	8-h max O ₃ (per 30 ppb): Cincinnati: Lag 2: 1.16 (1.00, 1.37) Cleveland: Lag 2: 1.03 (0.92, 1.16) Columbus: Lag 3: 1.16 (0.98, 1.37) Three cities: 1.09 (1.00, 1.19)
Jones et al. (1995) Baton Rouge, LA Jun-Aug 1990	Daily emergency department visits for respiratory complaints over a 3-month period in pediatric (age 0-17 years), adult (age 18-60 years), and geriatric (age >60 years) subgroups. Time-series study.	1-h max O ₃ : 69.1 ppb SD 28.7 24-h avg O ₃ : 28.2 ppb SD 11.7	Mold, pollen	Not specified.	Relatively simple statistical approach using ordinary least squares regression to model effects of O ₃ by itself and of O ₃ along with pollen counts, mold counts, temperature, and relative humidity. No direct control of cycles but authors reported nonsignificant autocorrelations among model residuals. Data restriction to 3-month period may have reduced any cyclic behavior. Significant associations between respiratory emergency department visits and O ₃ observed for adult age group only in multiple regression models.	24-h avg O ₃ (per 20 ppb): Pediatric: 0.87 (0.65, 1.09) Adult: 1.20 (1.01, 1.39) Geriatric: 1.27 (0.93, 1.61)

Table AX7-3 (cont'd). Effects of O₃ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
United States (cont'd)						
Wilson et al. (2005) Portland, ME 1998-2000 Manchester, NH 1996-2000	Daily emergency room visits for total respiratory and asthma examined for all ages and age groups 0-14, 15-64, and 65+ years. Time-series study.	8-h max O ₃ : Portland: Spring: 43.7 ppb SD 10.2 Summer: 46.1 ppb SD 15.4 Manchester: Spring: 43.4 ppb SD 9.7 Summer: 42.8 ppb SD 14.6	SO ₂	0	Poisson GAM with stringent convergence criteria. Positive associations for asthma in the larger city, Portland. Authors expressed the view that larger cities might be needed to conduct such studies.	8-h max O ₃ (per 30 ppb): Warm season (Apr-Sep): All ages: Portland: Total respiratory: 0.970 (0.915, 1.029) Asthma: 1.094 (1.032, 1.160) Manchester: Total respiratory: 0.970 (0.915, 1.029) Asthma: 0.970 (0.863, 1.092)
Cassino et al. (1999) New York City Jul 1992-Dec 1995	Daily time-series study of emergency department visits in a cohort of 1,115 adult asthmatics aged 18-84. Stratified into 552 never-smokers, 278 light smokers, and 285 heavy smokers.	1-h max O ₃ : 37.2 ppb IQR 28 24-h avg O ₃ : 17.5 ppb IQR 14	CO, NO ₂ , SO ₂	0, 1, 2, 3	Used Poisson GAM with default convergence criteria. No warm-season results presented. Significant O ₃ effects seen only at lag 2 among heavy-smokers. Copollutants did not have effects. Short-term cycles and episodic variations in asthma may not have been controlled adequately with 3-month period LOESS. Multiple tests performed, and inconsistent results across smoking strata and lags raise possibility of chance findings. No PM results included.	1-h max O ₃ (per 100 ppb): Never smokers: Lag 2: 0.80 (0.58, 1.14) Light smokers: Lag 2: 0.89 (0.62, 1.16) Heavy smokers: Lag 2: 1.59 (1.08, 2.36) 24-h avg O ₃ (per 50 ppb): All subjects: Lag 2: 1.22 (0.98, 1.53) Never smokers: Lag 2: 0.88 (0.57, 1.12) Light smokers: Lag 2: 0.88 (0.60, 1.28) Heavy smokers: Lag 2: 1.72 (1.13, 2.62)

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Table AX7-3 (cont'd). Effects of O₃ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
United States (cont'd)						
Weisel et al. (2002) New Jersey May-Aug 1995	Daily asthma emergency department visits for all ages. Time-series study.	1-h max O ₃ ; 5-h avg O ₃ (10 a.m.-3 p.m.); and 8-h avg O ₃ (2 p.m.-10 p.m.) analyzed. Levels not reported.	Pollen, spores	0, 1, 2, 3	No control for time, but authors report no autocorrelation, which alleviates concerns about lack of control. Significant O ₃ effects reported, even after adjusting for potential confounding by pollen. All three O ₃ indices gave essentially same results.	Slope estimate (visits/day/ppb): Excluding data from May when pollen levels are high: O ₃ only model: Lag 0: 0.039, p = 0.049 O ₃ with pollen model: Lag 0: 0.040, p = 0.014
Friedman et al. (2001) Atlanta, GA Jun-Sep 1996	Emergency department visits and hospital admissions for asthma in children aged 1-16 years. Outcomes measures during 1996 Summer Olympics were compared to a baseline period of 4 weeks before and after the Olympic Games. Time-series study.	1-h max O ₃ : Baseline: 81.3 ppb SD not provided. Intervention period: 58.6 ppb SD not provided.	NO ₂ , SO ₂ , CO, PM ₁₀ , mold	0, 0-1, 0-2	Analysis using Poisson GEE models addressing serial autocorrelation. An overall decrease was observed when comparing the number of visits and hospitalizations during the Olympic Games to the baseline period. However, significant associations between O ₃ and asthma events were found during the Olympic Games.	1-h max O ₃ (per 50 ppb): Pediatric emergency departments: Lag 0: 1.2 (0.99, 1.56) Lag 0-1: 1.4 (1.04, 1.79) Lag 0-2: 1.4 (1.03, 1.86)

Table AX7-3 (cont'd). Effects of O₃ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
United States (cont'd)						
Metzger et al. (2004) Atlanta, GA 1993-2000	Emergency department visits for total and cause-specific cardiovascular diseases by age groups 19+ years and 65+ years. Time-series study.	8-h max O ₃ : Mar-Nov: Median 53.9 ppb 10th %-90th % 13.2-44.7	NO ₂ , SO ₂ , CO, PM _{2.5} , PM ₁₀ , PM _{10-2.5} , ultrafine PM count, SO ₄ ²⁻ , H ⁺ , EC, OC, metals, oxygenated hydrocarbons	0-2	Poisson GLM regression used for analysis. A priori models specified a lag of 0 to 2 days. Secondary analyses performed to assess alternative pollutant lag structures, seasonal influences, and age effects. Cardiovascular visits were significantly associated with several pollutants, including NO ₂ , CO, and PM _{2.5} , but not O ₃ .	8-h max O ₃ (per 25 ppb): All ages: Total cardiovascular: 1.008 (0.987, 1.030) Dysrhythmia: 1.008 (0.967, 1.051) Congestive heart failure: 0.965 (0.918, 1.014) Ischemic heart disease: 1.019 (0.981, 1.059) Peripheral vascular and cerebrovascular disease: 1.028 (0.985, 1.073)
Peel et al. (2005) Atlanta, GA 1993-2000	Emergency department visits for total and cause-specific respiratory diseases by age groups 0-1, 2-18, 19+, and 65+ years. Time-series study.	8-h max O ₃ : Mar-Nov: 55.6 ppb SD 23.8	NO ₂ , SO ₂ , CO, PM _{2.5} , PM ₁₀ , PM _{10-2.5} , ultrafine PM count, SO ₄ ²⁻ , H ⁺ , EC, OC, metals, oxygenated hydrocarbons	0-2	Poisson GEE and GLM regression used for analysis. A priori models specified a lag of 0 to 2 days. Also performed secondary analyses estimating the overall effect of pollution over the previous 2 weeks. Seasonal analyses indicated stronger associations with asthma in the warm months. Quantitative results not presented for multipollutant, age-specific, and seasonal analyses.	8-h max O ₃ (per 25 ppb): All ages: All available data: Total respiratory: 1.024 (1.008, 1.039) Upper respiratory infections: 1.027 (1.009, 1.045) Asthma: 1.022 (0.996, 1.049) Pneumonia: 1.015 (0.981, 1.050) COPD: 1.029 (0.977, 1.084) Warm season (Apr-Oct): Asthma: 1.026 (1.002, 1.051)

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Table AX7-3 (cont'd). Effects of O₃ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
United States (cont'd)						
Tolbert et al. (2000) Atlanta, GA Jun-Aug 1993-1995	Pediatric (aged 0-16 years) asthma emergency department visits over three summers in Atlanta. A unique feature of the study was assignment of O ₃ exposures to zip code centroids based on spatial interpolation from nine O ₃ monitoring stations. Time-series study.	1-h max O ₃ : 68.8 ppb SD 21.1 8-h max O ₃ : 59.3 ppb SD 19.1	PM ₁₀ , NO ₂ , mold, pollen	1	A priori specification of model, including a lag of 1 day for all pollutants and meteorological variables. Secondary analysis using logistic regression of the probability of daily asthma visits, referenced to total visits (asthma and nonasthma). Significant association with O ₃ and PM ₁₀ in 1-, but not in 2-pollutant models (correlation between O ₃ and PM ₁₀ : r = 0.75). Secondary analysis indicated nonlinearity, with O ₃ effects clearly significant only for days ≥100 ppb vs. days <50 ppb.	8-h max O ₃ (per 20 ppb): Poisson regression: O ₃ only model: 1.040 (1.008, 1.074) Logistic regression: O ₃ only model: 1.042 (1.017, 1.068) O ₃ with PM ₁₀ model: 1.024 (0.982, 1.069)
Zhu et al. (2003) Atlanta, GA Jun-Aug 1993-1995	Asthma emergency department visits in children (age 0-16 years) over three summers in Atlanta. Time-series study.	8-h max O ₃ : Levels not reported.	None	1	Used Bayesian hierarchical modeling to address model variability and spatial associations. Data were analyzed at the zip code level to account for spatially misaligned longitudinal data. A positive, but nonsignificant relationship between O ₃ and emergency room visits for asthma.	8-h max O ₃ (per 20 ppb): Posterior median: 1.016 (0.984, 1.049)

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Table AX7-3 (cont'd). Effects of O₃ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Canada						
Delfino et al. (1997b) Montreal, Quebec, Canada Jun-Sep 1992-1993	Daily time-series ecologic study of emergency department visits for respiratory complaints within five age strata (<2, 2-18, 19-34, 35-64, >64 years).	1-h max O ₃ : 1992: 33.2 ppb SD 12.6 1993: 36.2 ppb SD 13.8 8-h max O ₃ : 1992: 28.8 ppb SD 11.3 1993: 30.7 ppb SD 11.5	PM ₁₀ , PM _{2.5} , SO ₄ ²⁻ , H ⁺	0, 1, 2	Used ordinary least squares, with 19-day weighted moving average pre-filter to control cycles; weather also controlled. Significant effects reported for 1-day lag O ₃ in 1993 only for age >64 years. This O ₃ effect reported to be robust in two-pollutant models. Low O ₃ levels raise plausibility concerns. Short data series, multiple tests performed, and inconsistent results across years and age groups raise possibility of chance findings.	1993 (age >64 years): 1-h max O ₃ (per 36.2 ppb): Lag 1: 1.214 (1.084, 1.343) 8-h max O ₃ (per 30.7 ppb): Lag 1: 1.222 (1.091, 1.354) No significant O ₃ effects in 1992 or in other age groups at the p < 0.02 level (chosen to take into account multiple testing bias).

Table AX7-3 (cont'd). Effects of O₃ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Canada (cont'd)						
Delfino et al. (1998b) Montreal, Quebec, Canada Jun-Aug 1989-1990	Daily time-series ecologic study of emergency department visits for respiratory complaints across all ages and within four age strata (<2, 2-34, 35-64, >64 years).	1-h max O ₃ : 1989: 44.1 ppb SD 18.3 1990: 35.4 ppb SD 12.9 8-h max O ₃ : 1989: 37.5 ppb SD 15.5 1990: 29.9 ppb SD 11.2	Estimated PM _{2.5}	0, 1, 2	Same analytical approach used in Delfino et al., 1997. Results presented only for 1989. Significant effects reported for 1-day lag O ₃ in 1989 only for age >64 years. This O ₃ effect reported to be robust in 2-pollutant models. Ozone concentrations were significantly higher in 1989 than 1990 (p < 0.001).	1989 (age >64 years): 1-h max O ₃ (per 44.1 ppb): Lag 1: 1.187 (0.969, 1.281) 8-h max O ₃ (per 37.5 ppb): Lag 1: 1.218 (1.097, 1.338) No significant O ₃ effects in 1990 or in other age groups at the p < 0.05 level.
Stieb et al. (1996) Saint John, New Brunswick, Canada May-Sep 1984-1992	Daily emergency department visits for asthma in all ages, age <15 years and 15+ years. Time-series study.	1-h max O ₃ : 41.6 ppb Range 0-160 95th % 75	SO ₂ , NO ₂ , SO ₄ ²⁻ , TSP	0, 1, 2, 3	Poisson analysis with control of time based on 19-day moving average filter. Also controlled day of week and weather variables. Ozone was only pollutant consistently associated with emergency department visits for asthma, but effect appeared nonlinear, with health impacts evident only above 75 ppb O ₃ .	All ages: 1-h max O ₃ (per 40 ppb): Lag 2: 1.09 (1.00, 1.19) 1-h max O ₃ >75 ppb vs. ≤75 ppb: Lag 2: 1.33 (1.10, 1.56)

Table AX7-3 (cont'd). Effects of O₃ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Europe						
Sunyer et al. (1997) Four European cities: Barcelona, Helsinki, London, and Paris 1986-1992	Emergency admissions for asthma in children (<15 years) and adults (15-64 years). Time-series study.	1-h max O ₃ : Barcelona: Median 72 µg/m ³ Range 7-283 Helsinki: Median 27 µg/m ³ Range 1-78 London: Median 40 µg/m ³ Range 1-188 Paris: Median 36 µg/m ³ Range 1-230	BS, SO ₂ , NO ₂	0, 1, 2, 3	Poisson analysis using APHEA methodology. Significant O ₃ effects on emergency admissions for asthma observed among 15-64 year olds in Barcelona and London. Across all cities, there was no strong evidence for associations involving O ₃ .	1-h max O ₃ (per 50 µg/m ³): Weighted mean effect (best lag selected for each city): Age <15 years: 3-city pooled estimate (Barcelona data not available): 1.006 (0.976, 1.037) Age 15-64 years: 4-city pooled estimate: 1.015 (0.955, 1.078)
Atkinson et al. (1999a) London, England 1992-1994	Emergency department visits for respiratory complaints, asthma for all ages and age 0-14, 15-64, and 65+ years. Time-series study.	8-h max O ₃ : 17.5 ppb SD 11.5	NO ₂ , SO ₂ , CO, PM ₁₀	0, 1, 2, 3 0-1, 0-2, 0-3	Poisson GLM regression used for analysis. No warm-season analysis attempted. PM ₁₀ positively associated.	8-h max O ₃ (per 25.7 ppb): All ages: Total respiratory: Lag 1: 1.017 (0.991, 1.043) Asthma: Lag 1: 1.027 (0.983, 1.072)
Hajat et al. (1999; 2002) London, England 1992-1994	Daily doctor consults for asthma, lower respiratory diseases, and upper respiratory diseases for age 0-14, 15-64, and ≥65 years. Time-series study.	8-h max O ₃ : All year: 17.5 ppb SD 11.5 Warm season: 22.7 ppb SD 12.2 Cold season: 12.1 ppb SD 7.6	BS, SO ₂ , NO ₂ , CO, PM ₁₀ , pollen	0-3	Used Poisson GAM with default convergence criteria. Conducted all-year and seasonal analyses. Single- and two-pollutant models analyzed. Significant negative effects for O ₃ . This may reflect residual confounding by seasonal factors or highly negative correlation with other pollutants.	Upper respiratory diseases, age ≥65 years: All year: 8-h max O ₃ (per 25.7 ppb) Lag 2: -8.3% (-13.3, -3.0) Warm season: 8-h max O ₃ (per 28.5 ppb) Lag 2: -0.6% (-6.1, 5.1) Cool season: 8-h max O ₃ (per 19.8 ppb) Lag 2: -7.9% (-12.9, 2.7)

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Table AX7-3 (cont'd). Effects of O₃ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Europe (cont'd)						
Thompson et al. (2001) Belfast, N Ireland 1993-1995	Asthma emergency department admissions in children (age unspecified). Time-series study.	24-h avg O ₃ : Warm season: 18.7 ppb IQR 9 Cold season: 17.1 ppb IQR 12	PM ₁₀ , SO ₂ , NO ₂ , CO, benzene	0, 0-1, 0-2, 0-3	GLM with sinusoids. Pre-adjustment. Very low O ₃ levels in both seasons. No O ₃ effect in warm season. Significant inverse O ₃ associations in full-year and cold-season models. After adjusting for benzene in model O ₃ was no longer negatively associated with asthma visits.	24-h avg O ₃ (per 10 ppb): All year: O ₃ only model: Lag 0-1: 0.93 (0.87, 1.00) O ₃ with benzene model: Lag 0-1: 1.08 (0.97, 1.21) Warm season: O ₃ only model: Lag 0-1: 0.99 (0.89, 1.10) Cold season: O ₃ only model: Lag 0-1: 0.89 (0.82, 0.97)
Bourcier et al. (2003) Paris, France Jan 1999-Dec 1999	Ophthalmological emergency examination; conjunctivitis and related ocular surface problems. Time-series study.	24-h avg O ₃ : 35.7 µg/m ³ Range 1-97	PM ₁₀ , SO ₂ , NO ₂	0, 1, 2, 3	Logistic Regression	Results indicate a strong relation to NO ₂ and NO. 24-h avg O ₃ (per 69 µg/m ³): Conjunctivitis: Lag 0: 1.13 (0.90, 1.42)
Castellsague et al. (1995) Barcelona, Spain 1985-1989	Daily emergency department visits for asthma in persons aged ≥14 years. Time-series study.	1-h max O ₃ : Summer: 43 ppb IQR 22 Winter: 29 ppb IQR 16	BS, SO ₂ , NO ₂	Not specified.	Poisson regression with year and month dummy variables and extensive control for weather factors (minimum, maximum, mean temperature, relative humidity, dewpoint temperature; continuous and categorical parameterizations)	1-h max O ₃ (per 12.7 ppb): Summer: 0.991 (0.939, 1.045) Winter: 1.055 (0.998, 1.116)

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Table AX7-3 (cont'd). Effects of O₃ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Europe (cont'd)						
Tobías et al. (1999) Barcelona, Spain 1986-1989	Daily asthma emergency department visits. Investigated sensitivity of results to four alternative methods for controlling asthma epidemics. Time-series study.	Levels not reported.	BS, NO ₂ , SO ₂	Not specified.	Poisson analysis using APHEA methodology. Asthma epidemics either not controlled, or controlled with one, six, or individual epidemic dummy variables.	O ₃ results were sensitive to method used to control asthma epidemics, with regression coefficients ranging over 5-fold depending on the model. Only 1 of 8 models reported had a significant O ₃ effect.
Tenías et al. (1998; 2002) Valencia, Spain 1994-1995	Daily emergency department visits for asthma and COPD in persons aged >14 years. Time-series study.	1-h max O ₃ : All year: 62.8 µg/m ³ Range 13.3-157.3 Warm season: 74.0 µg/m ³ Cool season: 51.4 µg/m ³	BS, NO ₂ , SO ₂ , CO	0, 1, 2, 3, 4, 5	Poisson analysis using APHEA methodology. Compared warm and cold season effects. GAM explored in sensitivity analysis. For asthma, both O ₃ and NO ₂ significant in single- and two-pollutant models, and O ₃ effect larger in warm season. For COPD, both O ₃ and CO significant in both single- and two-pollutant models and no difference in O ₃ effects by season.	1-h max O ₃ (per 10 µg/m ³): Asthma: All year: Lag 1: 1.06 (1.01, 1.11) Warm season: Lag 1: 1.08 (1.02, 1.05) Cold season: Lag 1: 1.04 (0.97, 1.11) COPD: All year: Lag 5: 1.06 (1.02, 1.10)
Latin America						
Hernández-Garduño et al. (1997) Mexico City May 1992-Jan 1993	Visits to clinics for respiratory diseases in persons aged 1 month to 92 years. Time-series study.	Percent time exceeding 1-h max O ₃ of 120 ppb: 6.1-13.2% by location	SO ₂ , NO ₂ , CO	0, 1, 2, 3, 4, 5	GLM with pre-adjustment. Ozone at lags 0 and 5 days significantly associated with daily visits for all ages, age <14 years, and 15+ years. Neither O ₃ nor NO ₂ significant in two-pollutant model.	1-h max O ₃ (per maximum less average, value not given): Lag 0: 1.19 (SE 0.08), p < 0.05 Lag 5: 1.19 (SE 0.08), p < 0.05

Table AX7-3 (cont'd). Effects of O₃ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Latin America (cont'd)						
Lin et al. (1999) São Paulo, Brazil May 1991-Apr 1993	Daily pediatric (age unspecified) respiratory emergency department visits. Time-series study.	1-h max O ₃ : 34 ppb SD 22	SO ₂ , CO, PM ₁₀ , NO ₂	0, 1, 0-1, 0-2, 0-3, 0-4, 0-5	Seasonal control using month dummy variables. Also controlled day of week, temperature. Both O ₃ and PM ₁₀ associated with outcome alone and together.	1-h max O ₃ (per 5 ppb): O ₃ only model: Lag 0-4: 1.022 (1.016, 1.028) O ₃ with PM ₁₀ model: Lag 0-4: 1.015 (1.009, 1.021)
Martins et al. (2002) São Paulo, Brazil May 1996-Sep 1998	Daily emergency department visits for chronic lower respiratory diseases in persons aged >64 years. Time-series study.	1-h max O ₃ : 34 ppb SD 21 IQR 21	CO, NO ₂ , SO ₂ , PM ₁₀	0-1, 0-2, 0-3, 0-4, 0-5, 0-6.	Analyzed using Poisson GAM with default convergence criteria. Only O ₃ and SO ₂ significant in single-pollutant models. Ozone effect remained significant when SO ₂ included in two-pollutant model.	1-h max O ₃ (per 18.26 ppb): Lag 0-3: 1.14 (1.04, 1.23)
Ilabaca et al. (1999) Santiago, Chile Feb 1995-Aug 1996	The association between pollutant levels and emergency visits for pneumonia and other respiratory illnesses among children. Time-series study.	1-h max O ₃ : Warm season: 66.6 µg/m ³ SD 25.2 Cold season: 27.6 µg/m ³ SD 20.2	PM ₁₀ , PM _{2.5} , SO ₂ , NO ₂	1, 2, 3, 1-7	Poisson regression analysis.	Warm season: 1-h max O ₃ (per 30 µg/m ³): Lag 2: 1.019 (1.003, 1.035) Cold season: 1-h max O ₃ (per 24 µg/m ³): Lag 2: 0.995 (0.978, 1.011)
Asia						
Hwang and Chan (2002) 50 communities in Taiwan 1998	Daily clinic visits for lower respiratory illnesses for all ages. Time-series study.	1-h max O ₃ : Means for 50 communities: 54.2 ppb SD 10.2 Range 38.9-78.3	NO ₂ , SO ₂ , PM ₁₀ , CO	0, 1	Analysis using general linear regressions with moving-average residual processes and Bayesian hierarchical modeling. All pollutants except O ₃ were associated with daily clinic visits.	1-h max O ₃ (per 40 ppb): Bayesian hierarchical model: 1.003 (0.983, 1.023)

Table AX7-3 (cont'd). Effects of O₃ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Asia (cont'd)						
Chew et al. (1999) Singapore Jan 1990-Dec 1994	Emergency department visits for asthma in persons aged 3-21 years. Time-series study.	1-h max O ₃ : 23 ppb SD 15	TSP, PM ₁₀ , SO ₂ , NO ₂	0, 1, 2	Simplistic but probably adequate control for time by including 1-day lagged outcome as covariate. In adjusted models that included covariates, O ₃ had no significant effect.	No quantitative results presented for O ₃ .

Table AX7-4. Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
United States						
Neidell (2004) California 1992-1998	Asthma hospital admissions within five age strata (0-1, 1-3, 3-6, 6-12, and 12-18 years). Time-series study.	O ₃ (index not specified): 38.9 ppb SD 17.8 Low SES: 40.1 ppb High SES: 38.3 ppb	CO, NO ₂ , PM ₁₀ ; multipollutant models	Not specified.	Statistical analysis using naturally occurring seasonal variations in pollutant concentrations within zip codes. Linear regression analyses. Consistent significant positive effects only observed for CO. Negative O ₃ effect observed in all age groups. Number of smog alerts was negatively associated with asthma hospitalizations, indicating avoidance behavior on high O ₃ days. Interaction term with indicator variable for low SES was positive in all age groups and statistically significant in age 3-6 years and 12-18 years, after adjusting for number of smog alerts.	Slope estimate (adjusting for number of smog alerts): O ₃ with CO, NO ₂ , and PM ₁₀ models: Age 3-6 years: -0.038 (SE 0.014) Age 6-12 years: -0.044 (SE 0.013) Age 12-18 years: -0.022 (SE 0.011) O ₃ × low SES interaction term: Age 3-6 years: 0.092 (SE 0.026) Age 6-12 years: 0.024 (SE 0.024) Age 12-18 years: 0.042 (SE 0.019)
Mann et al. (2002) South Coast air basin, CA 1988-1995	Ischemic heart disease admissions for age 40+ years. Time-series study.	8-h max O ₃ : 50.3 ppb SD 30.1 IQR 39.6	PM ₁₀ , CO, NO ₂	0, 1, 2, 3, 4, 5, 0-1, 0-2, 0-3, 0-4	Poisson GAM with cubic B-splines; co-adjustment. No significant O ₃ effects observed overall or in warm season. CO and NO ₂ significant in full-year analyses.	O ₃ coefficients all negative, but no consistent, significant effect.

Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
United States (cont'd)						
Linn et al. (2000) Los Angeles, CA 1992-1995	Total respiratory and total cardiovascular admissions for age 30+ years. Time-series study.	24-h avg O ₃ : Winter: 14 ppb SD 7 Spring: 32 ppb SD 10 Summer: 33 ppb SD 8 Fall: 15 ppb SD 9	PM ₁₀ , CO, NO ₂	0	Poisson GLM; co-adjustment. Only significant O ₃ effects observed were inverse associations with total cardiac admission in full-year and winter season, suggesting residual confounding. No significant effects of O ₃ on respiratory admissions.	24-h avg O ₃ (per 10 ppb): All year: Respiratory: 1.008 (1.000, 1.016) Cardiovascular: 0.993 (0.987, 0.999) Summer: Respiratory: 1.006 (0.992, 1.020) Cardiovascular: 1.001 (0.991, 1.011)
Nauenberg and Basu (1999) Los Angeles, CA 1991-1994	Unscheduled asthma admissions for all ages. Time-series study.	24-h avg O ₃ : All year: 19.88 ppb SD 11.13 Nov-Mar: 7.52 ppb SD 4.34	PM ₁₀	0, 0-7	Poisson GLM with pre-adjustment. No significant effects of O ₃ . No warm-season results presented.	24-h avg O ₃ (per 20 ppb): Nov-Mar: Lag 0: 1.01 (0.93, 1.08)
Sheppard et al. (1999; reanalysis Sheppard, 2003) Seattle, WA 1987-1994	Asthma admissions for age <65 years. Time-series study.	8-h max O ₃ : 30.4 ppb IQR 20	PM _{2.5} , PM ₁₀ , PM _{10-2.5} , SO ₂ , CO	1, 2, 3	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Results stratified by season. Ozone significant predictor of outcome. No two-pollutant model results reported for O ₃ .	8-h max O ₃ (per 20 ppb): GLM with natural splines: Lag 2: 1.07 (1.01, 1.13)

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Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
United States (cont'd)						
Schwartz (1996) Spokane, WA Apr-Oct 1988-1990	Total respiratory admissions in persons aged 65+ years.	1-h max O ₃ : 79 µg/m ³ IQR 23 24-h avg O ₃ : 56 µg/m ³ IQR 17	PM ₁₀	2	Poisson GAM with default convergence criteria. Results available only for warm season. Ozone and PM ₁₀ both significant predictors of outcome. No two-pollutant models reported. Ozone effects robust to more extensive temperature specification.	1-h max O ₃ (per 50 µg/m ³): Lag 2: 1.244 (1.002, 1.544) 24-h avg O ₃ (per 50 µg/m ³): Lag 2: 1.284 (0.926, 1.778)
Koken et al. (2003) Denver, CO Jul-Aug 1993-1997	Cause-specific cardiovascular admissions for age >65 years. Cause categories include acute MI, coronary atherosclerosis, pulmonary heart disease, cardiac dysrhythmia, and congestive heart failure. Time-series study.	24-h avg O ₃ : 25.0 ppb SD 6.61 Range 5.4-40.2	PM ₁₀ , NO ₂ , SO ₂ , CO	0, 1, 2, 3, 4	Analysis using Poisson GLM. Results suggest that O ₃ increases the risk of hospitalization for coronary atherosclerosis and pulmonary heart disease. No association was found for PM ₁₀ . Strong O ₃ effects observed in this seasonal study compared to other studies examining year-round data. Male gender and higher temperatures were found to be important risk factors for cardiovascular disease. No multipollutant analyses were reported.	24-h avg O ₃ (per 9.7 ppb): Acute MI: 0.824 (0.733, 0.925) Coronary atherosclerosis: 1.123 (1.040, 1.214) Pulmonary heart disease: 1.214 (1.040, 1.418)

Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
United States (cont'd)						
Moolgavkar et al. (1997) Minneapolis/St. Paul, MN and Birmingham, AL 1986-1991	Pneumonia and COPD admissions for age 65+ years. Time-series study.	24-h avg O ₃ : Minneapolis/ St. Paul: 26.2 ppb IQR 15.3 Birmingham: 25.1 ppb IQR 12.7	PM ₁₀ , SO ₂ , NO ₂	0, 1, 2, 3	Poisson GLM with co-adjustment. Both O ₃ and PM ₁₀ significant in MN; not in AL. Ozone, but not PM ₁₀ , effects were robust to NO ₂ and SO ₂ .	24-h avg O ₃ (per 15 ppb): Minneapolis/St. Paul: Pneumonia and COPD: Lag 1: 1.060 (1.033, 1.087) Pneumonia: Lag 1: 1.066 (1.034, 1.098) COPD: Lag 0: 1.045 (0.995, 1.067) Birmingham: Pneumonia and COPD: Lag 2: 1.006 (0.971, 1.042)
Lippmann et al. (2000; reanalysis Ito, 2003, 2004) Detroit, MI 1992-1994	Pneumonia, COPD, ischemic heart disease, dysrhythmias, heart failure, and stroke admissions for age 65+ years. Time-series study.	24-h avg O ₃ : 25 ppb Maximum 55	PM ₁₀ , PM _{2.5} , PM _{10-2.5} , SO ₄ ²⁻ , H ⁺ , NO ₂ , SO ₂ , CO	0, 1, 2, 3, 0-1, 0-2, 0-3	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. At various lags, no consistent O ₃ effect observed for any cause-specific hospital admission. No two-pollutant models reported.	24-h avg O ₃ (per 28 ppb): Poisson GLM: Pneumonia: Lag 0: 0.93 (0.83, 1.05) COPD: Lag 0: 0.94 (0.83, 1.08) Ischemic heart disease: Lag 0: 1.01 (0.94, 1.09) Dysrhythmias: Lag 0: 0.98 (0.86, 1.12) Heart failure: Lag 0: 1.00 (0.91, 1.09) Stroke: Lag 0: 0.99 (0.90, 1.09)
Schwartz et al. (1996) Cleveland, OH Apr-Oct 1988-1990	Total respiratory admissions for age 65+ years. Time-series study.	1-h max O ₃ : 56 ppb IQR 28	PM ₁₀ , SO ₂	1-2	Poisson GLM with sinusoids; co-adjustment. Results available only for warm season. Ozone and PM ₁₀ both significant predictors of outcome. No two-pollutant models reported.	1-h max O ₃ (per 100 µg/m ³): 1.09 (1.02, 1.16)

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Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
United States (cont'd)						
Gwynn and Thurston (2001) New York City 1988-1990	Respiratory admissions for all ages, stratified by race and insurance status. Time-series study.	24-h avg O ₃ : 22.1 ppb IQR 14.1 Maximum 80.7	H ⁺ , SO ₄ ²⁻ , PM ₁₀	1	GLM with high-pass filter. Ozone associated with respiratory admissions; effects larger for nonwhites and for those uninsured or on medicaid.	24-h avg O ₃ (per 58.6 ppb): White: 1.032 (0.987, 1.079) Non-white: 1.122 (1.074, 1.172) Uninsured: 1.138 (1.084, 1.194)
Gwynn et al. (2000) Buffalo, NY May 1988-Oct 1990	Total respiratory admissions for all ages. Time-series study.	24-h avg O ₃ : 26.2 ppb IQR 14.8	PM ₁₀ , SO ₄ ²⁻ , H ⁺ , COH, CO, NO ₂ , SO ₂	0, 1, 2, 3	Used Poisson with GAM default convergence criteria for control of temperature; moving average control for time. Ozone significant predictor of outcome. No two-pollutant models reported.	24-h avg O ₃ (per 14.8 ppb): Lag 1: 1.029 (1.013, 1.045)
Weisel et al. (2002) New Jersey May-Aug 1995	Asthma admissions for all ages. Time-series study.	1-h max O ₃ ; 5-h avg O ₃ (10 a.m.-3 p.m.); and 8-h avg O ₃ (2 p.m.-10 p.m.) analyzed. Levels not reported.	Pollen, spores	0, 1, 2, 3	No control for time, but authors report no autocorrelation, which alleviates concerns about lack of control. Significant O ₃ effects reported after adjusting for potential confounding by pollen.	Slope estimate (admissions/day/ppb): 5-h avg O ₃ and 8-h avg O ₃ : O ₃ only model: Lag 2: 0.099, p = 0.057 All three O ₃ indices: O ₃ with pollen model: Lag 2: 0.11, p = 0.033

Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Canada						
Burnett et al. (1997a) 16 Canadian cities 1981-1991	Total respiratory admissions for all ages, age <65 years and 65+ years. Time-series study.	1-h max O ₃ : All year: 31 ppb 95th % 60 Mean range across cities: 26-38 ppb 95th % 45-84 Jan-Mar: 26 ppb Apr-Jun: 40 ppb Jul-Sep: 38 ppb Oct-Dec: 21 ppb 9.6% of O ₃ data missing.	SO ₂ , NO ₂ , CO, coefficient of haze	0, 1, 2, 0-1, 0-2, 1-2	Poisson GLM with co-adjustment. Results stratified by season. Significant O ₃ effect observed in warm season only. No O ₃ effects on control outcomes. Results consistent across cities.	1-h max O ₃ (per 30 ppb): All ages: Jan-Mar: Lag 1: 0.994 (0.964, 1.025) Apr-Jun: Lag 1: 1.042 (1.012, 1.073) Jul-Sep: Lag 1: 1.050 (1.026, 1.074) Oct-Dec: Lag 1: 1.028 (0.998, 1.059)
Burnett et al. (1995) 168 Hospitals in Ontario, Canada 1983-1988	Respiratory and cardiovascular admissions for all ages and within age strata. Study focused mainly on testing for sulfate effects. Time-series study.	1-h max O ₃ : 36.3 ppb	SO ₄ ²⁻	1	GLM with pre-adjustment of outcome variables. Results stratified by season. Authors report that O ₃ associated with respiratory admission in warm season only.	No quantitative results presented for O ₃ .

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Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Canada (cont'd)						
Burnett et al. (1997b) Toronto, Ontario, Canada Summers 1992-1994	Unscheduled respiratory and cardiovascular admissions for all ages. Time-series study.	1-h max O ₃ : 41.2 ppb IQR 22	PM _{2.5} , PM ₁₀ , H ⁺ , SO ₄ ²⁻ , SO ₂ , NO ₂ , CO, coefficient of haze	0, 1, 2, 3, 4, 2 to 5 multiday periods lagged 1 to 4 days	Poisson GLM with co-adjustment. Results stratified by season. Ozone and coefficient of haze strongest predictors of outcomes. Ozone effects on both outcomes were robust to PM. PM effects were not robust to O ₃ .	12-h avg O ₃ (8 a.m.-8 p.m.) (per 11.5 ppb): Models adjusted for temperature and dewpoint: Respiratory : Lag 1-3: 1.064 (1.039, 1.090) Cardiovascular: Lag 2-4: 1.074 (1.035, 1.115)
Burnett et al. (1999) Toronto, Ontario, Canada 1980-1994	Cause-specific respiratory and cardiovascular admissions for all ages. Cause categories included asthma, COPD, respiratory infections, heart failure, ischemic heart disease, and cerebrovascular disease. Time-series study.	24-h avg O ₃ : 19.5 ppb IQR 19	Estimated PM _{2.5} , PM ₁₀ , PM _{10-2.5} , CO, NO ₂ , SO ₂	0, 1, 2, 0-1, 0-2, 1-2, 1-3, 2-3, 2-4	Poisson GAM with LOESS pre-filter applied to pollution and hospitalization data. Ozone effects seen for respiratory outcomes only. Ozone effect robust to PM; not vice versa. No seasonal stratification.	24-h avg O ₃ (per 19.5 ppb): Asthma: Lag 1-3: 1.063 (1.036, 1.091) COPD: Lag 2-4: 1.073 (1.038, 1.107) Respiratory infection: Lag 1-2: 1.044 (1.024, 1.065)
Burnett et al. (2001) Toronto, Ontario, Canada 1980-1994	Acute respiratory disease admissions for age <2 years. Time-series study.	1-h max O ₃ : Summer: 45.2 ppb IQR 25	Estimated PM _{2.5} , PM ₁₀ , PM _{10-2.5} , CO, NO ₂ , SO ₂	0, 1, 2, 3, 4, 5, 0-4	Poisson GAM with LOESS pre-filter applied to pollution and hospitalization data. Sensitivity analyses using co-adjustment. Results stratified by season. Ozone effects significant only in summer. Ozone effect robust to PM; not vice versa.	1-h max O ₃ (per 45.2 ppb): Summer: O ₃ only model: Lag 0-4: 1.348 (1.193, 1.524) O ₃ with PM _{2.5} model: Lag 0-4: 1.330 (1.131, 1.565)

Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Canada (cont'd)						
Lin et al. (2003) Toronto, Ontario, Canada 1981-1993	Asthma admission for age 6-12 years. Case-crossover design.	1-h max O ₃ : 30 ppb IQR 20	CO, SO ₂ , NO ₂	0, 0-1, 0-2, 0-3, 0-4, 0-5, 0-6	Conditional logistic regression model analysis. No O ₃ effects observed. Positive relations to CO, SO ₂ and NO ₂ observed.	1-h max O ₃ (per 20 ppb): Odds ratios: Males: Lag 0: 0.96 (0.88, 1.04) Females: Lag 0: 0.86 (0.78, 1.04)
Fung et al. (2005) Windsor, Ontario, Canada Apr 1995-Dec 2000	Cardiovascular hospital admissions for age <65 and ≥65 years. Time-series study.	1-h max O ₃ : 39.3 ppb SD 21.4 Range 1-129	NO ₂ , SO ₂ , CO, PM ₁₀ , coefficient of haze, total reduced sulfur compounds	0, 0-1, 0-2	Conducted both time-series analysis using Poisson GLM with natural splines. Strongest effect observed for SO ₂ in individuals aged ≥65 years. No associations were found any other pollutant, including O ₃ .	1-h max O ₃ (per 29 ppb): Age <65 years: Lag 0: 0.999 (0.913, 1.093) Lag 0-2: 1.042 (0.923, 1.177) Age ≥65 years: Lag 0: 0.974 (0.924, 1.027) Lag 0-2: 1.014 (0.941, 1.092)
Luginaah et al. (2005) Windsor, Ontario, Canada Apr 1995-Dec 2000	Respiratory hospital admissions by gender for all ages and age 0-14, 15-64, and 65+ years. Time-series study.	1-h max O ₃ : 39.3 ppb SD 21.4 Range 1-129	NO ₂ , SO ₂ , CO, PM ₁₀ , coefficient of haze, total reduced sulfur compounds	0, 0-1, 0-2	Conducted both time-series analysis using Poisson GLM with natural splines and bidirectional case-crossover analysis using conditional logistic regression models. For case-crossover analysis, control periods selected 2 weeks before and after the case period. Results were consistent for the time-series and case-crossover analyses. Significant associations were found for all pollutants except O ₃ and total reduced sulfur compounds.	1-h max O ₃ (per 29 ppb): All ages: Time-series analysis: Males: Lag 0: 1.04 (0.92, 1.17) Females: Lag 0: 0.95 (0.82, 1.10) Case-crossover analysis: Males: Lag 0: 1.06 (0.93, 1.22) Females: Lag 0: 1.01 (0.77, 1.34)

Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Canada (cont'd)						
Lin et al. (2004) Vancouver, British Columbia, Canada 1987-1998	Asthma admissions for age 6-12 years. Time-series study.	1-h max O ₃ : 28.02 ppb SD 11.54 IQR 14.81	CO, SO ₂ , NO ₂	0, 0-1, 0-2, 0-3, 0-4, 0-5, 0-6	Poisson GAM with LOESS (using default convergence criteria). Repeated analysis with natural cubic splines using 1,000 iterations with convergence criteria 10 ⁻¹⁵ . Results were similar for both analyses. NO ₂ exposure associated for males in low SES but not high. No association for CO and O ₃ in either SES group.	1-h max O ₃ (per 14.8 ppb): Males: Low SES: Lag 1: 0.85 (0.76, 0.94) High SES: Lag 1: 0.93 (0.83, 1.04) Females: Low SES: Lag 1: 1.11 (0.97, 1.28) High SES: Lag 1: 0.91 (0.78, 1.05)
Yang et al. (2003) Vancouver, British Columbia, Canada Jan 1986-Dec 1998	Daily respiratory admissions in children aged <3 years and adults aged 65+ years. Bidirectional case-crossover. Conditional logistic regression.	24-h avg O ₃ : 13.41 ppb SD 6.61 IQR 9.74	CO, NO ₂ , SO ₂ , coefficient of haze	1, 2, 3, 4, 5	Used bidirectional case-crossover analysis, comparing air pollution on day of admission to levels 1 week before and after. SES evaluated. Ozone was positively associated with respiratory hospital admissions among young children and the elderly.	24-h avg O ₃ (per 9.74 ppb): Odds ratios: Age <3 years: Lag 4: 1.22 (1.15, 1.30) Age 65+ years: Lag 4: 1.13 (1.09, 1.18)

Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Europe						
Anderson et al. (1997) Five European cities: London, Paris, Amsterdam, Rotterdam, Barcelona Study periods vary by city, ranging from 1977-1992	Emergency COPD admissions for all ages. Each city analyzed previously by individual teams. Results combined here via meta-analysis. Time-series study.	1-h max O ₃ : Median range across five cities: All year: 36-77 µg/m ³ Warm season: 48-91 µg/m ³ Cool season: 20-64 µg/m ³	TSP, SO ₂ , NO ₂ , BS	0, 1, 2, 3, 4, 5	Poisson GLM using APHEA methodology. Results stratified by season. Ozone most consistent and significant predictor of admissions. Warm-season effect larger.	1-h max O ₃ (per 50 µg/m ³): Weighted mean effect across five cities (best lag selected for each city): All year: 1.03 (1.01, 1.05) Warm season: 1.03 (1.01, 1.05) Cool season: 1.01 (0.98, 1.05)
AX7-61 Atkinson et al. (2001) Eight European cities: Barcelona, Birmingham, London Milan, Netherlands, Paris, Rome, and Stockholm Study periods vary by city, ranging from early to middle 1990s	Total respiratory, asthma, and COPD admissions for all ages and age 0-14, 15-64 and 65+ years. Time-series study.	8-h max O ₃ : Mean range: 26.0 µg/m ³ (Rome) to 66.6 µg/m ³ (Stockholm)	PM ₁₀ , NO ₂ , SO ₂ , CO	N/A	Study focused on PM ₁₀ effects. Copollutants included only as effect modifiers. No direct O ₃ results shown. Ozone appeared to modify the PM ₁₀ effect on respiratory admissions for persons over age 64 years of age.	No results presented for O ₃ .

Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Europe (cont'd)						
Le Tertre et al. (2002b) Eight European cities: Barcelona, Birmingham, London Milan, Netherlands, Paris, Rome, and Stockholm Study periods vary by city, ranging from early to middle 1990s	Total cardiovascular, ischemic heart disease, and stroke admissions for all ages and age 0-64 and 65+ years. Time-series study.	8-h max O ₃ : Mean range: 26.0 µg/m ³ (Rome) to 66.6 µg/m ³ (Stockholm)	PM ₁₀ , BS, NO ₂ , SO ₂ , CO	N/A	Main focus on PM ₁₀ and BS. Gaseous copollutants evaluated as effect modifiers. Greater PM ₁₀ effects seen in cities with lower annual O ₃ levels. No risk estimates presented for O ₃ .	No results presented for O ₃ .
Wong et al. (2002) London, England 1992-1994 Hong Kong 1995-1997	Total respiratory (>64 years), asthma (15-64 years), total cardiovascular (all ages), and ischemic heart disease (all ages) admissions. Time-series study.	8-h max O ₃ : London: All year: 34.9 µg/m ³ SD 23.1 Warm season: 45.3 µg/m ³ Cool season: 24.0 µg/m ³ Hong Kong: 33.5 µg/m ³ SD 23.0 Warm season: 32.0 µg/m ³ Cool season: 35.1 µg/m ³	PM ₁₀ , NO ₂ , SO ₂	0, 1, 2, 3 0-1	Poisson GAM with default convergence criteria. Most consistent associations found with total respiratory admissions. Ozone associated with total respiratory admissions in all-year and warm-season analyses in both cities. Associations in cool-season analyses observed only in Hong Kong. All-year O ₃ effects robust to copollutants.	8-h max O ₃ (per 10 µg/m ³): Total respiratory: London: All year: Lag 0-1: 1.008 (1.002, 1.014) Warm season: Lag 0-1: 1.010 (1.003, 1.017) Cool season: Lag 0-1: 1.002 (0.993, 1.012) Hong Kong: All year: Lag 0-1: 1.008 (1.003, 1.013) Warm season: Lag 0-1: 1.008 (1.002, 1.014) Cool season: Lag 0-1: 1.010 (1.002, 1.017)

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Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Europe (cont'd)						
Anderson et al. (1998) London, England 1987-1992	Admissions for asthma in all ages and age 0-14, 15-64, and 65+ years. Time-series study.	8-h max O ₃ : 15.5 ppb IQR 13 1-h max O ₃ : 20.6 ppb IQR 16	SO ₂ , NO ₂ , BS, pollens	0, 1, 2, 0-1, 0-2	Poisson GLM using APHEA method; co-adjustment. Ozone significantly associated with asthma admissions in the warm season for all ages and for age 15-64 years. Warm-season O ₃ effect robust in two-pollutant models. Inverse associations observed in the cool season for some age groups.	8-h max O ₃ (per 10 ppb): All ages: Warm season: Lag 1: 1.022 (1.006, 1.038) Cool season: Lag 1: 0.968 (0.946, 0.992)
Atkinson et al. (1999b) London, England 1992-1994	Total and cause-specific respiratory and cardiovascular admissions in all ages and in all ages and age 0-14, 15-64, and 65+ years. Time-series study.	8-h max O ₃ : 17.5 ppb SD 11.5	NO ₂ , SO ₂ , CO, PM ₁₀ , BS	0, 1, 2, 3, 0-1, 0-2, 0-3	Poisson GLM using APHEA methodology. No significant associations seen between O ₃ and respiratory admissions. Ozone was positively associated with total cardiovascular admissions in age 65+ years. Seasonal analyses were not conducted.	8-h max O ₃ (per 25.7 ppb): All ages: Total respiratory: Lag 1: 1.012 (0.990, 1.035) Total cardiovascular: Lag 2: 1.023 (1.002, 1.046)
Ponce de Leon et al. (1996) London, England Apr 1987-Feb 1992	Total respiratory admissions in several age strata: all ages, 0-14, 15-64, 65+ years. Time-series study.	8-h avg O ₃ (9 a.m.-5 p.m.): 15.6 ppb SD 12 IQR 14	BS, SO ₂ , NO ₂	0, 1, 2, 0-1, 0-2, 0-3,	Poisson GLM using APHEA co-adjustment methodology. Ozone significant predictor overall. Effect larger and more significant in warm season. Effect robust to copollutants. Effects varied by age.	All ages: All year: 8-h avg O ₃ (per 26 ppb): Lag 1: 1.029 (1.011, 1.048) Warm season: 8-h avg O ₃ (per 29 ppb): Lag 1: 1.048 (1.025, 1.073) Cool season: 8-h avg O ₃ (per 20 ppb): Lag 1: 0.996 (0.972, 1.021)

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Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Europe (cont'd)						
Poloniecki et al. (1997) London, England Apr 1987-Mar 1994	Cause-specific and total circulatory admissions for all ages. Time-series study.	8-h avg O ₃ (9 a.m.-5 p.m.): Median 13 ppb Range 0-94	BS, NO ₂ , SO ₂ , CO	0	Poisson regression using APHEA methodology. No association was found between O ₃ and circulatory diseases in all-year analyses. Results from acute MI suggest potential seasonal effect.	8-h avg O ₃ (per 25 ppb): Total circulatory: All year: 0.9726 (0.9436, 1.0046) Acute MI: All year: 0.9825 (0.9534, 1.0142) Warm season: 1.0126 (0.9560, 1.0228) Cool season: 0.9680 (0.9208, 1.0202)
Prescott et al. (1998) Edinburgh, Scotland 1992-1995	Total respiratory and cardiovascular admissions for age <65 years and 65+ years. Time-series study.	24-h avg O ₃ : 14.5 ppb Range 1-37	BS, PM ₁₀ , NO ₂ , SO ₂ , CO	0, 1, 1-3	Poisson GLM, month dummy variables; co-adjustment. No O ₃ or other pollution effects on respiratory admissions. Significant inverse association of O ₃ with cardiac admissions in older age group. Very low O ₃ concentrations.	24-h avg O ₃ (per 10 ppb): Respiratory: Age <65 years: Lag 1-3: 0.971 (0.885, 1.068) Age 65+ years: Lag 1-3: 1.009 (0.916, 1.111) Cardiovascular: Age <65 years: Lag 1-3: 1.041 (0.946, 1.144) Age 65+ years: Lag 1-3: 0.941 (0.886, 0.999)

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Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Europe (cont'd)						
Schouten et al. (1996) Amsterdam and Rotterdam, the Netherlands 1977-1989	Unscheduled total respiratory, asthma, and COPD admissions in all ages. Time-series study.	8-h max O ₃ : Amsterdam: Summer: 86 µg/m ³ 5th % to 95th % 28-152 Winter: 53 µg/m ³ 5th % to 95th % 3-104 Rotterdam: Summer: 81 µg/m ³ 5th % to 95th % 25-199 Winter: 45 µg/m ³ 5th % to 95th % 3-96	SO ₂ , NO ₂ , BS	0, 1, 2, 0-1, 0-2, 0-3, 0-4, 0-5	Poisson GLM using APHEA methodology; co-adjustment. No consistent O ₃ effects. Concern regarding multiple comparisons.	1-h max O ₃ (per 100 µg/m ³): Amsterdam and Rotterdam: Total respiratory, all ages: Summer: Lag 2: 1.051 (1.029, 1.073) Winter: Lag 2: 0.976 (0.951, 1.002)
Hagen et al. (2000) Drammen, Norway Nov 1994-Dec 1997	Total respiratory admissions for all ages. Time-series study.	24-h avg O ₃ : 44.48 µg/m ³ SD 18.40 IQR 26.29	PM ₁₀ , NO ₂ , SO ₂ , benzene, toluene, formaldehyde	0	Poisson GAM with partial splines; co-adjustment. Single and multipollutant models evaluated. No O ₃ effects. Ozone levels low and cycles may not have been adequately controlled.	24-h avg O ₃ (per 26.29 µg/m ³): Lag 0: 0.964 (0.899, 1.033)
Oftedal et al. (2003) Drammen, Norway 1995-2000	Admissions for respiratory disease. Time-series study.	24-h avg O ₃ : 44.6 µg/m ³ SD 19.2 IQR 26.9	Benzene, formaldehyde, toluene, PM ₁₀ , NO ₂ , SO ₂	0	Benzene had the strongest association.	24-h avg O ₃ (per 26.9 µg/m ³): 0.996 (0.942, 1.053)

Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Europe (cont'd)						
Pönkä and Virtanen (1996) Helsinki, Finland 1987-1989	Asthma admissions for age 0-14 years and 15-64 years. Time-series study.	8-h max O ₃ : All year: 22 µg/m ³ Winter: 20 µg/m ³ Spring: 30 µg/m ³ Summer: 23 µg/m ³ Fall: 15 µg/m ³	TSP, SO ₂ , NO ₂	0, 1, 2, 3, 4, 5	Poisson GLM using APHEA methodology. Reported significant O ₃ effect for age 0-14 years, but also for control (digestive disease) conditions. Ozone levels very low.	Not quantitatively useful.
Ballester et al. (2001) Valencia, Spain 1994-1996	Emergency total cardiovascular admissions for all ages. Time-series study.	8-h max O ₃ : 23 ppb Range 5-64	SO ₂ , NO ₂ , CO, BS	0, 1, 2, 3, 4, 5	Poisson GLM using APHEA methodology. Results stratified by season. No O ₃ effects.	8-h max O ₃ (per 5 ppb): Lag 2: 0.99 (0.97, 1.01)
Latin America						
Gouveia and Fletcher (2000a) São Paulo, Brazil Nov 1992-Sep 1994	Total respiratory, pneumonia, and asthma admissions for age <5 years. Time-series study.	1-h max O ₃ : 63.4 µg/m ³ SD 38.1 IQR 50.3	PM ₁₀ , NO ₂ , SO ₂ , CO	0, 1, 2	Poisson GLM with co-adjustment using sine/cosine waves. Significant O ₃ effects on total respiratory and pneumonia admissions. Ozone effects fairly robust to NO ₂ and PM ₁₀ .	1-h max O ₃ (per 119.6 µg/m ³): Total respiratory: Lag 0: 1.054 (1.003, 1.107) Pneumonia: Lag 0: 1.076 (1.014, 1.142) Asthma: Lag 2: 1.011 (0.899, 1.136)

Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Australia						
Morgan et al. (1998a) Sydney, Australia 1990-1994	Admissions for asthma (age 1-14 years, 15-64 years), COPD (age 65+ years), and heart disease (all ages, 0-64 years, 65+ years). Time-series study.	1-h max O ₃ : 25 ppb SD 13 IQR 11	B _{scatter} , NO ₂	0, 1, 2, 0-1, 0-2	Poisson with GEE. No significant effects of O ₃ in single or multipollutant models.	1-h max O ₃ (per 28 ppb): Asthma, age 1-14 years: Lag 1: 0.975 (0.932, 1.019) Asthma, age 15-64 years: Lag 0: 1.025 (0.975, 1.078) COPD, age 65+ years: Lag 0: 1.010 (0.960, 1.062) Heart disease, all ages: Lag 0: 1.012 (0.990, 1.035)
Petroeschevsky et al. (2001) Brisbane, Australia 1987-1994	Unscheduled asthma, total respiratory and total cardiovascular admissions in several age strata: all ages, 0-4, 5-14, 15-64, 65+ years. Time-series study.	8-h avg O ₃ (10 a.m.-6 p.m.): All year: 19.0 ppb Range 1.7-64.7 Winter: 16.1 ppb Spring: 23.3 ppb Summer: 19.9 ppb Fall: 16.7 ppb	B _{scatter} , SO ₂ , NO ₂	0, 1, 2, 3, 0-2, 0-4	Poisson GLM using APHEA co-adjustment methodology. Seasonal variations in O ₃ effects also investigated. Only a few significant interactions observed between O ₃ and season. Strong O ₃ effects observed in all-year models. Ozone significantly related to asthma and total respiratory admissions, not for cardiac admissions. Effects varied by age group. Ozone effects robust to copollutants.	8-h avg O ₃ (per 10 ppb): All year, all ages: Total respiratory: Lag 2: 1.023 (1.003, 1.043) Asthma: Lag 0-4: 1.090 (1.042, 1.141) Total cardiovascular: Lag 3: 0.987 (0.971, 1.002)
Asia						
Lee et al. (2002) Seoul, Korea Dec 1997-Dec 1999	Asthma admissions for age <15 years. Time-series study.	1-h max O ₃ : 36.0 ppb SD 18.6 IQR 21.7	SO ₂ , NO ₂ , CO, PM ₁₀	0, 1, 2, 3, 4, 0-1, 1-2, 2-3, 3-4	Poisson GAM using default convergence criteria. Ozone associated with asthma admissions in single- and two-pollutant models.	1-h max O ₃ (per 21.7 ppb): O ₃ only model: Lag 1: 1.12 (1.07, 1.16) O ₃ with PM ₁₀ model: Lag 1: 1.10 (1.05, 1.15)

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Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Asia (cont'd)						
Chang et al. (2005) Taipei, Taiwan 1997-2001	Total cardiovascular hospital admissions for all ages. Cool days (<20 °C) and warm days (≥20 °C) were evaluated. Case-crossover approach.	24-h avg O ₃ : 19.74 ppb IQR 10.87 Range 2.30-53.93	PM ₁₀ , SO ₂ , NO ₂ , CO	0-2	Conditional logistic regression. All cardiovascular admissions chosen because similar risks have been observed for major subcategories and combining counts provide greater power. Subtropical climate in Taipei. In the analysis of warm days only, all pollutants except SO ₂ were associated with cardiovascular admissions. Ozone effect slightly diminished in two-pollutant model adjusting for PM ₁₀ .	24-h avg O ₃ (per 10.87 ppb): Odds ratios: O ₃ only models: Warm: 1.189 (1.154, 1.225) Cool: 1.073 (1.022, 1.127) O ₃ with PM ₁₀ models: Warm: 1.066 (1.038, 1.094) Cool: 0.980 (0.924, 1.039)
Yang et al. (2004a) Kaohsiung, Taiwan 1997-2000	Total cardiovascular hospital admissions for all ages. Cool days (<25 °C) and warm days (≥25 °C) were evaluated. Case-crossover approach.	24-h avg O ₃ : 25.02 ppb IQR 21.20 Range 1.25-83.00	PM ₁₀ , SO ₂ , NO ₂ , CO	0-2	Conditional logistic regression. All pollutants except SO ₂ associated with cardiovascular admissions on warm days. On cool days, O ₃ effect was diminished. Ozone effect was robust to adjustment to copollutants. Results from tropical city may restrict generalization to other locations.	24-h avg O ₃ (per 21.20 ppb): Odds ratios: O ₃ only models: Warm: 1.351 (1.279, 1.427) Cool: 1.057 (0.962, 1.162) O ₃ with PM ₁₀ models: Warm: 1.308 (1.219, 1.404) Cool: 0.820 (0.732, 0.912)

Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Asia (cont'd)						
Tsai et al. (2003a) Kaohsiung, Taiwan 1997-2000	Stroke admissions (subarachnoid hemorrhagic stroke, primary intracerebral hemorrhage, ischemic stroke, and others) for all ages. Cool days (<20 °C) and warm days (≥20 °C) were evaluated. Case-crossover approach.	24-h avg O ₃ : 25.02 ppb IQR 21.20 Range 1.25-83.00	PM ₁₀ , SO ₂ , NO ₂ , CO	0-2	Conditional logistic regression. Warm day associations were positive while cool days were generally negative with some positive associations. Ozone effect was robust to adjustment for SO ₂ and CO, but not PM ₁₀ .	24-h avg O ₃ (per 21.20 ppb): Odds ratios: O ₃ only models: Primary intracerebral hemorrhage: Warm: 1.20 (1.06, 1.35) Cool: 0.57 (0.24, 1.34) Ischemic stroke: Warm: 1.15 (1.07, 1.23) Cool: 0.88 (0.50, 1.53) O ₃ with PM ₁₀ models: Primary intracerebral hemorrhage: Warm: 0.98 (0.85, 1.14) Ischemic stroke: Warm: 0.96 (0.88, 1.05)
Wong et al. (1999a) Hong Kong 1994-1995	Total and cause-specific respiratory and cardiovascular admissions in several age strata: all ages, 0-4, 5-64, 65+ years. Time-series study.	8-h max O ₃ : 20.2 µg/m ³ Median 24.15 IQR 31.63	NO ₂ , SO ₂ , PM ₁₀	0, 1, 2, 3, 4, 5, 0-1, 0-2, 0-3, 0-4, 0-5	Poisson GLM using APHEA methodology. Ozone significantly associated with total and cause specific respiratory and cardiac outcomes. Ozone results robust to adjustment for high PM ₁₀ , but not high NO ₂ . Effects of O ₃ persisted in cold season.	8-h max O ₃ (per 10 µg/m ³): All ages: Total respiratory: Lag 0-3: 1.022 (1.015, 1.029) Total cardiovascular: Lag 0-5: 1.013 (1.005, 1.021)

Table AX7-4 (cont'd). Effects of O₃ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean O ₃ Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Asia (cont'd)						
Wong et al. (1999b) Hong Kong Jan 1995-Jun 1997	Cause-specific cardiovascular admissions for age ≥65 years. Time-series study.	8-h avg O ₃ : Warm season: 31.2 µg/m ³ Cool season: 34.8 µg/m ³	NO ₂ , SO ₂ , respirable PM	0, 1, 2, 3, 4, 5, 0-1, 0-2, 0-3, 0-4, 0-5	GLM with sinusoids; co-adjustment. Ozone significantly associated with total and cause-specific cardiovascular admissions in cool season only, when O ₃ levels are higher in Hong Kong. Details missing in brief report.	O ₃ (per 50 µg/m ³): O ₃ with NO ₂ models: Total cardiovascular: All year: Lag 0-1: 1.03 (1.00, 1.07) Warm season: Lag 0-1: 1.01 (0.95, 1.07) Cool season: Lag 0-1: 1.08 (1.02, 1.14)

Table AX7-5. Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Meta-analysis						
Bell et al. (2005) Various U.S. and non-U.S. cities Varying study periods	All cause; cardiovascular; respiratory; all ages; age 64+ or 65+ years.	Not applicable.	Various PM indices	0, 1, 2, or 0-1	Meta-analysis. Bayesian hierarchical model; included up to 144 estimates from 39 studies. Risk estimates obtained for yearly vs. warm-season data; cause-specific; PM adjustment; U.S. vs. non-U.S.; various lags; and GAM vs. non-GAM. Comparisons with NMMAPS estimates (Bell et al., 2004).	24-h avg O ₃ (per 10 ppb): Posterior means: All cause: All year: 0.87% (0.55, 1.18) Warm: 1.50% (0.72, 2.29) Cardiovascular: All year: 1.11% (0.68, 1.53) Warm: 2.45% (0.88, 4.10) Respiratory: All year: 0.47% (-0.51, 1.47) O ₃ with PM model: All cause: All year: 0.97% (-0.03, 1.98) Meta-analysis results were consistently larger than those from NMMAPS. In addition, heterogeneity of city-specific estimates in the meta-analysis were larger compared to NMMAPS. These findings indicate possible publication bias.

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Meta-analysis (cont'd)						
Ito et al. (2005) Various U.S. and non-U.S. cities Varying study periods	All cause	Not applicable.	Various PM indices	Reported lags up to 3-day lags	Meta-analysis. DerSimonian-Laird approach; included up to 43 estimates from 38 studies. Risk estimates obtained for yearly vs. warm-season data; PM adjustment; correction for asymmetry in funnel plot; and GAM vs. non-GAM. Seven U.S. cities time-series study with various sensitivity analyses.	24-h avg O ₃ (per 20 ppb): O ₃ only model: All year: 1.6% (1.1, 2.0) Warm: 3.5% (2.1, 4.9) O ₃ with PM model: All year: 1.5% (0.8, 2.2) Non-GAM-affected: All year: 1.4% (0.8, 2.0) GAM-affected: All year: 1.9% (1.0, 2.8) Correction for funnel plot asymmetry: All year: 1.4% (0.9, 1.9) Seven U.S. cities analysis found that including PM in the model did not substantially reduce the O ₃ risk estimates. However, differences in the weather adjustment model could result in a 2-fold difference in risk estimates.

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Meta-analysis (cont'd)						
Levy et al. (2005) Various U.S., Canadian and European cities Varying study periods	All cause	Not applicable.	PM ₁₀ , PM _{2.5} , SO ₂ , NO ₂ , CO	0, 1-2	Meta-analysis. Empirical Bayes metaregression; included up to 48 estimates from 28 studies. Risk estimates obtained by season; copollutant adjustment; North America vs. Europe; various lags; temperature adjustment; GAM vs. non-GAM; and annual mean O ₃ . Examined relationship between O ₃ personal exposure and ambient concentrations using cooling degree days and residential central air-conditioning prevalence.	1-h max O ₃ (per 10 µg/m ³): O ₃ only model: All year: 0.21% (0.16, 0.26) Warm: 0.43% (0.29, 0.56) Cool: -0.02 (-0.17, 0.14) Non-GAM-affected: All year: 0.23% (0.15, 0.31) GAM-affected: All year: 0.20% (0.13, 0.27) Nonlinear specification of temperature: All year: 0.20% (0.13, 0.27) Linear specification of temperature: All year: 0.06 (-0.03, 0.16) In the metaregression, air-conditioning prevalence and lag time were the strongest predictors of between-study variability.

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
United States						
Bell et al. (2004) 95 U.S. communities 1987-2000	All cause; cardiopulmonary; all ages; age <65 years; age 65-74 years; age ≥75 years	24-h avg O ₃ : 26 ppb across the 95 communities. 55 communities with all-year data: Median range: 14.38 ppb (Newark, NJ) to 37.30 ppb (Bakersfield, CA) 40 communities with warm-season only data: Median range: 20.41 ppb (Portland, OR) to 36.15 ppb (Memphis, TN)	PM ₁₀ , PM _{2.5} ; two- pollutant models	0, 1, 2, 3, 0-6	Poisson GLM; Bayesian hierarchical model. Time-series study.	24-h avg O ₃ (per 10 ppb): Posterior means: All cause, all ages: All-available data: Lag 0: 0.25% (0.12, 0.39) Lag 0-6: 0.52% (0.27, 0.77) Warm season: Lag 0: 0.22% (0.08, 0.38) Lag 0-6: 0.39% (0.13, 0.65) All cause: All-available data: Age <65 years: Lag 0-6: 0.50% (0.10, 0.92) Age 65-74 years: Lag 0-6: 0.70% (0.28, 1.12) Age ≥75 years: Lag 0-6: 0.52% (0.18, 0.87) Cardiopulmonary, all ages: All-available data: Lag 0-6: 0.64% (0.31, 0.98)

AX7-74

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
United States (cont'd)						
Samet et al. (2000; reanalysis Dominici et al., 2003) 90 U.S. cities (80 U.S. cities with O ₃ data) 1987-1994	All cause; cardiopulmonary	24-h avg O ₃ : Mean range: Approximately 12 ppb (Des Moines, IA) to 36 ppb (San Bernardino, CA)	PM ₁₀ , NO ₂ , SO ₂ , CO; two-pollutant models	0, 1, 2	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	24-h avg O ₃ (per 10 ppb): Posterior means: All cause: All available data: Lag 0: 0.42% (0.22, 0.62) Lag 1: 0.19% (0.03, 0.35) Summer: Lag 1: 0.51% (0.23, 0.78) Winter: Lag 1: -0.53% (-1.10, 0.05)
Huang et al. (2005) 19 large U.S. cities Jun-Sept 1987-1994	Cardiopulmonary	24-h avg O ₃ : Mean range: Approximately 18 ppb (Oakland, CA) to 56 ppb (San Bernardino, CA) Daily range across 19 U.S. cities: 0-100 ppb	PM ₁₀ , PM _{2.5} ; two-pollutant models	0, 1, 2, 0-6	Poisson GLM; Bayesian hierarchical model. Time-series study.	24-h avg O ₃ (per 10 ppb): Posterior means: Single-day lag models: O ₃ only model: Lag 0: 0.73% (0.27, 1.19) O ₃ with PM ₁₀ model: Lag 0: 0.74% (-0.33, 1.72) Cumulative lag models: O ₃ only model: Lag 0-6: 1.25% (0.47, 2.03) Model adjusted for heat waves: Lag 0-6: 1.11% (0.38, 1.86)

AX7-75

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
United States (cont'd)						
Schwartz (2005) 14 U.S. cities 1986-1993	All cause	1-h max O ₃ : Median range: 35.1 ppb (Chicago, IL) to 60.0 ppb (Provo, UT)	PM ₁₀ ; two-pollutant models	0	Case-crossover analysis; conditional logical regression controlled for temperature using nonlinear regression splines and matching	1-h max O ₃ (per 10 ppb): Analysis with temperature regression splines: All year: 0.19% (0.03, 0.35) Warm season: 0.26% (0.07, 0.44) Cold season: 0% (-0.27, 0.27) Analysis with temperature matched controls: All year: 0.23% (0.01, 0.44) Warm season: 0.37% (0.11, 0.62) Cold season: -0.13% (-0.53, 0.28)
Kinney and Özkaynak (1991) Los Angeles County, CA 1970-1979	All cause; respiratory; circulatory	1-h max total oxidants (O _x): 75 ppb SD 45	KM (particle optical reflectance), NO ₂ , SO ₂ , CO; multipollutant models	1	OLS (ordinary least squares) on high-pass filtered variables. Time-series study.	All cause: Multipollutant model: Slope estimate: 0.030 deaths/ppb (SE 0.009), p = 0.0005 Cardiovascular: O ₃ only model: Slope estimate: 0.023 deaths/ppb (SE 0.006), p < 0.0001
Kinney et al. (1995) Los Angeles County, CA 1985-1990	All cause	1-h max O ₃ : 70 ppb SD 41	PM ₁₀ , NO ₂ , SO ₂ , CO; two-pollutant models	1	Linear, log-linear, and Poisson. Time-series study.	1-h max O ₃ (per 143 ppb): O ₃ only model: 2% (0, 5) O ₃ with PM ₁₀ model: 0% (-6, 6)

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
United States (cont'd)						
Ostro (1995) San Bernardino County and Riverside County, CA 1980-1986	All cause	1-h max O ₃ : 140 ppb Range 20-370	PM _{2.5}	0	Autoregressive linear; Poisson. Time-series study.	1-h max O ₃ (per 100 ppb): Warm season: 2.0% (0.0, 5.0)
Ostro et al. (2000) Coachella Valley, CA 1989-1998	All cause; respiratory; cardiovascular	1-h max O ₃ : Palm Springs: 67 ppb Range 0-190 Indio: 62 ppb Range 0-180	PM ₁₀ , PM _{2.5} , PM _{10-2.5} , NO ₂ , CO	0	Poisson GAM with default convergence criteria. Time-series study.	1-h max O ₃ (per 40 ppb): All cause: -1% (-4, 3) Respiratory: 3% (-9, 16) Cardiovascular: -4% (-9, 1)
Fairley (1999; reanalysis Fairley, 2003) Santa Clara County, CA 1989-1996	All cause; respiratory; cardiovascular	8-h max O ₃ : 29 ppb SD 15 24-h avg O ₃ : 16 ppb SD 9 O ₃ ppb-h >60 ppb: Levels not reported.	PM ₁₀ , PM _{2.5} , PM _{10-2.5} , SO ₄ ²⁻ , coefficient of haze, NO ₃ ⁻ , NO ₂ , SO ₂ ; two-pollutant models	0	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	GAM with stringent convergence criteria: All cause: 8-h max O ₃ (per 33 ppb): 3.1% (-0.3, 6.6) O ₃ ppb-h >60 ppb (increment not reported): 3.8% (1.4, 6.3) Cardiovascular: 8-h max O ₃ (per 33 ppb): 2.6% (-2.3, 7.8) O ₃ ppb-h >60 ppb (increment not reported): 4.3% (0.4, 8.3)

AX7-77

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
United States (cont'd)						
Gamble (1998) Dallas, TX 1990-1994	All cause; respiratory; cardiovascular; cancer; other	24-h avg O ₃ : All year: 22 ppb Range 0-160 Summer: 30 ppb Range 0-160 Winter: 12 ppb Range 0-75	PM ₁₀ , NO ₂ , SO ₂ , CO; two-pollutant models	1-2	Poisson GLM. Time-series study.	All year: 24-h avg O ₃ (per 14.7 ppb): All cause: 2.7% (0.6, 4.8) Cardiovascular: 2.4% (-1.1, 6.0) Summer: 24-h avg O ₃ (per 13.1 ppb): All cause: 3.5% (p < 0.05) Cardiovascular: 3.3% (p > 0.05) Winter: 24-h avg O ₃ (per 7.7 ppb): All cause: 2.4% (p > 0.05) Cardiovascular: 1.5% (p > 0.05)
Dockery et al. (1992) St. Louis, MO and Eastern Tennessee 1985-1986	All cause	24-h avg O ₃ : St. Louis, MO: 22.5 ppb SD 18.5 Eastern Tennessee: 23.0 ppb SD 11.4	PM ₁₀ , PM _{2.5} , SO ₄ ²⁻ , H ⁺ , NO ₂ , SO ₂	1	Poisson with GEE. Time-series study.	24-h avg O ₃ (per 20 µg/m ³): St. Louis, MO: 0.6% (t = 0.38) Eastern Tennessee: -1.3% (t = -0.37)

AX7-78

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
United States (cont'd)						
Ito and Thurston (1996) Cook County, IL 1985-1990	All cause; respiratory; circulatory; cancer; race/gender subcategories	1-h max O ₃ : 38.1 ppb SD 19.9	PM ₁₀ , NO ₂ , SO ₂ , CO; two-pollutant models	0-1	Poisson GLM. Time-series study.	1-h max O ₃ (per 100 ppb): All cause: O ₃ only model: 10% (6, 15) O ₃ with PM ₁₀ model: 7% (1, 12) Circulatory (results given in graphic format): O ₃ only model: 12% (6, 20)
Moolgavkar (2003) Cook County, IL and Los Angeles County, CA 1987-1995	All cause; cardiovascular	24-h avg O ₃ : Cook County: Median 18 ppb Range 0.2-67 Los Angeles County: Median 24 ppb Range 0.6-77	PM _{2.5} , PM ₁₀ , NO ₂ , SO ₂ , CO; two- pollutant models	0, 1, 2, 3, 4, 5	Poisson GAM with default convergence criteria. Time-series study.	24-h avg O ₃ (per 100 ppb): All cause, all year: Cook County: Lag 0: 1.4% (t = 6.3) Los Angeles County Lag 0: 0.4% (t = 2.3) All cause, summer: Cook County: Lag 0: 2.9% (t = 7.2) Los Angeles County Lag 0: 1.0% (t = 2.8) Cardiovascular, all year: Cook County: Lag 0: 1.8% (t = 5.5) Los Angeles County Lag 0: 0.2% (t = 0.9) Cardiovascular, summer: Cook County: Lag 0: 3.3% (t = 5.6) Los Angeles County Lag 0: 0.8% (t = 1.7)

AX7-79

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
United States (cont'd)						
Moolgavkar (2000) Cook County, IL; Los Angeles County, CA; and Maricopa County, AZ 1987-1995	Cardiovascular; cerebrovascular; COPD	24-h avg O ₃ :	PM _{2.5} , PM ₁₀ , NO ₂ , SO ₂ , CO; two- and three-pollutant models	0, 1, 2, 3, 4, 5	Poisson GAM with default convergence criteria. Time-series study.	24-h avg O ₃ (per 100 ppb):
		Cook County: Median 18 ppb Range 0.2-67				Cook County: Cardiovascular, all year: Lag 0: 1.51% (0.78, 2.24) COPD, all year: Lag 0: 1.53% (-0.49, 3.55)
		Los Angeles County: Median 24 ppb Range 0.6-77				Los Angeles County and Maricopa County: O ₃ results not presented. Noted as negative or small and nonsignificant in all-year and warm-season analyses.
Lippmann et al. (2000; reanalysis Ito, 2003, 2004) Detroit, MI 1985-1990 1992-1994	All cause; respiratory; circulatory; cause-specific	24-h avg O ₃ :	PM ₁₀ , PM _{2.5} , PM _{10-2.5} , SO ₄ ²⁻ , H ⁺ , NO ₂ , SO ₂ , CO; two-pollutant models	0, 1, 2, 3, 0-1, 0-2, 0-3	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	Poisson GLM:
		1985-1990: 20.9 ppb IQR 12.0-27.5				All lags and outcomes during both study periods (n = 140): 24-h avg O ₃ (per 5th to 95th % increment): Median 1.6% Range -1.8-2.6
		1992-1994: 25 ppb IQR 18-30				1985-1990: 24-h avg O ₃ (per 36 ppb): All cause: Lag 0: 1.08% (-1.08, 3.30) Circulatory: Lag 0: 1.84% (-1.26, 5.04)
						1992-1994 24-h avg O ₃ (per 28 ppb): All cause: Lag 0: 2.58% (-2.41, 7.82) Circulatory: Lag 0: 2.13% (-5.04, 9.85)

AX7-80

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
United States (cont'd)						
Lipfert et al. (2000a) Seven counties in Philadelphia, PA area 1991-1995	All cause; respiratory; cardiovascular; all ages; age 65+ years; age <65 years; various subregional boundaries	1-h max O ₃ : 44.76 ppb SD 25.68 24-h avg O ₃ : 23.44 ppb SD 13.86	PM ₁₀ , PM _{2.5} , PM _{10-2.5} , SO ₄ ²⁻ , NO ₃ ⁻ ; other PM indices, NO ₂ , SO ₂ , CO; two-pollutant models	0-1	Linear with 19-day weighted average Shumway filters. Time-series study.	1-h max O ₃ (per 45 ppb less background, not reported): All cause, all ages: O ₃ only model: 3.19%, p < 0.055 O ₃ with PM _{2.5} model: 3.34%, p < 0.055 Cardiovascular, all ages: O ₃ only model: 3.98%, p < 0.055 O ₃ with PM _{2.5} model: 5.35%, p < 0.055
Moolgavkar et al. (1995) Philadelphia, PA 1973-1988	All cause	24-h avg O ₃ : Spring: 25.9 ppb Range 2.9-74.0 Summer: 35.5 ppb Range 1.3-159.0 Fall: 16.2 ppb Range 0.2-63.8 Winter: 11.9 ppb Range 0.0-32.9	TSP, SO ₂ ; multipollutant models	1	Poisson; GEE and nonparametric bootstrap methods. Time-series study.	24-h avg O ₃ (per 100 ppb): O ₃ with TSP and SO ₂ models: Spring: 2.0% (-6.7, 11.5) Summer: 14.9% (6.8, 23.6) Fall: -4.5% (-13.9, 5.9) Winter: 0.4% (-15.6, 19.4)

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
United States (cont'd)						
Chock et al. (2000) Pittsburgh, PA 1989-1991	All cause; age <74 years; age 75+ years	1-h max O ₃ : Levels not reported.	PM ₁₀ , NO ₂ , SO ₂ , CO; two-, five-, and six-pollutant models	0	Poisson GLM. Time-series study.	1-h max O ₃ (per 40 ppb): Age <74 years: O ₃ only model: -1.5% (t = -0.68) O ₃ with PM ₁₀ model: -2.0% (t = -0.93) Age 75+ years: O ₃ only model: -1.8% (t = -0.82) O ₃ with PM ₁₀ model: -2.2% (t = -0.98)
De Leon et al. (2003) New York City 1985-1994	Circulatory and cancer with and without contributing respiratory causes	24-h avg O ₃ : 21.59 ppb 5th %-95th % 7.00-44.97	PM ₁₀ , NO ₂ , SO ₂ , CO; two-pollutant models	0 or 1	Poisson GAM with stringent convergence criteria; Poisson GLM. Time-series study.	Quantitative results not given. Circulatory deaths: Larger O ₃ effect estimates with contributing respiratory causes than without (RR nonsignificant). Cancer deaths: Smaller O ₃ effect estimates with contributing respiratory causes than without (RR nonsignificant).

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
United States (cont'd)						
Klemm and Mason (2000); Klemm et al. (2004) Atlanta, GA Aug 1998-July 2000	All cause; respiratory; cardiovascular; cancer; other; age <65 years; age 65+ years	8-h max O ₃ : 47.03 ppb SD 24.71	PM _{2.5} , PM _{10-2.5} , EC, OC, NO ₂ , SO ₄ ²⁻ , NO ₃ , SO ₂ , CO	0-1	Poisson GLM using quarterly, monthly, or biweekly knots for temporal smoothing. Time-series study.	All cause, age 65+ years: Quarterly knots: Slope estimate: 0.00079 (SE 0.00099), t = 0.80 Monthly knots: Slope estimate: 0.00136 (SE 0.00111), t = 1.22
Canada						
Vedal et al. (2003) Vancouver, British Columbia, Canada 1994-1996	All cause; respiratory; cardiovascular	1-h max O ₃ : 27.3 ppb SD 10.2	PM ₁₀ , NO ₂ , SO ₂ , CO	0, 1, 2	Poisson GAM with stringent convergence criteria. Time-series study.	1-h max O ₃ (per 10.2 ppb): Summer: All cause: Lag 0: 4.0% (1.4, 6.7) Respiratory: Lag 0: 1.5% (-6.6, 9.6) Cardiovascular: Lag 0: 3.9% (-0.3, 8.0)
Villeneuve et al. (2003) Vancouver, British Columbia, Canada 1986-1999	All cause; respiratory; cardiovascular; cancer; socioeconomic status	24-h avg O ₃ : 13.4 ppb Range 0.6-38.6	PM _{2.5} , PM ₁₀ , PM _{2.5-10} , TSP, coefficient of haze, SO ₄ ²⁻ , SO ₂ , NO ₂ , CO	0, 1, 0-2	Poisson GLM with natural splines. Time-series study.	24-h avg O ₃ (per 13.7 ppb): All year: All cause: Lag 0: 1.4% (-0.9, 3.6) Respiratory: Lag 0: 1.6% (-4.5, 8.1) Cardiovascular: Lag 0: 0.7% (-2.7, 4.3) Cancer: Lag 0: 2.6% (-1.2, 6.5) No effect modification of O ₃ -mortality effects by socioeconomic status.

AX7-83

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Canada (cont'd)						
Goldberg et al. (2003) Montreal, Quebec, Canada 1984-1993	Congestive heart failure as underlying cause of death vs. those classified as having congestive heart failure 1 year prior to death	24-h avg O ₃ : 29.0 µg/m ³ SD 17.1	PM _{2.5} , coefficient of haze, SO ₄ ²⁻ , SO ₂ , NO ₂ , CO	0, 1, 0-2	Poisson GLM with natural splines. Time-series study.	24-h avg O ₃ (per 21.3 µg/m ³): Congestive heart failure as underlying cause of death: Lag 0-2: 4.54% (-5.64, 15.81) Having congestive heart failure 1 year prior to death: Lag 0-2: 2.34% (-1.78, 6.63)
Goldberg et al. (2001) Montreal, Quebec, Canada 1984-1993	All cause; cause-specific; all ages; age <65 years; age ≥65 years	24-h avg O ₃ : 29.0 µg/m ³ SD 17.1	PM _{2.5} , coefficient of haze, SO ₂ , NO ₂ , NO, CO	0, 1, 0-2	Poisson GAM with default convergence criteria. Time-series study.	24-h avg O ₃ (per 21.3 µg/m ³): All cause, all year: All ages: Lag 0-2: 2.26% (1.23, 3.29) Age <65 years: Lag 0-2: 0.18% (-1.79, 2.20) Age ≥65 years: Lag 0-2: 2.84% (1.66, 4.04) Cardiovascular, all year: All ages: Lag 0-2: 3.00% (1.44, 4.59) Age <65 years: Lag 0-2: 1.33% (-2.30, 5.09) Age ≥65 years: Lag 0-2: 3.33% (1.62, 5.08)

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Europe						
Gryparis et al. (2004) 23 European cities Study periods vary by city, ranging from 1990-1997	All cause; respiratory; cardiovascular	1-h max O ₃ : Median range: Warm season: 44 ppb (Tel Aviv, Israel) to 117 ppb (Torino, Italy) Cold season: 11 ppb (Milan, Italy) to 57 ppb (Athens, Greece) 8-h max O ₃ : Median range: Warm season: 30 ppb (Rome, Italy) to 99 ppb (Torino, Italy) Cold season: 8 ppb (Milan, Italy) to 49 ppb (Budapest, Hungary)	PM ₁₀ , NO ₂ , SO ₂ , CO; two-pollutant models	0-1	Poisson GAM with stringent convergence criteria; Bayesian hierarchical model. Time-series study.	8-h max O ₃ (per 10 µg/m ³): Weighted mean effect across 21 cities with 8-h max O ₃ concentrations: Random effects model: All cause: All year: 0.03% (-0.18, 0.21) Warm season: O ₃ only model: 0.31% (0.17, 0.52) O ₃ with PM ₁₀ model: 0.27% (0.08, 0.49) Cold season: O ₃ only model: 0.12% (-0.12, 0.37) O ₃ with PM ₁₀ model: 0.22% (-0.08, 0.51) Respiratory: Warm season: 1.13% (0.74, 0.51) Cold season: 0.26% (-0.50, 0.84) Cardiovascular: Warm season: 0.46% (0.22, 0.73) Cold season: 0.07% (-0.28, 0.41)

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Europe (cont'd)						
Touloumi et al. (1997) Four European cities: London, Paris Barcelona, Athens Study periods vary by city, ranging from 1986-1992	All cause	1-h max O ₃ : London: 41.2 µg/m ³ SD 26.0 Paris: 46.1 µg/m ³ SD 32.9 Barcelona: 72.4 µg/m ³ SD 34.9 Athens: 93.8 µg/m ³ SD 42.8	BS, NO ₂ ; two-pollutant models	0, 1, 2, 3, 0-1, 0-2, 0-3	Poisson autoregressive. Time-series study.	1-h max O ₃ (per 50 µg/m ³): Weighted mean effect across four cities (best lag selected for each city): Single-day lag, random effects models: O ₃ only model: 2.9% (1.0, 4.9) O ₃ with BS model: 2.8% (0.5, 5.0) Cumulative lag, fixed effects model: O ₃ only model: 2.4% (1.2, 3.7)
Zmirou et al. (1998) Four European cities: London, Paris, Lyon, Barcelona Study periods vary by city, ranging from 1985-1992	Respiratory; cardiovascular	8-h avg O ₃ (9 a.m.-5 p.m.): London: Cold: 21.0 µg/m ³ Warm: 40.8 µg/m ³ Paris: Cold: 11.5 µg/m ³ Warm: 42.7 µg/m ³ Lyon: Cold: 21.0 µg/m ³ Warm: 40.8 µg/m ³ Barcelona: Cold: 51.5 µg/m ³ Warm: 89.7 µg/m ³	BS, TSP, SO ₂ , NO ₂	0, 1, 2, 3, 0-1, 0-2, 0-3	Poisson GLM. Time-series study.	8-h avg O ₃ (per 50 µg/m ³): Weighted mean effect across four cities (best lag selected for each city): Random effects models: Respiratory: 5% (2, 8) Cardiovascular: 2% (0, 3)

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Europe (cont'd)						
Anderson et al. (1996) London, England 1987-1992	All cause; respiratory; cardiovascular	1-h max O ₃ : 20.6 ppb SD 13.2 8-h avg O ₃ (9 a.m.-5 p.m.): 15.5 ppb SD 10.9	BS, NO ₂ , SO ₂ ; two-pollutant models	0	Poisson GLM. Time-series study.	All year: 8-h avg O ₃ (per 26 ppb): All cause: 2.43% (1.11, 3.76) Respiratory: 6.03% (2.22, 9.99) Cardiovascular: 1.44% (-0.45, 3.36) Warm season: 8-h avg O ₃ (per 29 ppb): All cause: 3.48% (1.73, 5.26) Respiratory: 5.41% (0.35, 10.73) Cardiovascular: 3.55% (1.04, 6.13) Cool season: 8-h avg O ₃ (per 20 ppb): All cause: 0.77% (-0.88, 2.44) Respiratory: 6.20 (1.67, 10.94) Cardiovascular: -1.69% (-3.99, 0.68)
Bremner et al. (1999) London, England 1992-1994	All cause; respiratory; cardiovascular; all cancer; all others; all ages; age specific (0-64, 65+, 65-74, 75+ years)	1-h max O ₃ : 22.6 ppb SD 13.4 8-h max O ₃ : 17.5 ppb SD 11.5	BS, PM ₁₀ , NO ₂ , SO ₂ , CO; two- pollutant models	Selected best from 0, 1, 2, 3, (all cause); 0, 1, 2, 3, 0-1, 0-2, 0-3 (respiratory, cardiovascular)	Poisson GLM. Time-series study.	8-h max O ₃ (per 26 ppb): All ages: All cause: Lag 2: -0.7% (-2.3, 0.9) Respiratory: Lag 2: -3.6% (-7.7, 0.8) Cardiovascular: Lag 2: 3.5% (0.5, 6.7)

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Europe (cont'd)						
Anderson et al. (2001) West Midlands region, England 1994-1996	All cause; respiratory; cardiovascular; all ages; age 0-14 years; age 15-64 years; age 65+ years	8-h max O ₃ : 24.0 ppb SD 13.8	PM ₁₀ , PM _{2.5} , PM _{2.5-10} , BS, SO ₄ ²⁻ , NO ₂ , SO ₂ , CO	0-1	Poisson GAM with default convergence criteria. Time-series study.	8-h max O ₃ (per 30.8 ppb): All ages: All cause: 2.9% (-0.1, 6.0) Respiratory: 2.2% (-5.4, 10.4) Cardiovascular: 0.9% (-3.4, 5.4)
Prescott et al. (1998) Edinburgh, Scotland 1992-1995	All cause; respiratory; cardiovascular; all ages; age <65 years; age ≥65 years	24-h avg O ₃ : 14.5 ppb SD 2.3	BS, PM ₁₀ , NO ₂ , SO ₂ , CO; two- pollutant models	0	Poisson GLM. Time- series study.	24-h avg O ₃ (per 10 ppb): All cause, all ages: -4.2% (-8.1, -0.1) Cardiovascular, age ≥65 years: 2.2% (-5.1, 10.3)
Le Tertre et al. (2002a) Le Havre, Lyon, Paris, Rouen, Strasbourg, and Toulouse, France Study periods vary by city, ranging from 1990-1995	All cause; respiratory; cardiovascular	8-h max O ₃ : Le Havre: 43.4 µg/m ³ Lyon: 52.0 µg/m ³ Paris: 26.0 µg/m ³ Rouen: 57.9 µg/m ³ Strasbourg: 37.0 µg/m ³ Toulouse: 68.0 µg/m ³	BS, NO ₂ , SO ₂	0-1	Poisson GAM with default convergence criteria. Time-series study.	8-h max O ₃ (per 50 µg/m ³): Six-city pooled estimates: All cause: 2.7% (1.3, 4.1) Respiratory: 0.8% (-4.8, 6.2) Cardiovascular: 2.4% (-0.3, 5.1)

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Europe (cont'd)						
Dab et al. (1996) Paris, France 1987-1992	Respiratory	1-h max O ₃ : 43.9 µg/m ³ 5th %-99th % 6.0-147.0 8-h max O ₃ : 27.7 µg/m ³ 5th %-99th % 3-110	BS, PM ₁₃ , NO ₂ , SO ₂ , CO	0	Poisson autoregressive. Time-series study.	1-h max O ₃ (per 100 µg/m ³): 1.074 (0.934, 1.235) 8-h max O ₃ (per 100 µg/m ³): 1.040 (0.934, 1.157)
Zmirou et al. (1996) Lyon, France 1985-1990	All cause; respiratory; cardiovascular; digestive	1-h max O ₃ : 15.23 µg/m ³ Range 0-152 8-h avg O ₃ (9 a.m.-5 p.m.): 9.94 µg/m ³ Range 0-78.92	PM ₁₃ , SO ₂ , NO ₂	Selected best from 0, 1, 2, 3	Poisson GLM. Time- series study.	8-h avg O ₃ (per 50 µg/m ³): All cause: Lag 0: 3% (-5, 12) Respiratory: Lag 1: 1% (-8, 10) Cardiovascular: Lag 1: 0% (-11, 12)
Sartor et al. (1995) Belgium Summer 1994	All cause; age <65 years; age 65+ years	24-h avg O ₃ : Geometric mean: During heat wave (42-day period): 72.4 µg/m ³ Range 34.5-111.5 Before heat wave (43-day period): 52.4 µg/m ³ Range 30.7-92.0 After heat wave (39-day period): 38.6 µg/m ³ Range 18.8-64.9	TSP, NO, NO ₂ , SO ₂	0, 1, 2	Log-linear regression. Time-series study.	No individual regression coefficient for O ₃ alone; interaction with temperature suggested. 24-h avg O ₃ (from 18.8 to 111.5 µg/m ³) and temperature (from 10.0 to 27.5°C): Age <65 years: Lag 1: 16% increase in mortality (5.3% expected) Age 65+ years: Lag 1: 36.5% increase in mortality (4% expected)

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Europe (cont'd)						
Hoek et al. (2000; reanalysis Hoek, 2003) The Netherlands: entire country, four urban areas 1986-1994	All cause; COPD; pneumonia; cardiovascular	8-h avg O ₃ (12 p.m.-8 p.m.): Median: 47 µg/m ³ Range 1-226	PM ₁₀ , BS, SO ₄ ²⁻ , NO ₃ , NO ₂ , SO ₂ , CO; two-pollutant models	1, 0-6	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	Poisson GLM: All cause: 8-h avg O ₃ (per 150 µg/m ³): Lag 1: 4.3% (2.4, 6.2) 8-h avg O ₃ (per 120 µg/m ³): Lag 0-6: 5.9% (3.1, 8.7)
Hoek et al. (2001; reanalysis Hoek, 2003) The Netherlands 1986-1994	Total cardiovascular; myocardial infarction; arrhythmia; heart failure; cerebrovascular; thrombosis-related	8-h avg O ₃ (12 p.m.-8 p.m.): Median: 47 µg/m ³ Range 1-226	PM ₁₀ , NO ₂ , SO ₂ , CO	1	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	8-h avg O ₃ (per 150 µg/m ³): Poisson GLM: Total cardiovascular: 6.2% (3.3, 9.2) Myocardial infarction: 4.3% (0.1, 8.6) Arrhythmia: 11.4% (-1.2, 25.5) Heart failure: 10.2% (1.2, 19.9) Cerebrovascular: 9.1% (2.9, 15.7) Thrombosis-related: 16.6% (2.8, 32.2)
Roemer and van Wijnen (2001) Amsterdam, the Netherlands 1987-1998	All cause	8-h max O ₃ : Background sites: 43 µg/m ³ Maximum 221 Traffic sites: 36 µg/m ³ Maximum 213	BS, PM ₁₀ , NO ₂ , SO ₂ , CO	1, 2, 0-6	Poisson GAM with default convergence criteria (only one smoother). Time-series study.	8-h max O ₃ (per 100 µg/m ³): Total population using background sites: Lag 1: -0.3% (-4.1, 3.7) Total population using traffic sites: Lag 1: 0.2% (-3.6, 4.2)

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Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Europe (cont'd)						
Verhoeff et al. (1996) Amsterdam, the Netherlands 1986-1992	All cause; all ages; age 65+ years	1-h max O ₃ : 43 µg/m ³ Maximum 301	PM ₁₀ , NO ₂ , SO ₂ , CO; multipollutant models	0, 1, 2	Poisson. Time-series study.	1-h max O ₃ (per 100 µg/m ³) All ages: Lag 0: 1.8% (-3.8, 7.8) Lag 1: 0.1% (-4.7, 5.1) Lag 2: 4.9% (0.1, 10.0)
Peters et al. (2000b) NE Bavaria, Germany 1982-1994 Coal basin in Czech Republic 1993-1994	All cause; respiratory; cardiovascular; cancer	24-h avg O ₃ : Czech Republic: 40.3 µg/m ³ SD 25.0 Bavaria, Germany: 38.2 µg/m ³ SD 21.9	TSP, PM ₁₀ , NO ₂ , SO ₂ , CO	0, 1, 2, 3	Poisson GLM. Time-series study.	24-h avg O ₃ (per 100 µg/m ³): Czech Republic: All cause: Lag 2: 7.8% (-1.8, 18.4) Bavaria, Germany: All cause: Lag 0: 8.2% (0.4, 16.7) Cardiovascular: Lag 0: 6.1% (-3.7, 17.0)
Pönkä et al. (1998) Helsinki, Finland 1987-1993	All cause; cardiovascular; age <65 years, age 65+ years	24-h avg O ₃ : Median 18 µg/m ³ 5th %-95th % 3-51	TSP, PM ₁₀ , NO ₂ , SO ₂	0, 1, 2, 3, 4, 5, 6, 7	Poisson GLM. Time-series study.	24-h avg O ₃ (per 20 µg/m ³): All cause: Age <65 years: Not significant, values not reported. Age 65+ years: Not significant, values not reported. Cardiovascular: Age <65 years: Lag 0: -2.0% (-9.5, 6.1) Lag 1: 6.2% (-2.2, 15.5) Age 65+ years: Not significant, values not reported.

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Europe (cont'd)						
Saez et al. (2002) Barcelona, Spain 1991-1995 Madrid, Spain 1992-1995 Valencia, Spain 1994-1996	All cause; respiratory; cardiovascular	8-h max O ₃ : Barcelona: 67.5 µg/m ³ SD 32.2 Madrid: 42.1 µg/m ³ SD 27.8 Valencia: 45.5 µg/m ³ SD 19.7	NO ₂ , PM, SO ₂ , CO; multipollutant models	0-5	Poisson GAM with default convergence criteria. Time-series study.	8-h max O ₃ (per 10 µg/m ³): Three-city pooled estimates: All cause: 0.23% (-0.15, 0.61) Respiratory: 0.29% (-0.05, 0.63) Cardiovascular: 0.60% (0.08, 1.13)
AX7-92 Garcia-Aymerich et al. (2000) Barcelona, Spain 1985-1989	All cause; respiratory; cardiovascular; general population; patients with COPD	1-h max O ₃ : Levels not reported.	BS, NO ₂ , SO ₂ ,	Selected best single-day lag	Poisson GLM. Time-series study.	1-h max O ₃ (per 50 µg/m ³): All cause: General population: Lag 5: 2.4% (0.6, 4.2) COPD patients: Lag 3: 4.0% (-4.7, 13.4) Respiratory: General population: Lag 5: 3.5% (-1.9, 9.2) COPD patients: Lag 3: 5.7% (-7.9, 21.4) Cardiovascular: General population: Lag 1: 2.9% (0.4, 5.4) COPD patients: Lag 3: 1.1% (-14.2, 19.2)
Saez et al. (1999) Barcelona, Spain 1986-1989	Asthma mortality; age 2-45 years	1-h max O ₃ : Levels not reported.	BS, NO ₂ , SO ₂ ,	0-2	Poisson with GEE. Time-series study.	Slope estimate: 0.021 (SE 0.011), p = 0.054

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Europe (cont'd)						
Sunyer et al. (1996) Barcelona, Spain 1985-1991	All cause; respiratory; cardiovascular; all ages; age 70+ years	1-h max O ₃ : Summer: 86.5 µg/m ³ Range 9.5-283.5 Winter: 55.2 µg/m ³ Range 7-189.2	BS, SO ₂ , NO ₂	Selected best single-day lag	Autoregressive Poisson. Time-series study.	1-h max O ₃ (per 100 µg/m ³): All cause, all ages: All year: Lag 0: 4.8% (1.2, 8.6) Summer: Lag 0: 5.8% (1.7, 10.1) Winter: Lag 0: 2.6% (-3.5, 9.1) Respiratory, all ages: All year: Lag 5: 7.1% (-3.8, 19.2) Summer: Lag 5: 5.0% (-7.3, 18.8) Winter: Lag 5: 14.0% (-7.6, 40.6) Cardiovascular, all ages: All year: Lag 1: 5.8% (0.9, 11.1) Summer: Lag 1: 8.8% (2.8, 15.2) Winter: Lag 1: -0.8% (-8.9, 7.9)
Sunyer and Basagana (2001) Barcelona, Spain 1990-1995	Mortality in a cohort of patients with COPD	1-h max O ₃ : Mean not reported IQR 21 µg/m ³	PM ₁₀ , NO ₂ , CO	0-2	Conditional logistic (case-crossover)	1-h max O ₃ (per 21 µg/m ³): Odds ratio: 0.979 (0.919, 1.065)

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Europe (cont'd)						
Sunyer et al. (2002) Barcelona, Spain 1986-1995	All cause, respiratory, and cardiovascular mortality in a cohort of patients with severe asthma	1-h max O ₃ : Median 69.3 µg/m ³ Range 6.6-283.0 8-h max O ₃ : Median 54.4 µg/m ³ Range 3.9-244.5	PM ₁₀ , BS, SO ₂ , NO ₂ , CO, pollen	0-2	Conditional logistic (case-crossover)	1-h max O ₃ (per 48 µg/m ³): Odds ratios: Patients with only one admission: All cause: 1.096 (0.820, 1.466) Cardiovascular: 1.397 (0.854, 2.285) Patients with more than one admission: All cause: 1.688 (0.978, 2.643) Cardiovascular: 1.331 (0.529, 3.344) Patients admitted for both asthma and COPD: All cause: 0.946 (0.674, 1.326) Cardiovascular: 0.985 (0.521, 1.861)
Díaz et al. (1999) Madrid, Spain 1990-1992	All cause; respiratory; cardiovascular	24-h avg O ₃ : Levels not reported.	TSP, NO ₂ , SO ₂ , CO	1, 4, 10	Autoregressive linear. Time-series study.	24-h avg O ₃ (per 25 µg/m ³): For O ₃ levels higher than 35 µg/m ³ : All cause: Lag 4: 12% (p < 0.01) U-shaped (quadratic) O ₃ -mortality relationship with a minimum of 35 µg/m ³ .

AX7-94

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Latin America						
Borja-Aburto et al. (1997) Mexico City 1990-1992	All cause; respiratory; cardiovascular; all ages; age <5 years; age >65 years	1-h max O ₃ : Median 155 ppb 8-h max O ₃ : Median 94 ppb 10-h avg O ₃ (8 a.m.-6 p.m.): Median 87 ppb 24-h avg O ₃ : Median 54 ppb	TSP, SO ₂ , CO; two-pollutant models	0, 1, 2	Poisson iteratively weighted and filtered least-squares method. Time-series study.	1-h max O ₃ (per 100 ppb): All ages: O ₃ only model: All cause: Lag 0: 2.4% (1.1, 3.9) Respiratory: Lag 0: 2.3% (-1.9, 6.7) Cardiovascular: Lag 0: 3.6% (0.6, 6.6) O ₃ with TSP model: All cause: Lag 0: -1.8% (-10.0, 6.4) Respiratory: Lag 0: -1.9% (-11.0, 8.2) Cardiovascular: Lag 0: 2.4 (-4.4, 9.6)
Borja-Aburto et al. (1998) SW Mexico City 1993-1995	All cause; respiratory; cardiovascular; other; all ages; age >65 years	1-h max O ₃ : 163 ppb SD 57 24-h avg O ₃ : 44.0 ppb SD 15.7	PM _{2.5} , NO ₂ , SO ₂ ; two-pollutant models	0, 1, 2, 3, 4, 5, 1-2	Poisson GAM with default convergence criteria (only one smoother). Time series study.	24-h avg O ₃ (per 10 ppb): All cause, all ages: Lag 1-2: 0.6% (-0.3, 1.5) All cause, age > 65 years: Lag 1-2: 0.8% (-0.4, 2.0) Respiratory, all ages: Lag 1-2: -0.7% (-3.6, 2.1) Cardiovascular, all ages: Lag 1-2: 1.8% (0.1, 3.5) Other noninjury, all ages: Lag 1-2: 0.3% (-0.9, 1.4)

AX7-95

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Latin America (cont'd)						
O'Neill et al. (2004) Mexico City 1996-1998	All cause; all ages; age 65+ years; SES gradient	24-h avg O ₃ : 35.3 ppb SD 11.0	PM ₁₀	0-1	Poisson GAM with stringent convergence criteria. Time-series study.	24-h avg O ₃ (per 10 ppb): All ages: 0.65% (0.02, 1.28) Age 65+ years: 1.39% (0.51, 2.28) SES gradient did not show any consistent pattern.
Télez-Rojo et al. (2000) Mexico City 1994	Respiratory; COPD mortality; age 65+ years; within medical unit; outside of medical unit	1-h max O ₃ : 134.5 ppb SD 33.4	PM ₁₀ , NO ₂ , SO ₂	1, 2, 3, 4, 5, 1-3, 1-5, 1-7	Poisson, iteratively weighted and filtered least-squares method. Time-series study.	1-h max O ₃ (per 40 ppb): Outside medical unit: Respiratory: Lag 1-5: 14.0% (4.1, 24.9) COPD mortality: Lag 1-5: 15.6% (4.0, 28.4)
Loomis et al. (1999) Mexico City 1993-1995	Infant mortality	24-h avg O ₃ : 44.1 ppb SD 15.7	PM _{2.5} , NO ₂	0, 1, 2, 3, 4, 5, 2-3	Poisson GAM with default convergence criteria. Time-series study.	24-h avg O ₃ (per 10 ppb): O ₃ only model: 2.45% (-0.54, 5.43) O ₃ with PM _{2.5} model: 1.40% (-1.92, 4.72)
Gouveia and Fletcher (2000b) São Paulo, Brazil 1991-1993	All ages (all cause); age <5 years (all cause, respiratory, pneumonia); age 65+ years (all cause, respiratory, cardiovascular)	1-h max O ₃ : 67.9 µg/m ³ SD 42.1	PM ₁₀ , NO ₂ , SO ₂ , CO	0, 1, 2	Poisson GLM. Time-series study.	1-h max O ₃ (per 106 µg/m ³): All ages: All cause: Lag 0: 0.8% (-1.1, 2.7) Age 65+ years: All cause: Lag 2: 2.3% (0, 4.6) Respiratory: Lag 2: 5.1% (-0.6, 11.1) Cardiovascular: Lag 0: 3.1% (-0.4, 6.7)

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Latin America (cont'd)						
Pereira et al. (1998) São Paulo, Brazil 1991-1992	Intrauterine mortality	1-h max O ₃ : 67.5 µg/m ³ SD 45.0	PM ₁₀ , NO ₂ , SO ₂ , CO	0	Poisson, linear with M-estimation. Time-series study.	Slope estimate: 0.0000 (SE 0.0004)
Saldiva et al. (1994) São Paulo, Brazil 1990-1991	Respiratory; age <5 years	24-h avg O ₃ : 12.14 ppb SD 9.94	PM ₁₀ , NO ₂ , SO ₂ , CO; multipollutant models	0-2	OLS of transformed data. Time-series study.	Slope estimate: 0.01048 deaths/day/ppb (SE 0.02481), p = 0.673
Saldiva et al. (1995) São Paulo, Brazil 1990-1991	All cause; age 65+ years	1-h max O ₃ : 38.3 ppb SD 29.7 24-h avg O ₃ : 12.5 ppb SD 11.5	PM ₁₀ , NO ₂ , SO ₂ , CO; two-pollutant models	0-1	OLS; Poisson with GEE. Time-series study.	Slope estimate: 1-h max O ₃ : 0.0280 deaths/day/ppb (SE 0.0213), p > 0.05 24-h avg O ₃ : 0.0093 deaths/day/ppb (SE 0.0813), p > 0.05
Cifuentes et al. (2000) Santiago, Chile 1988-1966	All cause	1-h max O ₃ : Summer: 108.2 ppb IQR 48.0	PM _{2.5} , PM _{10-2.5} , CO, SO ₂ , NO ₂	0, 1, 2, 3, 4, 5, 1-2, 1-3, 1-4, 1-5	Poisson GAM with default convergence criteria; Poisson GLM. Time-series study.	1-h max O ₃ per (108.2 ppb): Poisson GLM: Summer: O ₃ only model: Lag 1-2: 0.3% (t = 0.3) Multipollutant model: Lag 1-2: -0.1% (t = -0.1)
Ostro et al. (1996) Santiago, Chile 1989-1991	All cause	1-h max O ₃ : 52.8 ppb Range 11-264	PM ₁₀ , NO ₂ , SO ₂ ; two-pollutant models	1	OLS, several other methods. Time-series study.	All year: 1-h max O ₃ (per 52.8 ppb): -3% (-4, -2) Summer: 1-h max O ₃ (per 100 ppb): 4% (0, 9)

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Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Australia						
Morgan et al. (1998b) Sydney, Australia 1989-1993	All cause; respiratory; cardiovascular	1-h max O ₃ : 24 ppb SD 13	PM by nephelometer, NO ₂ ; multipollutant models	0	Poisson with GEE. Time-series study.	1-h max O ₃ (per 28 ppb): All cause: 2.04% (0.37, 3.73) Respiratory: -0.84% (-7.16, 5.91) Cardiovascular: 2.52% (-0.25, 5.38)
Simpson et al. (1997) Brisbane, Australia 1987-1993	All cause; respiratory; cardiovascular; all ages; age <65 years; age 65+ years	8-h avg O ₃ (10 a.m.-6 p.m.): All year: 18.1 ppb Range 1.7-63.4 Summer: 20.2 ppb Range 2.7-63.4 Winter: 16.1 ppb Range 1.7-56.9	PM ₁₀ , PM by nephelometer, NO ₂ , SO ₂ , CO	0	Autoregressive Poisson with GEE. Time-series study.	8-h avg O ₃ (per 10 ppb): All cause, all ages: All year: 2.4% (0.8, 4.0) Summer: 3.0% (1.0, 5.0) Winter: 1.3% (-1.4, 4.1)
Asia						
Kim et al. (2004) Seoul, Korea 1995-1999	All cause	1-h max O ₃ : All year: 35.16 ppb SD 18.31 Summer: 46.87 ppb SD 22.46 Winter: 21.26 ppb SD 6.92	PM ₁₀ , NO ₂ , SO ₂ , CO; two-pollutant models	1	Poisson GAM with stringent convergence criteria (linear model); GLM with cubic natural spline; GLM with B-mode spline (threshold model). Time-series study.	1-h max O ₃ (per 21.5 ppb): All year: Linear model: 2.6% (1.7, 3.5) Threshold model: 3.4% (2.3, 4.4) Summer: Linear model: 1.9% (0.5, 3.3) Threshold model: 3.8% (2.0, 5.7)

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Asia (cont'd)						
Lee et al. (1999) Seoul and Ulsan, Korea 1991-1995	All cause	1-h max O ₃ : Seoul: 32.4 ppb 10th %-90th % 14-55 Ulsan: 26.0 ppb 10th %-90th % 16-39	TSP, SO ₂	0	Poisson with GEE. Time-series study.	1-h max O ₃ (per 50 ppb): Seoul: 1.5% (0.5, 2.5) Ulsan: 2.0% (-11.1, 17.0)
Lee and Schwartz (1999) Seoul, Korea 1991-1995	All cause	1-h max O ₃ : Seoul: 32.4 ppb 10th %-90th % 14-55	TSP, SO ₂	0	Conditional logistic regression. Case-crossover with bidirectional control sampling.	1-h max O ₃ (per 50 ppb): Two controls, plus and minus 1 week: 1.5% (-1.2, 4.2) Four controls, plus and minus 2 weeks: 2.3% (-0.1, 4.8)
Kwon et al. (2001) Seoul, Korea 1994-1998	Mortality in a cohort of patients with congestive heart failure	1-h max O ₃ : 31.8 ppb IQR 20.5 Range 4.3-102.8	PM ₁₀ , NO ₂ , SO ₂ , CO	0	Time-series analysis using Poisson GAM with default convergence criteria; case-crossover analysis using conditional logistic regression.	1-h max O ₃ (per 20.5 ppb): Odds ratios from case-crossover study design: General population: 1.9% (1.0, 2.9) Congestive heart failure cohort: 5.1% (-3.6, 14.7)

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Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Asia (cont'd)						
Ha et al. (2003) Seoul, Korea 1995-1999	All cause; respiratory; postneonatal (1 month to 1 year); age 2-64 years; age ≥65 years	8-h avg O ₃ : 21.2 ppb SD 11.6 Range 2.9-69.1	PM ₁₀ , NO ₂ , SO ₂ , CO	0	Poisson GAM with default convergence criteria. Time-series study.	8-h avg O ₃ (per 16.1 ppb): Respiratory: Postneonatal: 22.6% (-41.2, 155.8) Age 2-64 years: 9.8% (6.8, 13.0) Age ≥65 years: 3.7% (2.6, 4.8)
Hong et al. (2002) Seoul, Korea 1995-1998	Acute stroke mortality	8-h avg O ₃ : 22.6 ppb SD 12.4 IQR 9.3	PM ₁₀ , NO ₂ , SO ₂ , CO	0	Poisson GAM with default convergence criteria. Time-series study.	8-h avg O ₃ (per 9.3 ppb): O ₃ only model: 2.9% (0.3, 5.5) PM ₁₀ < median: 5.5% PM ₁₀ ≥ median: -2.5%
Tsai et al. (2003b) Kaohsiung, Taiwan 1994-2000	All cause; respiratory; cardiovascular; tropical area	24-h avg O ₃ : 23.6 ppb Range 1.2-83.0	PM ₁₀ , SO ₂ , NO ₂ , CO	0-2	Conditional logistic regression. Case- crossover analysis.	24-h avg O ₃ (per 19.2 ppb): Odds ratios: All cause: 0.994 (0.995, 1.035) Respiratory: 0.996 (0.848, 1.169) Cardiovascular: 1.005 (0.919, 1.098)
Yang et al. (2004b) Taipei, Taiwan 1994-1998	All cause; respiratory; cardiovascular; subtropical area	24-h avg O ₃ : 17.18 ppb Range 2.3-43.47	PM ₁₀ , SO ₂ , NO ₂ , CO	0-2	Conditional logistic regression. Case- crossover analysis.	24-h avg O ₃ (per 9.34 ppb): Odds ratios: All cause: 0.999 (0.972, 1.026) Respiratory: 0.991 (0.897, 1.094) Cardiovascular: 1.004 (0.952, 1.058)

Table AX7-5 (cont'd). Effects of Acute O₃ Exposure on Mortality

Reference, Study Location and Period	Outcome Measure	Mean O ₃ Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates
Asia (cont'd)						
Wong et al. (2001) Hong Kong 1995-1997	All cause; respiratory; cardiovascular	8-h avg O ₃ (9 a.m.-5 p.m.): Warm: 32.0 ppb SD 24.5 Range 0-168.9 Cool: 35.1 ppb SD 21.3 Range 0-101.6	PM ₁₀ , NO ₂ , SO ₂ ; two-pollutant models	3, 4, 5	Poisson GAM with default convergence criteria. Time-series study.	8-h avg O ₃ (per 16.1 ppb): All cause: Warm: Lag 5: -1% (-3, 2) Cool: Lag 5: 4% (1, 6) Respiratory: Warm: Lag 4: -1% (-6, 5) Cool: Lag 4: 8% (2, 15) Cardiovascular: Warm: Lag 3: -2% (-6, 3) Cool: Lag 3: 5% (0, 11)
Hedley et al. (2002) Hong Kong 1985-1995 Intervention Jul 1990 (switch to low sulfur- content fuel)	All cause; cardiovascular; respiratory; neoplasms and other causes; all ages; age 15-64 years; age 65+ years	Average monthly O ₃ : Baseline: 18.5 µg/m ³ SD 7.5 1 year after intervention: 21.3 µg/m ³ SD 9.1 2-5 years after intervention: 22.1 µg/m ³ SD 10.2	SO ₂ (main pollutant of interest, 45% reduction observed 5 years after intervention), PM ₁₀ , SO ₄ ²⁻ , NO ₂	Monthly averages considered without lags	Poisson regression of monthly averages to estimate changes in the increase in deaths from warm to cool season. Annual proportional change in death rate before and after the intervention was also examined.	Declines observed in all cause (2.1%, p = 0.001), respiratory (3.9%, p = 0.001), and cardiovascular (2.0%, p = 0.020) mortality after the intervention. Analysis not specific for O ₃ effects. As O ₃ levels did not change before and after the intervention, O ₃ likely did not play a role in the decline in observed mortality.

Table AX7-6. Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
United States			
Galizia and Kinney (1999; exposure data Kinney et al., 1998) U.S. nationwide 1995	1-h max O ₃ : 10-year mean Jun-Aug: 61.2 ppb SD 15.5 Range 13-185	Cross-sectional study of a nationwide sample of 520 young adults. Subjects were nonsmokers, aged 17-21 years, 50% males. Each subject provided one spirometric lung function measurement in the spring of their 1st year at Yale College in New Haven, CT, and completed a questionnaire addressing residential history, respiratory diseases, and activity patterns. Long-term O ₃ exposure was treated as a high/low dichotomous variable, with subjects assigned to the high O ₃ category if they lived for 4+ years in counties with 10-year summer mean O ₃ levels greater than 80 ppb. Four lung function variables (FVC, FEV ₁ , FEF ₂₅₋₇₅ , FEF ₇₅) were regressed on O ₃ exposure, controlling for age, height, height squared, sex, race, parental education, and maternal smoking history. Respiratory symptom histories (cough, phlegm, wheeze apart from colds, and composite index for any of the three symptoms) were logistically regressed on O ₃ exposure, controlling for sex, race, parental education, and maternal smoking.	<p>Significant decrements in FEV₁ and FEF₂₅₋₇₅ in relation to O₃ exposure were observed for all subjects and for males alone, but not for females alone. Similar patterns observed for FVC and FEF₇₅, but not with statistical significance.</p> <p>Percent difference in lung function for high vs. low O₃ exposure groups:</p> <p>FEV₁: All subjects: -3.07% (-0.22, -5.92) Females: -0.26% (3.79, -4.31) Males: -4.71% (-0.66, -8.76)</p> <p>FEF₂₅₋₇₅: All subjects: -8.11% (-2.32, -13.90) Females: -1.96% (6.39, -10.30) Males: -13.02% (-4.87, -21.17)</p> <p>Wheeze and respiratory symptom index were significantly elevated for high O₃ exposure group.</p> <p>Odds ratios for symptoms:</p> <p>Wheeze: 1.97 (1.06, 3.66) Respiratory symptom index: 2.00 (1.15, 3.46)</p>
Goss et al. (2004) U.S. nationwide 1999-2000	1-h max O ₃ : 51.0 ppb SD 7.3	Cohort study of 11,484 cystic fibrosis patients over the age of 6 years. Exposure to O ₃ , PM _{2.5} , PM ₁₀ , NO ₂ , SO ₂ , and CO assessed by linking Aerometric Information Retrieval System with patients' home zip code. Studied exacerbation and lung function. Mortality was also of interest, but study was underpowered to examine this outcome. Logistic regression models were used to analyze the exacerbations and multiple linear regression was used to study lung function. O ₃ monitoring season and regional effects also were examined.	<p>Ozone may increase the risk for pulmonary exacerbations in cystic fibrosis patients.</p> <p>Odds ratios for two or more exacerbations (per 10 ppb increase in 1-h max O₃):</p> <p>O₃ only model: 1.10 (1.03, 1.17) O₃ with PM_{2.5} model: 1.08 (1.01, 1.15)</p> <p>PM_{2.5}, but not O₃, was significantly associated with declines in lung function in these patients.</p>

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Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
United States (cont'd)			
Kinney and Lippmann (2000) Fort Sill, OK; Fort Leonard Wood, MO; Fort Dix, NJ; Fort Benning, GA; West Point, NY Apr-Sep 1990	1-h max O ₃ : Mean during 5-week summer training period:	Prospective cohort study of 72 nonsmoking students (mean age 20.25 years) at the U.S. Military Academy at West Point, NY were measured for lung function and respiratory symptoms before (Apr) and after (Aug-Sep) taking part in an intensive, largely outdoor, summer training over 5 weeks (Jul 11-Aug 15) at four U.S. military bases. Ozone levels in the Fort Dix, NJ area were consistently higher than at the three remaining three locations. Analysis assessed change in lung function and respiratory symptoms measured before and soon after the summer training, and examined whether adverse trends would be more pronounced in students exposed to higher O ₃ levels during summer training.	Mean FEV ₁ declined significantly over the two measurement points for all subjects combined, which may reflect combined effects of O ₃ with exposures to dust, vehicle exhaust, and environmental tobacco smoke as reported by subjects from all four locations in the post-summer questionnaire. However, a larger mean decline was seen at the higher O ₃ site, Fort Dix, than at the remaining three sites, suggesting an influence of O ₃ exposures. A larger decline was observed in subjects with post-summer measurements in the 1st and 2nd weeks after returning from training vs. those measured in the 3rd and 4th weeks, which is consistent with the lung function effects being somewhat transient. Change in lung function over the summer: FEV ₁ : All locations: -44 mL (SE 21), p = 0.035 Fort Dix: -78 mL (SE 41), p = 0.07 Forts Sill, Leonard Wood, and Benning combined: -31 mL (SE 24), p = 0.21
	Fort Benning, GA: 55.6 ppb (0 h O ₃ >100 ppb)		
	Fort Dix, NJ: 71.3 ppb (23 h O ₃ >100 ppb)		
	Fort Leonard Wood, MO: 55.4 ppb (1 h O ₃ >100 ppb)		
Fort Sill, OK: 61.7 ppb (1 h O ₃ >100 ppb)			
Greer et al. (1993) California 1973-1987	Annual mean O ₃ : Levels not reported.	Prospective cohort study of 3,914 nonsmoking adults aged 25+ years at enrollment in 1977 completed questionnaires at two time points, 1977 and 1987. To be eligible, subjects had to have lived 10 or more years within 5 miles of current residence. Residential histories used to interpolate air pollution levels to zip centroids over a 20-year period (1966-1987). New asthma cases defined as answering yes to doctor diagnosed asthma at 1987 followup among those answering no at enrollment in 1977. Multiple logistic regression used to test for associations between new-onset asthma and long-term exposures to air pollution, controlling for age, education, pneumonia or bronchitis before age 16 years, and years worked with a smoker through 1987. All models stratified by gender.	There were 27 incident cases of asthma among 1,305 males and 51 incident cases among 2,272 females. In logistic regression analyses, long-term O ₃ exposures were associated with increased risk of incident asthma among males but not females. Relative risks for incident cases of asthma (per 10 ppb increase in annual mean O ₃): Males: 3.12 (1.61, 5.85) Females: 0.94 (0.65, 1.34)

Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
United States (cont'd)			
McDonnell et al. (1999) California 1973-1992	8-h avg O ₃ (9 a.m.-5 p.m): 20-year mean: 46.5 ppb SD 15.3	This prospective cohort study continued the work of Greer et al. (1993). 3,091 nonsmoking adults completed questionnaires at one additional time point, 1992. Residential histories used to interpolate air pollution levels to zip centroids over the period 1973-1992, yielding annual mean exposure estimates for O ₃ , PM ₁₀ , SO ₂ , and NO ₂ . New asthma cases defined as answering yes to doctor diagnosed asthma at either 1987 or 1992. Multiple logistic regression used to test for associations between new-onset asthma and long-term exposures to air pollution, controlling for age, education, pneumonia or bronchitis before age 16, and ever smoking. All models run separately for males and females.	There were 32 incident cases of asthma among 972 males and 79 incident cases among 1,786 females. In logistic regression analyses, long-term O ₃ exposures were associated with increased risk of incident asthma among males but not females. Other pollutants were neither associated with asthma incidence nor were confounders of the O ₃ association in males. Relative risks for incident cases of asthma (per 27 ppb increase in annual mean 8-h avg O ₃): Males: 2.09 (1.03, 4.16) Females: 0.86 (0.58, 1.26)
Peters et al. (1999a,b) 12 Southern California communities 1993-1994	1-h max O ₃ : Mean range: 1986-1990: 30.2 ppb (Santa Maria) to 109.2 ppb (San Dimas) 1994: 35.5 ppb (Santa Maria) to 97.5 ppb (Lake Gregory)	3,676 children aged 9-16 years enrolled into the 1st cohort of the Children's Health Study in 1993. Subjects provided questionnaire data on respiratory disease histories and symptoms. 3,293 subjects also underwent pulmonary function testing, of which 2,781 were used in air pollution regressions. Air pollution data for O ₃ , PM ₁₀ , PM _{2.5} , NO ₂ , and inorganic acid vapors analyzed from 1986-1990 and 1994. For cross-sectional analysis of respiratory diseases, individual pollutants were tested for associations with ever asthma, current asthma, bronchitis, cough, and wheeze after controlling for covariates. For analysis of lung function, individual pollutants and pairs of pollutants were regressed with FVC, FEV ₁ , FEF ₂₅₋₇₅ , and PEF, controlling for usual demographic and anthropometric covariates.	Acids and NO ₂ , but not O ₃ , were associated significantly with prevalence of wheeze. No associations of O ₃ with any of the respiratory diseases or symptoms. Decreased lung function was associated with multiple pollutants among females but not males. For O ₃ exposure in females, all four lung function variables declined with increasing exposure. Associations were stronger for current (1994) exposure compared to previous (1986-1990) exposure. In males who spent more time outdoors, FVC and FEV ₁ declined significantly with higher current exposure to O ₃ . Change in lung function (per 40 ppb 1-h max O ₃ from 1986-1990): Females: PEF: -187.2 mL/s (SE 50.1), p < 0.005 FEF ₂₅₋₇₅ : -102.2 mL/s (SE 28.8), p < 0.01 Males: PEF: 31.1 mL/s (SE 48.8), p > 0.05 FEF ₂₅₋₇₅ : 11.7 mL/s (SE 26.7), p > 0.05

Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
United States (cont'd)			
Gauderman et al. (2000; 2004a,b) 12 Southern California communities 1993-2001	8-h avg O ₃ (10 a.m.-6 p.m.): Mean range: Approximately 28 ppb (Long Beach) to 65 ppb (Lake Arrowhead)	Analysis of longitudinal lung function change in relation to long-term air pollution levels in the Children's Health Study cohort. Children from 4th (n = 1,498), 7th (n = 802), and 10th (n = 735) grade enrolled in 1993. Children enrolled in 7th and 10th grade were followed until 1997; 4th graders were followed until 2001. Baseline questionnaires completed and annual pulmonary function tests (FVC, FEV ₁ , FEF ₂₅₋₇₅ , FEF ₇₅) performed. Air pollution monitoring stations established in the 12 study communities beginning in 1994 to measure O ₃ , NO ₂ , PM ₁₀ , PM _{2.5} , and inorganic acid. Analysis using adjusted linear regression models.	In the 7th and 10th grade cohorts, difference in lung function growth from the least to the most polluted community was not associated with any of the air pollutants, including O ₃ . Among the 4th graders, decreased lung growth was associated with exposures to PM _{2.5} , NO ₂ , acid vapor, and elemental carbon, but not with O ₃ . It should be noted, however, that there was only about a 2- to 2.5-fold difference in O ₃ concentrations from the least to most polluted communities, compared to the other pollutants which had a 4- to 8-fold difference in concentrations. In addition, these results should be interpreted with caution given the potential for substantial misclassification of O ₃ exposure.
Gauderman et al. (2002) 12 Southern California communities 1996-1999	8-h avg O ₃ (10 a.m.-6 p.m.): Mean range: Approximately 27 ppb (Long Beach) to 67 ppb (Lake Gregory)	Second cohort of the longitudinal cohort Children's Health Study. 2,081 4th graders (mean age 9.9 years) enrolled in 1996. Baseline questionnaires were completed and annual pulmonary function tests (FVC, FEV ₁ , FEF ₂₅₋₇₅ , FEF ₂₅₋₇₅ /FVC, PEF) were performed. 1,672 children had at least two pulmonary function test data. Air pollutants examined include O ₃ , NO ₂ , PM ₁₀ , PM _{2.5} , inorganic acid, elemental carbon, and organic carbon. Adjusted linear regression model was used.	In this cohort, a significant association between O ₃ and PEF and FVC was noted in children spending more time outdoors. Percent difference in annual increases in lung function from least to most polluted community (per 36.6 ppb increase in annual mean 8-h avg O ₃): PEF: All children: -1.21% (-2.06, -0.36) Children more outdoors: -1.62% (-2.93, -0.29) Children less outdoors: -0.87% (-2.09, 0.37)
McConnell et al. (1999) 12 Southern California communities 1993	1-h max O ₃ : Estimated annual mean: 65.6 ppb Range 35.5-97.5	First cohort of the Children's Health Study. Association of O ₃ with prevalence of chronic lower respiratory tract symptoms among children with a history of asthma was examined in a cross-sectional study in 12 communities. Questionnaires were completed by parents of 3,676 4th, 7th, and 10th graders, of which 493 had asthma. Exposure data (O ₃ , NO ₂ , PM ₁₀ , PM _{2.5} , and inorganic acid vapors) collected in 1994 used to estimate exposure. Analysis using logistic regression method.	Children with asthma were much more likely to have bronchitis or related symptoms than children without such history. Among the asthmatic children, significant relationship were observed between phlegm and all pollutants studied, with the exception of O ₃ .

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Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
United States (cont'd)			
McConnell et al. (2003) 12 Southern California communities 1996-1999	8-h avg O ₃ (10 a.m.-6 p.m.): 4-year average across 12 communities: 47.2 ppb SD 11.3 Range 28.3-65.8 Range of yearly variability within the 12 communities: 5.3 ppb SD 3.2 Range 1.7-13.2	A total of 475 children with asthma from the 1st and 2nd cohorts of the Children's Health Study were recruited to examine the relationship between bronchitic symptoms and air pollutants. Analysis involved three stages using logistic mixed effects models. Within-community variability in air pollution was assessed in the first stage; individual level time-independent confounders were assessed in the second stage; and the effects of 4-year average air pollutants were examined in the third stage. Other copollutants examined include NO ₂ , PM ₁₀ , PM _{2.5} , PM _{10-2.5} , inorganic acid, organic acid, EC, and OC.	Symptoms were generally associated with the various air pollutants. Within-community effects were greater than the between-community effects. Authors note that if the larger within-community effect estimates are correct, then other cross-sectional (between-community) studies may have underestimated the true effect of air pollution on respiratory symptoms in children. These differences may be attributable to confounding by poorly measured or unmeasured risk factors that vary between communities. Ozone effect estimates were markedly reduced in two-pollutant models (odds ratios not provided). Odds ratios for bronchitic symptoms (per ppb O ₃): Within-community effects: 1.06 (1.00, 1.12) Between-community effects: 0.99 (0.98, 1.01)
McConnell et al. (2002) 12 Southern California communities 1993-1998	1-h max O ₃ : 4-year average (1994-1997): Low-pollution communities (n = 6): 50.1 ppb Range 37.7-67.9 High-pollution communities (n = 6): 75.4 ppb Range 69.3-87.2	Prospective cohort study of 3,535 children (age 9-16 years) without a history of asthma recruited in 1993 and 1996, and followed with annual surveys through 1998 to determine incidence of new onset asthma. Participation in sports assessed at baseline. Copollutants included PM ₁₀ , PM _{2.5} , NO ₂ , and inorganic acid vapors. Asthma incidence was examined as a function of number of sports played in high- and low-pollution communities, controlling for age, sex, and ethnic origin.	Asthma incidence was not higher in the high-pollution communities as compared with the low-pollution communities, regardless of the pollutant used to define high/low. In fact, the high-O ₃ communities had generally lower asthma incidence. However, in high-O ₃ communities, there was an increased risk of asthma in children playing three or more sports vs. those playing no sports; no such increase was observed in the low-O ₃ communities. No other pollutant showed this association. These results suggest that high levels of physical activity is associated with risk of new asthma development for children living in communities with high O ₃ levels. Relative risk of developing asthma in children playing three or more sports vs. those playing no sports: Low-pollution communities: 0.8 (0.4, 1.6) High-pollution communities: 3.3 (1.9, 5.9)

Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
United States (cont'd)			
Avol et al. (2001) 12 Southern California communities and six western states Baseline 1994 Follow-up 1998	8-h avg O ₃ (10 a.m.-6 p.m.): Mean range of baseline levels: 30.4 ppb for Santa Maria to 70.8 ppb for Lake Gregory Mean range of changes: 11.7 ppb increase to 27.0 ppb decrease in O ₃ levels	110 children enrolled in Children's Health Study in 1993 and 1994 followed after moving to different western states. Age 10-11 years at time of enrollment). Follow-up pulmonary function testing carried out in 1998. Change in lung function over time tested in relation to change in exposures to PM ₁₀ , NO ₂ , and O ₃ .	Negative but nonsignificant associations were found between lung function parameters and changes in O ₃ . The relationship was strongest with PM ₁₀ . Subjects who moved to areas of lower PM ₁₀ showed greater increases in FEV1 compared subjects who moved to areas with higher PM ₁₀ . Change in lung function (per 10 ppb increase in changes in annual mean 8-h avg O ₃): FEV ₁ : 0.1 mL (-8.7, 8.9) FVC: -1.4 mL (-10.8, 8.0) MMEF (maximal midexpiratory flow): -3.4 mL/s (-23.6, 16.8) PEF: -8.9 mL/s (-41.6, 23.8)
Ritz and Yu (1999) Southern California 1989-1993	Last trimester average: 20.9 ppb Range 3.0-49.4	125,573 births within 2 miles of an air monitoring station were examined to determine associations between CO and low birth weight. Copollutants included only as potential confounders.	Exposure to higher levels of ambient CO during the last trimester was associated with a significantly increased risk for low birth weight. Effects of CO appeared more pronounced after adjustment for concurrent exposures to NO ₂ , PM ₁₀ , and O ₃ . Ozone effect estimates were not reported.
Ritz et al. (2000) Southern California 1989-1993	8-h avg O ₃ (9 a.m.-5 p.m.): 1st month of pregnancy: 36.9 ppb SD 20.7 Range 2.6-124 6 weeks before birth: 36.9 ppb SD 19.4 Range 3.3-117	Data on 97,158 singleton births over period 1989-1993 linked to air monitoring data during different periods of pregnancy to determine associations between pollution exposures and preterm birth. Besides O ₃ , pollutants of interest included PM ₁₀ , NO ₂ , and CO. Multiple regression analysis used, controlling for maternal age, race, education, parity, and other factors.	Both PM ₁₀ and CO during early or late pregnancy were associated with increased risk for preterm birth. No associations observed with O ₃ .

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Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
United States (cont'd)			
Ritz et al. (2002) Southern California 1987-1993	24-h avg O ₃ : Quartile means: 1st month of gestation: 6.4, 15.2, 23.9, 34.2 ppb 2nd month: 6.4, 15.6, 24.2, 34.9 ppb 3rd month: 6.8, 16.6, 24.9, 34.9 ppb	The effect of air pollution on the occurrence of birth defects was examined using a case-control study design. Analyses focused on CO and O ₃ . Six types of cardiac birth defects were investigated – aortic defects, defects of the atrium and atrium septum, endocardial and mitral valve defects, pulmonary artery and valve defects, conotruncal defects, and ventricular septal defects. A 1:10 case-control ratio was achieved for defect-specific analyses. Analyses were conducted using polytomous logistic regression. A two-stage hierarchical regression model was used to adjust for multiple comparisons.	Concentration-response patterns were observed for O ₃ concentrations during the 2nd month of gestation on aortic artery and valve defects, pulmonary artery and valve anomalies, and conotruncal defects. CO during the 2nd gestational month was found to be associated with ventricular septal defects. The results were inconclusive for NO ₂ and PM ₁₀ . Findings from this study suggest that there may be a vulnerable window of development to human malformations. Odds ratios for birth defects (per 10 ppb O ₃ during 2nd month of gestation): Aortic defects: 1.56 (1.16, 2.09) Pulmonary valve defects: 1.34 (0.96, 1.87) Conotruncal defects: 1.36 (0.91, 2.03)
Künzli et al. (1997); Tager et al. (1998) Los Angeles and San Francisco, CA; Berkeley, CA 1995	8-h avg O ₃ (10 a.m.-6 p.m.): Lifetime monthly average: Los Angeles: Median 51.5 ppb Range 25-74 San Francisco: Median 22.5 ppb Range 16-33	A pilot cohort study of 130 freshman students (age 17-21 years) at the University of California at Berkeley measured for lung function and histories of residential locations and indoor/outdoor activity patterns and levels. By design, students had previously resided in one of two metropolitan areas that differed greatly in O ₃ concentrations, San Francisco or Los Angeles. A key goal was to test whether measures of small airways function (e.g., nitrogen washout, FEF ₂₅₋₇₅ , FEF ₇₅) were sensitive measures of long-term O ₃ impacts. Lifetime exposures to O ₃ , PM ₁₀ and NO ₂ assigned by interpolation to sequence of residence locations from available monitoring stations. Multiple exposure measures were derived with varying degrees of incorporation of time-activity information, going from ecological concentration to individual time-activity weighted exposure. Performed linear regression analysis of lung function on O ₃ exposures, controlling for height, ethnicity, gender, and region.	Decreased FEF ₂₅₋₇₅ and FEF ₇₅ were associated with long-term O ₃ exposures. Results were similar whether O ₃ exposure was purely ecologic or incorporated time-activity information. FVC, FEV ₁ , and nitrogen washout were generally not associated with O ₃ levels. No evidence for PM ₁₀ or NO ₂ main effects or confounding of O ₃ . Similar patterns results using O ₃ hours >60 ppb as exposure metric instead of daily 8-h avg O ₃ . Surprisingly, region of residence was a major negative confounder as lung function was lower on average among students from the low O ₃ city, San Francisco, than among those who had lived in Los Angeles. Ozone exposures were significant predictors only after controlling the regional effect. Change in lung function (per 20 ppb increase in lifetime mean 8-h avg O ₃): FEF ₂₅₋₇₅ : -420 mL/s (-886, 46); 7.2% of population mean FEF ₇₅ : -334 mL/s (-657, -11); 14% decline of population mean

Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
United States (cont'd)			
Tager et al. (2005) Los Angeles and San Francisco, CA; Berkeley, CA 2000-2002	8-h avg O ₃ (10 a.m.-6 p.m.); Lifetime monthly average: Men: 36 ppb Range 19-64 Women: 33 ppb Range 18-65 Difference in median exposure between Los Angeles and San Francisco: 17 ppb	Similar study design to that of Künzli et al. (1997). A cohort study of 255 freshman students (age 16-19 years) at the University of California at Berkeley who previously resided in San Francisco or Los Angeles measured for lung function between Feb and May. Subjects were lifetime never-smokers without history of chronic respiratory diseases. Histories of residential locations, and indoor/outdoor activity patterns and levels also evaluated. Lifetime exposures to O ₃ , PM ₁₀ , and NO ₂ assigned by interpolation to sequence of residence locations from available monitoring stations. Multiple exposure measures were derived with varying degrees of incorporation of time-activity information, going from ecological concentration to individual time-activity weighted exposure. The base lung function model consisted of gender-specific linear regressions of each lung function measure on age, height, and weight. Modification of the air pollution effect on lung function by the FEF ₂₅₋₇₅ /FVC ratio (a measure of intrinsic airway size) was also examined.	In the models examining only the main effects of O ₃ , no associations were observed between lifetime exposure to O ₃ and lung function parameters in either men or women. However, after including an interaction term for FEF ₂₅₋₇₅ /FVC ratio, consistent inverse associations between increasing lifetime exposure to O ₃ and FEF ₂₅₋₇₅ and FEF ₇₅ were observed for both men and women. The adverse impact of increased lifetime exposure to O ₃ was found to decrease with increasing FEF ₂₅₋₇₅ /FVC ratio. Comparable regressions with PM ₁₀ and NO ₂ showed similar results. When PM ₁₀ and NO ₂ were added to the O ₃ model for FEF ₇₅ , there were no meaningful changes in the effect estimates for lifetime exposure to O ₃ or the interaction term while the effect parameters for PM ₁₀ and NO ₂ were reduced substantially. The potential effect of measurement error from the use of questionnaire responses to estimate exposure to O ₃ was assessed. The measurement error correction did not have a meaningful effect on the magnitude of the association with O ₃ . Change in lung function (per 17 ppb increase in lifetime mean 8-h avg O ₃), after including interaction term for FEF ₂₅₋₇₅ /FVC ratio: FEV ₁ : -19% (-39, 1) FEF ₇₅ : -37% (-41, -32) FEF ₂₅₋₇₅ : -29% (-33, 24)
Gong et al. (1998b) Glendora, CA 1977-1987	1-h max O ₃ ; Annual means range (1983-1987): 109-134 ppb	Longitudinal cohort study of 164 adults (mean age 45 years; 34% males) from a high O ₃ community underwent lung function testing in 1986-1987 (T3). Subjects were recruited from a cohort of 208 nonsmoking adults who had been tested on two previous occasions: 1977-1978 (T1) and 1982-1983 (T2). Analyzed changes in lung function at three time points. Subjects were also asked to undergo controlled exposures to 0.40 ppm O ₃ over 2 h with intermittent exercise. 45 subjects agreed to participate. Investigators hypothesized that acutely responsive subjects would show more rapid declines in function over the study period.	Mean FVC and FEV ₁ showed nonsignificant increase from T2 to T3, whereas an earlier analysis of the T1 to T2 change had found a significant decline in function (Detels et al., 1987). There was evidence for "regression to the mean," in that subject with larger declines in function from T1 to T2 tended to have larger increases in function from T2 to T3. A consistent decline in FEV ₁ /FVC ratio was observed at all three time points (p < 0.0001 by ANOVA). Acute changes in lung function, determined using controlled O ₃ exposures, were not associated with chronic lung function changes.

Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
United States (cont'd)			
Chen et al. (2002) Washoe County, NV 1991-1999	8-h max O ₃ : 27.23 ppb SD 10.62 Range 2.76-62.44	Birth weight for 36,305 single births analyzed in relation to mean PM ₁₀ , O ₃ , and CO levels in 1st, 2nd, and 3rd trimesters.	PM ₁₀ was the only air pollutant associated with decreased birth weights. Ozone levels quite low throughout study.
Kinney et al. (1996b) New York City 1992-1993	1-h max O ₃ : Summer (Jul-Sep 1992): 58 ppb Maximum 100	Study of 19 healthy adult joggers (age 23-38 years; 18 males) from the Governors Island U.S. Coast Guard facility in New York harbor underwent a series of two bronchoalveolar lavages, first in the summer of 1992 and then again in the winter of 1992. Because the summer of 1992 had lower than average O ₃ levels, six subjects underwent a third bronchoalveolar lavage in the summer of 1993. Study tested whether inflammatory markers in bronchoalveolar lavage fluid were elevated during the summer O ₃ season among adults who regularly exercised outdoors. Outcomes included cell differentials, release of IL-8 and TNF-α in bronchoalveolar lavage cells supernatants, release of reactive oxygen species by macrophages, and concentrations of protein, lactate dehydrogenase, IL-8, fibronectin, α1-antitrypsin (α1-AT), complement fragments (C3a), and PGE ₂ in bronchoalveolar lavage fluids.	There was no evidence of acute inflammation in the summer of 1992 compared to the winter; i.e., neutrophil differentials, IL-8 and TNF-α showed no significant differences. However, a measure of cell damage, lactate dehydrogenase, was elevated in the summer, suggesting possible O ₃ -mediated damage to the lung epithelium with repeated exposures to O ₃ while exercising. O ₃ levels during the summer of 1992 were atypically low for New York City. Among six subjects who agreed to undergo a third bronchoalveolar lavage test in the summer of 1993, lactate dehydrogenase was again elevated compared to winter. In addition, IL-8 was elevated in the summer of 1993, suggesting acute inflammation.
	Winter (Jan-Mar 1992): 32 ppb Maximum 64		
	Summer (Jul-Sep 1993): 69 ppb Maximum 142		

Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
Europe			
Charpin et al. (1999) Seven towns in SE France Jan-Feb 1993	8-h max O ₃ : Range of means: 30.2-52.1 µg/m ³ 24-h avg O ₃ : Range of means: 20.1-42.1 µg/m ³	Cross-sectional cohort study of 2,073 children (age 10-11 years) from seven towns tested for atopy based on skin prick testing (house dust mite, cat dander, grass pollen, cypress pollen, and <i>Alternaria</i>). Towns represented a range of ambient O ₃ and other pollutant (NO ₂ and SO ₂) levels. Tested hypothesis that atopy is greater in towns with higher photochemical pollution levels. To be eligible, subjects must have resided in current town for at least 3 years. Authors stated that Jan to Feb pollution levels correlated with levels observed throughout the year, though no data was given to support this.	In this cross-sectional analysis, no differences in atopy levels were seen across the seven towns. Authors concluded that long-term exposures to oxidant pollution do not favor increased allergy to common allergens. The very low winter O ₃ levels monitored and lack of long-term exposure data make it impossible to reach this conclusion in a definitive manner.
Ramadour et al. (2000) Seven towns in SE France Jan-Feb 1993	8-h max O ₃ : Range of means: 30.2-52.1 µg/m ³	Cross-sectional cohort study of 2,445 children (age 13-14 years) who had lived at their current residence for at least 3 years were recruited from schools in seven towns in SE France. This region has highest O ₃ levels in France. Subjects completed ISAAC survey of asthma and respiratory symptoms. In addition to O ₃ also collected data on SO ₂ and NO ₂ . Analyzed relationships between asthma and other respiratory conditions with mean air pollution levels across the seven towns using logistic regression, controlling for family history of asthma, personal history of early-life respiratory diseases, and SES. Also did simple univariate linear regressions.	In logistic regressions, no significant associations seen between O ₃ and 12-mo history of wheezing, history of asthma attack, exercise induced asthma and/or dry cough in last 12 months. In simple bivariate scatterplots of respiratory outcomes vs. mean O ₃ levels in the seven towns, there appeared to be strong positive relationships (r = 0.71 for wheezing in last 12 months and r = 0.96 for asthma attacks). No data on slope estimates given. Concerns about potential confounding across towns limits the interpretation of this study.

Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
Europe (cont'd)			
Ihorst et al. (2004) Nine communities in Lower Austria Apr 1994-Oct 1997 Six communities in Germany Feb 1996-Oct 1999	<p>½-h avg O₃: Semi-annual mean:</p> <p>Quartile ranges:</p> <p>Summer: 1st quartile: 22-30 ppb 2nd quartile: 30-38 ppb 3rd quartile: 38-46 ppb 4th quartile: 46-54 ppb</p> <p>Winter: 1st quartile: 4-12 ppb 2nd quartile: 12-20 ppb 3rd quartile: 20-28 ppb 4th quartile: 28-36 ppb</p>	<p>Longitudinal cohort study of 2,153 children (median age 7.6 years) were studied for the effects of semi-annual and 3½-year mean O₃ concentrations on FVC and FEV₁. As a measure of lung growth, the difference between two consecutive values for each child was divided by the number of days between tests. The effect of O₃ exposure on lung growth was analyzed by linear regression models, after adjusting for sex, age, height at start of the time period, and passive smoking exposure.</p>	<p>Higher semi-annual mean O₃ levels were associated with diminished lung function growth during the summer, but increased lung function growth in the winter.</p> <p>Change in lung function (4th quartile vs. 1st quartile semi-annual O₃ mean):</p> <p>Summer: FEV₁ (mL/100 days): -18.5 (-27.1, -9.8) FVC (mL/100 days): -19.2 (-27.8, -10.6)</p> <p>Winter: FEV₁ (mL/100 days): 10.9 (2.1, 19.7) FVC (mL/100 days): 16.4 (8.3, 24.6)</p> <p>No associations between longer term O₃ exposure (mean summer O₃ over a 3½-year period) and lung function growth was found.</p>
Kopp et al. (2000) Ten communities in Austria and SW Germany Mar 1994-Nov 1995	<p>½-h avg O₃: Mean from Apr-Oct 1994:</p> <p>Stratified by low, medium, high exposure: Low: 24-33 ppb Medium: 35-38 ppb High: 44-52 ppb</p>	<p>Longitudinal cohort study of 797 children with a mean age of 8.2 years. Four pulmonary function tests (FVC, FEV₁) performed on each child over two summers. Examined association between average daily lung function growth and exposure to O₃, PM₁₀, NO₂, and SO₂. Analysis using linear regression models.</p>	<p>Lower FVC and FEV₁ increases were observed in children exposed to high ambient O₃ levels vs. those exposed to lower O₃ levels during the summer. During the winter, children in higher O₃ areas showed a slightly greater increase in FVC and FEV₁ than those in the low O₃ areas, which might reflect that children make up for lung function deficits during the winter season.</p> <p>Change in lung function for high vs. low O₃ exposure groups (per ppb O₃):</p> <p>FEV₁: Summer of 1994: -0.303 mL/day, p = 0.007 Winter of 1994/1995: 0.158 mL/day, p = 0.006 Summer of 1995: -0.322 mL/day, p = 0.001</p>

Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
Europe (cont'd)			
Frischer et al. (1999) Nine communities in Austria 1994-1996	24-h avg O ₃ : Summer: 34.8 ppb SD 8.7 Winter: 23.1 ppb SD 7.7	Longitudinal cohort study of communities from two counties chosen to represent a broad range of O ₃ concentrations; a 2-fold range in mean levels was observed. 1,150 children (mean age 7.8 years; 52% males) from grades 1 and 2 performed spirometry in spring and fall over 3 years (total of six measurements per child) to determine if seasonal exposure to O ₃ would be associated with diminished lung function growth, especially over the summer seasons. Ozone levels were low during lung function testing periods. Participation rates were high. At baseline, respiratory histories were collected and subjects were tested for allergy by skin prick. Examined association between O ₃ levels and change in lung function (FVC, FEV ₁ , and MEF ₅₀ [maximal expiratory flow at 50% of vital capacity]) over each season, controlling for baseline function, atopy, gender, site, environmental tobacco smoke exposure, season, and change in height. Other pollutants studied included PM ₁₀ , SO ₂ , and NO ₂ .	Seasonal mean O ₃ exposures were associated with reductions in growth in all three lung function measures. Inconsistent results seen for other pollutants. Summer season lung function growth decrements per unit O ₃ were larger when data restricted to children who spent whole summer in their community. No evidence for nonlinear O ₃ effect. No confounding of O ₃ effect by temperature, ETS, or acute respiratory illnesses. Change in lung function (per ppb O ₃): FEV ₁ (mL/day): All subjects: Summer: -0.029 (SE 0.005), p < 0.001 Winter: -0.024 (SE 0.006), p < 0.001 Restricted to subjects who stayed in community: Summer: -0.034 (SE 0.009), p < 0.001 FVC (mL/day): All subjects: Summer: -0.018 (SE 0.005), p < 0.001 Winter: -0.010 (SE 0.006), p = 0.08 Restricted to subjects who stayed in community: Summer: -0.033 (SE 0.007), p < 0.001
Frischer et al. (2001) Nine communities in Austria Sep-Oct 1997	½-h avg O ₃ : 30-day mean: 31.57 ppb IQR 20.61	A cross-sectional cohort study of 877 school children (mean age 11.2 years). Analyzed for urinary eosinophil protein as a marker of eosinophil activation determined from a single spot urine sample using linear regression models.	Log-transformed urinary eosinophil protein-X concentrations were found to be significantly associated with O ₃ levels, after adjusting for gender, site, and atopy. Change in log urinary eosinophil protein-X (per ppb O ₃): 0.007 µg/mmol creatinine (SE 0.02), p < 0.001

Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
Europe (cont'd)			
Horak et al. (2002a,b) Eight communities in Austria 1994-1997	Seasonal mean O ₃ : Summer: 31.8 ppb Range 18.7-49.3 Winter: 19.8 ppb Range 12.7-35.9	This longitudinal cohort study continued the work of Frischer et al., 1999 by including one additional year of data, 1997. The major hypothesis considered PM ₁₀ . For this study, 80.6% of the 975 children (mean age 8.11 years) performed all six lung function tests. A total of 860 children were included in the GEE analysis. Multipollutant analysis for PM ₁₀ , SO ₂ , and NO ₂ .	Seasonal mean O ₃ showed a negative effect on lung function growth, confirming the previous shorter study. Ozone effects were robust to inclusion of PM ₁₀ into the model. However, for FEV ₁ in winter, the O ₃ effect slightly diminished after including PM ₁₀ . Taking into account only children who stayed at home the whole summer period did not affect the results. Change in lung function (per ppb O ₃): FEV ₁ (mL/day): O ₃ only models: Summer: -0.021, p < 0.001 Winter: -0.020, p < 0.001 O ₃ with PM ₁₀ models: Summer: -0.020, p < 0.001 Winter: -0.012, p = 0.04
Palli et al. (2004) Florence, Italy 1993-1998	24-h avg O ₃ : Range of monthly means from 1993-1998: Approximately 25-125 ppb	Cohort study of 320 residents (age 35-64 years) in the metropolitan area of Florence enrolled in a study investigating the correlation between levels of DNA bulky adducts and cumulative O ₃ exposure. One blood sample was collected for each subject. Various time windows of exposure were examined, ranging from 0-15 days to 0-90 days prior to the blood draw. Simple Spearman correlations between DNA adduct levels and different O ₃ exposure time windows were calculated after stratifying by smoking history, area of residence, and population type (random sample or exposed workers).	Consistent relationships between O ₃ exposure and DNA adduct levels were observed only among never smokers. Correlations were highest among never smokers who resided in the urban area and were not occupationally exposed to vehicle traffic pollution. Associations were significant up to a time window of 0-60 days prior to the blood draw in the subgroup of never smokers, with strongest relationships observed between 30-45 days prior.

Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
Latin America			
Calderón-Garcidueñas et al. (1995) SW Mexico City Nov 1993 Manzanillo, Mexico Jan 1994	1-h max O ₃ : SW Mexico City (urban): 4.4 h/day >120 ppb Maximum 307 ppb Manzanillo, Pacific port (control): No detectable air pollutants.	A cohort study in which nasal lavage samples collected from 38 urban (mean age 12.2 years) and 28 control (mean age 11.7 years) children. Urban children monitored four times in November; controls monitored twice in January. Samples analyzed for polymorphonuclear leukocyte counts, expression of human complement receptor type 3 (CD11b) on nasal polymorphonuclear leukocytes, and nasal cytologies.	Nasal cytologies revealed that children from Mexico City had abnormal nasal mucosae, including mucosal atrophy, marked decreases in the numbers of ciliated-type cells and goblet cells, and squamous metaplasia. Exposed children had significantly higher nasal polymorphonuclear leukocyte counts (p < 0.001) and nasal CD11b expression (p < 0.001) vs. controls. However, the inflammatory response did not seem to correlate with the previous day's O ₃ exposure, suggesting that there might be a competing inflammatory mechanism at the bronchoalveolar level. Overall, these results suggest that ambient O ₃ produces an inflammatory response in chronically exposed children. However, it should be noted that urban children were exposed to a complex pollution mix, making it difficult to attribute effects to O ₃ specifically.
Gouveia et al. (2004) São Paulo, Brazil 1997	1-h max O ₃ : 63.0 ppb SD 33.5	Birth weight for 179,460 single births analyzed in relation to PM ₁₀ , SO ₂ , CO, NO ₂ , and O ₃ levels in 1st, 2nd, and 3rd trimesters. GAM and logistic regression models used for analysis.	Exposures to PM ₁₀ and CO during 1st trimester were found to have significant negative associations with birth weight. No associations observed for the other air pollutants, including O ₃ .

Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
Asia			
Ha et al. (2001) Seoul, Korea 1996-1997	8-h avg O ₃ : 1st trimester: Median 22.4 ppb IQR 13.6 3rd trimester: Median 23.3 ppb IQR 16.1	Examined association between air pollution exposure during pregnancy and low birth weight among all full-term births for a 2-year period. These associations were evaluated after adjusting for gestational age, maternal age, parental educational level, parity, and infant sex. Analysis using GAM with default convergence criteria.	<p>Exposures during the 1st and 3rd trimesters were initially examined separately. For the 1st trimester exposure estimates, positive associations with risk of low birth weight were observed for CO, NO₂, SO₂, and TSP, but not O₃. For the 3rd trimester exposure estimates, a positive association was observed for O₃, but not the other pollutants. When exposures from both trimesters were examined simultaneously, the risk of low birth weight remained positive for CO, NO₂, SO₂, and TSP during the 1st trimester. However for O₃, the positive association with 3rd trimester exposure was diminished. These results suggest that exposures to CO, NO₂, SO₂, and TSP in the 1st trimester may be risk factors for low birth weight.</p> <p>Relative risk of low birth weight (per 13.6 ppb 8-h avg O₃ for 1st trimester; per 16.1 ppb 8-h avg O₃ for 3rd trimester):</p> <p>Stratified analyses by trimester: 1st trimester: 0.92 (0.88, 0.96) 3rd trimester: 1.09 (1.04, 1.14)</p> <p>Combined analyses of both trimesters: 1st trimester: 0.96 (0.87, 1.07) 3rd trimester: 1.06 (0.94, 1.18)</p>

Table AX7-6 (cont'd). Effects of Chronic O₃ Exposure on Respiratory Health

Reference, Study Location, and Period	Mean O ₃ Levels	Study Description	Results and Comments
Asia (cont'd)			
Kuo et al. (2002) Central Taiwan 1996	1-h max O ₃ ; Annual mean range across 7 of 8 schools: 18.6-27.3 ppb	Cross-sectional study. Respiratory questionnaire administered to 12,926 children aged 13-16 years at eight junior high schools in central Taiwan, to determine asthma prevalence. The association between asthma prevalence and air pollution exposure analyzed by simple Pearson correlations of prevalence with annual mean air pollution levels (O ₃ , SO ₂ , PM ₁₀ , and NO ₂), and by multiple logistic regression. The 775 asthmatics who were identified then provided follow-up data on symptoms and exacerbations over a 1-year period. Simple Pearson correlations were computed between monthly hospital admissions and air pollution levels, not controlling for covariates such as season or weather.	Asthma prevalence ranged from 5.5% to 14.5% across the 8 schools. Based on simple Pearson correlations, mean O ₃ (r = 0.51) and NO ₂ (r = 0.63) levels were correlated with variations in asthma prevalence. However, only NO ₂ remained significant in multiple logistic regression analyses after adjusting for various potential confounding factors. Longitudinal hospital admissions results are inconclusive due to analytical limitations. Monthly correlations of hospital admissions for asthmatics yielded variable results, all of which would be confounded by temporal factors.

Table AX7-7. Effects of Chronic O₃ Exposure on Mortality and Incidence of Cancer

Reference, Location, Study Period	Mean O ₃ Levels	Study Description	Results and Comments
United States			
Pope et al. (2002) U.S. nationwide 1982-1998	1-h max O ₃ : Mean from Jul-Sep: 59.7 ppb SD 12.8	Prospective cohort study of approximately 500,000 members of American Cancer Society cohort enrolled in 1982 and followed through 1998 for all cause, cardiopulmonary, lung cancer, and all other cause mortality. Age at enrollment was 30+ years. Air pollution concentrations in urban area of residence at time of enrollment assessed from 1982 through 1998. Other pollutants considered include TSP, PM ₁₅ , PM ₁₀ , PM _{2.5} , PM _{15-2.5} , SO ₄ ²⁻ , SO ₂ , NO ₂ , and CO.	No significant effect of O ₃ on mortality risk, though the association of Jul-Sep O ₃ concentrations with all cause and cardiopulmonary mortality were positive and nearly significant. Residential location was known only at enrollment to study in 1982. Thus, exposure misclassification is likely to be high.
Lipfert et al. (2000b; 2003) 32 Veterans Administration hospitals nationwide in the U.S. 1976-1996	95th % O ₃ : 1960-1974: 132 ppb 1975-1981: 140 ppb 1982-1988: 94 ppb 1989-1996: 85 ppb	Cohort study of approximately 50,000 U.S. veterans (all males) diagnosed with hypertension. Mean age at recruitment was 51 years. Exposure to O ₃ during four periods (1960-1974, 1975-1981, 1982-1988, 1989-1996) associated with mortality over three periods (1976-1981, 1982-1988, 1989-1996). Long-term exposures to TSP, PM ₁₅ , PM ₁₀ , PM _{2.5} , PM _{15-2.5} , SO ₄ ²⁻ , NO ₂ , and CO also analyzed. Used Cox proportional hazards regression, adjusting for race, smoking, age, systolic and diastolic blood pressure, body mass index, and socioeconomic factors.	Positive average concurrent responses for TSP, SO ₄ ²⁻ , NO ₂ , O ₃ in individual period analyses, but only O ₃ was significant for overall. Two-pollutants analyses indicate that responses to peak O ₃ are robust. Relative risks (per mean 95th % O ₃ less estimated background level, value not reported): Averaged over all four periods: Exposure concurrent with mortality: O ₃ only model: 9.4% (SE 4.6), p < 0.05 O ₃ with NO ₂ model: 12.2%, p < 0.05 Exposure before mortality: O ₃ only model: -0.2% (SE 6.3) p > 0.05 Analyses were robust to the deletion of diastolic blood pressure in the models, indicating that the association between mortality and O ₃ was not mediated through blood pressure.

Table AX7-7 (cont'd). Effects of Chronic O₃ Exposure on Mortality and Incidence of Cancer

Reference, Location, Study Period	Mean O ₃ Levels	Study Description	Results and Comments
United States (cont'd)			
Abbey et al. (1999) Three California air basins: San Francisco, South Coast (Los Angeles and eastward), San Diego 1977-1992	24-h avg O ₃ : Monthly average from 1973 to censor date: 26.11 ppb SD 7.65 IQR 12.0 O ₃ h/year >100 ppb: 330 h/year SD 295 IQR 551	Prospective cohort study of 6,338 nonsmoking non-Hispanic white adult members of the Adventist Health Study followed for all cause, cardiopulmonary, nonmalignant respiratory, and lung cancer mortality. Participants were aged 27-95 years at enrollment in 1977. 1,628 (989 females, 639 males) mortality events followed through 1992. All results were stratified by gender. Used Cox proportional hazards analysis, adjusting for age at enrollment, past smoking, environmental tobacco smoke exposure, alcohol use, education, occupation, and body mass index. Analyzed mortality from all natural causes, cardiopulmonary, nonmalignant respiratory, and lung cancer. Ozone results were presented for both metrics.	Of 16 regressions involving O ₃ exposures (two genders; four mortality causes; two O ₃ metrics), 11 were positive and one was statistically significant, for lung cancer in males for O ₃ h/year >100 ppb. Relative risks for lung cancer mortality in males: 24-h avg O ₃ (per 12.0 ppb): 2.10 (0.99, 4.44) O ₃ h/year >100 ppb (per 551 h/year): 4.19 (1.81, 9.69) Inconsistency across outcomes and genders raises possibility of spurious finding. The lack of cardiopulmonary effects raises plausibility concerns.
Beeson et al. (1998) Three California air basins: San Francisco, South Coast (Los Angeles and eastward), San Diego 1977-1992	24-h avg O ₃ : Monthly average from 1973 to 1992: 26.2 ppb SD 7.7 O ₃ h/year >100 ppb: 333 h/year SD 297 IQR 556	Prospective cohort study of 6,338 nonsmoking non-Hispanic white adult members of the Adventist Health Study aged 27-95 years at time of enrollment. 36 (20 females, 16 males) histologically confirmed lung cancers were diagnosed through 1992. Extensive exposure assessment, with assignment of individual long-term exposures to O ₃ , PM ₁₀ , SO ₄ ²⁻ , and SO ₂ , was a unique strength of this study. All results were stratified by gender. Used Cox proportional hazards analysis, adjusting for age at enrollment, past smoking, education, and alcohol use.	Males, but not females, showed moderate association for O ₃ and incident lung cancer risk. Relative risks for lung cancer incident in males: O ₃ h/year >100 ppb (per 556 h/year): All males: 3.56 (1.35, 9.42) Never smokers: 4.48 (1.25, 16.04) Past smokers: 2.15 (0.42, 10.89)

Table AX7-7 (cont'd). Effects of Chronic O₃ Exposure on Mortality and Incidence of Cancer

Reference, Location, Study Period	Mean O ₃ Levels	Study Description	Results and Comments
Latin America			
Pereira et al. (2005) São Paulo, Brazil Exposure period 1981-1990 Case period 1997	Mean avg of days/year when O ₃ levels exceeded air quality standards (units not provided): Lapa: 40.2 Moema: 19.6 Moóca: 67.1 Sé: 28.2	Annual records on larynx and lung cancer diseases obtained from the São Paulo Cancer Registry. The correlation between average air pollution data from 1981-1990 and cases of larynx and lung cancer from 1997 were assessed using Pearson correlation coefficients. Other pollutants examined included PM ₁₀ , NO ₂ , NO _x , SO ₂ , and CO.	Results from this ecologic study provide limited evaluation of the relationship between air pollution and cancer. There was a significant difference in the incidence of larynx and lung cancer among the São Paulo city districts. Of all the pollutants examined O ₃ was best correlated with cases of larynx and lung cancer. Pearson correlation coefficient: Larynx cancer: 0.9929 (p = 0.007) Lung cancer: 0.7234 (p = 0.277)

AX7.2 DESCRIPTION OF SUMMARY DENSITY CURVES

Introduction

The summary density was used in various figures in Chapter 7. It is important that the reader not confuse a summary density with an error density, which was also used in Chapter 7 figures. This section will explain the relationship between these two densities, previous use of similar densities, the theory behind the summary density, and how to interpret the graph of the summary density.

In explaining the equation for the summary density and the interpretation of it, the discussion will explain the need for the summary density and its construction. First, the preliminaries will be discussed. The statistically experienced reader can skip this portion except to read the definition of the error density.

The summary density has been used before (Flachaire and Nuñez, 2002). There, summary density was weighted by the population size and was used in an economic context to estimate income distributions. A meta-analytic method for use in the presence of non-normal distributions of effects with varying precision has been developed (Burr and Doss, 2005). This was used in an analysis of effects from multiple studies concerning the association of the platelet P1A polymorphism of glycoprotein IIIa and risk of coronary heart disease. A related density estimate, the kernel density estimate, has also been used in a publication (Kochi et al., 2005) referenced in a White Paper (Dockins et al., 2004) presentation to the U.S. EPA Science Advisory Board–Environmental Economics Advisory Board.

Preliminaries

The **error density** is the curve describing the distribution of uncertainty about the mean (or posterior mean) or the slope estimate. For a normal density, this is sometimes referred to as the “bell-shaped curve.” With a two-sided test, the area under the curve and to the left of the no-effect value for a positive (or right of the value for negative) estimate is less than 2.5% when the effect estimate is statistically significant.

The log odds and the log relative risk estimates are usually considered to have a normal distribution when the estimate is based on a large number of observations. Many times when the health effect is a continuous variable, the estimate (or a transformation of it) is assumed to have a normal distribution.

The two-sided confidence intervals for a health effect estimate are based on the error density of the estimate. The confidence intervals include 95% of the area under the error density, with equal portions of area beyond the intervals.

In displaying confidence limits for effect estimates obtained under different conditions (relative risk for different cities or studies), the **stick diagram** is often used (for an example, see Figure 7-1 in Section 7.2.3.2). The length of the line (stick) represents the confidence limit, with the estimated mean at the midpoint of this line. With confidence limits for relative risks or odds ratios, the mean estimates may not be at the midpoint, because their distributions are skewed.

What is Summary Density?

The summary density is the average of the error densities at each possible value of the estimate. Since each estimate is different, the summary density usually will not appear as a normal density. The summary density may have many modes (bumps) or appear skewed.

The summary density is used to portray the distribution of the heterogeneous effects while accounting for the differing error densities. Other graphics can also be used for the same purpose. The stick diagram (also called Forest Plots) also portrays the heterogeneity, but it is not easy to interpret. The stick diagram gives a distorted view, because the effects with the poorest estimates, and consequently the least informative, have the longest confidence intervals; thus, they are more eye catching than the most informative effects, which have shorter confidence intervals. A histogram could be constructed from these estimates, but it weights each estimate equally although some are more precise than others. Summary density curves can be viewed as smoothed histograms. However, unlike a histogram, summary density curves account for the varying standard errors of the individual mean effect estimates.

Many readers interpret stick diagrams by noting the fraction of significant effects. This method has limitations, as there may be an overall significant effect detectable by meta-analysis despite the many nonsignificant effects due to low power in the individual studies. The summary density of these effects may show a mode at a value different from zero. This suggests that the nonsignificant effects tend to cluster around a value other than zero. The summary density can also show two or more modes, indicating disagreement between estimates or the presence of a factor (or multiple factors) that varies between estimates.

Any summary density that does not appear to look similar to a normal density may be reflecting a distribution that is not normal. This is important because most meta-analyses assume that the heterogeneity distribution is normal. However, it should be noted that there may be too few estimates or too much uncertainty to determine the normality of the heterogeneity distribution based on the shape of the summary density.

Another method for portraying a distribution of effects that have different precision is the **radial plot** developed by Galbraith (1994). This is also a good method to summarize various effect estimates, but it may require more statistical experience to understand.

Theory of Summary Density

Statistical science has studied Kernel density estimates (Silverman, 1986), and the summary density belongs to the class called the Gaussian Variable Kernel Density. Gaussian is another name for the normal distribution. The summary density has a variable kernel: variances of each kernel differ because of the unequal lengths of the confidence intervals of the estimates. The kernel is the shape of the distribution used for each estimate. For example, other than the normal density, a triangular density could be used. The histogram is also a kernel density estimate. The kernel in this case is rectangular (a uniform density). The rectangular shape is not considered a good kernel, because as the number of observations increase, the histogram converges more slowly to the true density compared to other kernels.

The summary density is presented as a graphical description of the heterogeneity. It does not converge to the true distribution of the heterogeneity. To do so in an optimal way, the variance of the error density would have to decrease with the number of effects being studied and the standard deviation among them.

Rather than the summary density being only a descriptive tool, it can be used for inference. Research has yielded a formula for fixing the variance of the Gaussian kernel so that there is less than a 5% chance of erroneously concluding that a sample from a normal density is multimodal (has more than one bump) (Jones, 1983). As the kernel of the summary density does not use this formula, the significance of a multimodal summary density is unknown. Also because of the varying kernel of the summary density, the formula does not apply and likely calculates too small a value. However, a simulation could be carried out to compute the p value for each application of the summary density to data.

Extending the Summary Density to an Optimal Kernel Density Estimate

The Gaussian kernel density estimate is an average of normal density estimates and is given by the equation

$$K(x) = \frac{1}{n} \sum_{i=1}^n \frac{e^{-\frac{(x-\mu_i)^2/h^2}{2}}}{h\sqrt{2\pi}} \quad (\text{AX7-1})$$

where x is the value (in this case a possible value of the effect) at which the density is to be evaluated, μ_i is the effect estimate, n is the number of samples (number of effects) and h is the standard deviation of each Gaussian density. The value of h is a constant for each density estimate but varies depending on n . As n increases, smaller values of h are used so that the kernel density estimate converges to the true density.

The definition of the summary density is the same as the Gaussian kernel density except

$$h_i = \hat{\sigma}_i \quad (\text{AX7-2})$$

where $\hat{\sigma}_i$ is the estimate of the standard error of the i th sample (effect estimate). In this case, the summary density is called a variable kernel density estimate, as h_i varies depending on the standard error of each estimate.

To extend the summary density to an optimal density consider h_i of the form

$$h_i = \frac{kA}{n^{1/5}\sigma_g} \hat{\sigma}_i \quad (\text{AX7-3})$$

where k is a constant to be determined, σ_g is the geometric mean of the estimated standard errors and

$$A = \min(\hat{\sigma}_i, IQR_i / 1.34) \quad (\text{AX7-4})$$

where $\hat{\sigma}_i$ is the standard deviation and IQR_i is the interquartile range of the samples (effect estimates). Both $\hat{\sigma}_i$ and $IQR_i / 1.34$ are estimates of the true standard deviation when the

distribution of the effects is normal. The extension of the summary density to an optimal kernel density will be referred to as the **extension**.

Next, the choice of the h_i for the extension will be explained. Jones (1983) has shown for the (constant) kernel that

$$h = \frac{kA}{n^{1/5}} \quad (\text{AX7-5})$$

where $k = 1.25$. A normally distributed sample will have a multimodal kernel estimate 5% of the time with this choice of k . However, for the extension, a larger k is required to achieve the same critical value (5%) as Jones has achieved. This is due to the kernel being variable and prone to having more than one mode. Also, A is used rather than the more common estimate of σ , since A is used with the optimal kernel.

Another simpler, but somewhat unsatisfactory approach, is to use Jones' result directly on the effect size (the ratio of the effect estimate to its standard error). The variability of this ratio is approximately constant for effects estimated from long sampling periods.

Probably the best and yet somewhat subjective method is to adopt aspects of Silverman's method (Silverman, 1986). A multiple of the standard deviation is considered. This multiple is either increased or decreased until the density becomes visually multimodal. The effects are simulated using A as defined by Equation AX7-4 for the standard error and the mean of the effects for the error densities.

An Example of Calculating the Summary Density

Table AX7-8 shows the O₃-associated excess risk estimates for cardiovascular mortality in the warm season from select studies (see Figure 7-25 in Section 7.4.7 for the stick diagram of these estimates).

The estimated log relative risk is considered normally distributed, so the percent change is converted to log relative risk per standard unit (RR) by Equation AX7-6:

$$\log(\text{RR}) = \log[(\% \text{ change}/100) + 1] \quad (\text{AX7-6})$$

Table AX7-8. Ozone-Associated Cardiovascular Mortality Risk Estimates per Standardized Increment^a

Reference	Study Location	% Excess Risk in Mortality (95% CI)
Moolgavkar (2003) ^b	Los Angeles, CA	1.61 (-0.24, 3.50)
Moolgavkar (2003) ^b	Cook County, IL	6.82 (4.38, 9.32)
Lippmann et al. (2000) ^c	Detroit Area, MI	1.52 (-3.64, 6.95)
Vedal et al. (2003)	Vancouver, British Columbia, Canada	16.37 (-1.14, 36.98)
Anderson et al. (1996)	London, England	4.46 (1.30, 7.72)
Sunyer et al. (1996)	Barcelona, Spain	6.70 (2.15, 11.50)
Simpson et al. (1997)	Brisbane, Australia	7.37 (-3.41, 19.36)

^a The standardized increment is 40 ppb for 1-h max O₃; 30 ppb for 8-h max O₃; and 20 ppb for 24 h avg O₃.

^b Indicates use of Poisson GAM with default convergence criteria.

^c Reanalysis by Ito (2004) using Poisson GLM.

Then the above equation is applied to the confidence limits of the percent excess risks to get confidence limits for log(RR). The difference of these limits divided by 3.92 is used as the standard error of the log(RR).

The equation of the normal density is

$$K(x) = \sum_{i=1}^n \frac{e^{-\frac{(x-\mu_i)^2/\sigma_i^2}{2}}}{\sigma_i \sqrt{2\pi}} \quad (\text{AX7-7})$$

For each of the seven effect estimates, the log(RR) is substituted for μ_i and its standard error is substituted for σ_i . These densities are calculated over a range of x . For Figure AX7-1, x has been calculated every 0.0004 units of log(RR) from -0.2 to 0.2. Then the densities for each value of x are averaged, resulting in the summary density.

Figure AX7-1 shows each of the seven error densities and the summary density curve. The summary density is multiplied by the number of estimates ($n = 7$) to better illustrate the shape of the curve. In the figure, the summary density appears bimodal, but there are too few effects to confirm this statistically.

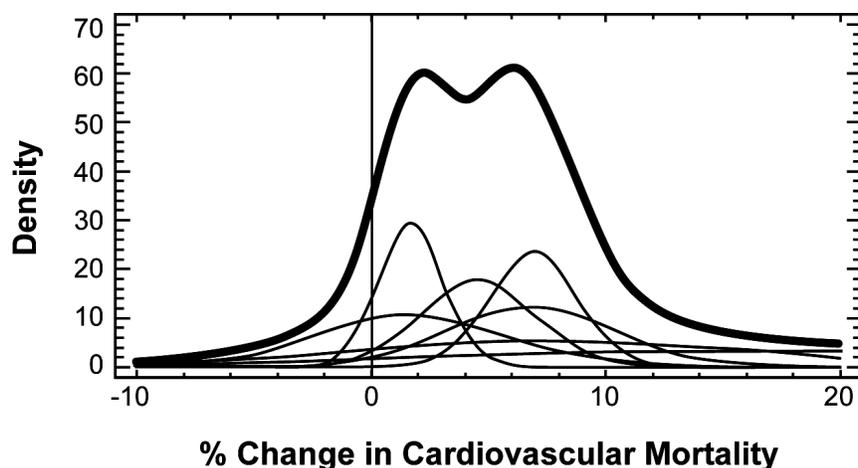


Figure AX7-1. Density curves of the O_3 -associated excess risk of cardiovascular mortality in the warm season per standardized increment. The thicker curve is the summary density curve of the seven effect estimates.

In Chapter 7, the summary density curves in Figures 7-29 and 7-30 were calculated using equation AX7-3 with A equal to the estimated standard deviation of the effects. Simulation indicated that the all-year curve in Figure 7-29 was not significantly multimodal.

Significance of a Summary Density

When there is no significant difference between effect estimates and the pooled analysis finds the overall effect to be significantly positive, the error density of the overall effect would have less than 2.5% of its area under the curve beyond the value of no effect. However, the summary density of the individual error densities will generally show more than 2.5% beyond the no-effect value. Results from Mortimer et al. (2002) reported in Chapter 7 found no significant effects of O_3 on PEF and incidence of symptoms in the individual cities, but indicated a significant overall effect when the data from all cities were combined (see Figures 7-4 and 7-7 in Sections 7.2.3.2 and 7.2.4, respectively). The summary density of the error densities from the eight cities had about 20 to 25% of the area beyond zero. Simulation under these conditions verified that these larger percentages of the area beyond the value of no effect are common. One of the reasons for this result is that the summary density does not treat each estimate as derived from random estimates of the same single true estimate.

Rather than treating the area beyond the value of no effect in a summary density as an indication of significance, it should be treated as an indication of disagreement. For example, there might be a mode at zero and a mode at a positive value. This could be due to some cities being always below the threshold and other cities being above the threshold. In this case, there could be appreciable area below zero while some of the cities indicate a positive effect. Even if this simple case were the true state, the summary density might appear normal due to wide error densities.

“Apples and Oranges” Issue

The argument that a summary analysis is mixing apples and oranges is based on a variety of reasons. One reason is the uncertainty arising when the analysis includes effects that vary with factors other than the factor of interest. Another reason is the combining of effects that lack commonality. That is, the effects may vary with a number of factors, but an average effect is estimated through some process. The summary density does not average effects; instead it considers common location through a clustering of effects. This allows a weaker assumption concerning the commonality of the effects.

Consider a summary density based on estimates of high precision that cluster together and one estimate of low precision that is significantly different from the rest (the confidence intervals do not overlap) and based on an older measurement method. The summary density could average out the outlying value while forming a high mode based on the other effects. Such a graph would lead one to ignore the results of the old measurement method. Disregarding previous results when more precise measurements become available is often practical under such circumstances.

Masking of Heterogeneity

When the variances are very large, the kernel density appears to be very similar to a normal density. Thus, large error densities can mask the true pattern of heterogeneity. There may be good reasons to suppose that the heterogeneity is other than normal, and the failure of the summary density to show this pattern is due to wide error densities. When such masking occurs, the summary density cannot reject the assumption of normality of heterogeneous effects in a meta-analysis.

Another reason that masking may occur with the summary density is the use of the standard error of the effect for the standard deviation of the effects error density. Kernel density theory permits decreasing the standard deviation when more effects are available. Narrower error densities should clarify the heterogeneity distribution. However, the ideal reduction in variance due to increasing observation size is not large for the numbers of effects usually considered. For example, ideally h decreases as $n^{-1/5}$ increases, which is rather slowly.

Conclusion

The summary density is not new. As it stands, it is a kernel density estimate without a fixed value of h . Others have fixed h either using graphics (Kochi et al., 2005) or ad hoc values (Burr and Doss, 2005). Flachaire and Nuñez (2002) used a weighted average of error densities, with the weights based on the population size. This and other types of weighting should be considered in the future. Also, efforts should be made to unmask the heterogeneity distribution in a statistically justified manner.

The summary density is a simple graphical method for portraying the distribution of heterogeneous effects in the presence of effects estimated with different precision. It has graphical advantages over both the stick diagram and the histogram. The summary density can be put on a more firm statistical footing. Inference concerning the presence of modes could be made reliably if p values were generated from simulations. The summary density is a graphical-diagnostic tool for the normality assumption in meta-analyses. A meta-analysis method has been developed for use when the distribution of effects is not normal and the precision varies (Burr and Doss, 2005). There is a need to develop other improvements to unmask the heterogeneity distribution in a statistically justified manner.

The summary density overcomes some issues with reliance on statistical tests. If effects were nonsignificant, one would expect them to cluster on either side of the no-effect value. If the summary density indicates a mode at a positive effect value, a tentative conclusion is that there is a positive nonrandom effect. Confirmation that the mode is statistically significant may need further study, mindful that effects can include spurious components.

AX7.3 ESTIMATING THE GOMPERTZ CONCENTRATION-RESPONSE MODEL

Estimating the Gompertz Concentration-Response Model for Mortality Risk and Long-Term O₃ Concentrations

A three-parameter Gompertz concentration-response model was fit to examine the association between mortality risk from acute O₃ exposure and long-term O₃ concentrations using data from the U.S. 95 communities study (Bell et al., 2004). Most single-city studies fit a linear relationship, not a Gompertz model, to mortality times-series data. This may be due to the limited range of the O₃ concentrations within a city, so that all the features (i.e., linear portion and two flat regions) of the Gompertz model cannot be estimated. The mortality risk estimates from the 95 communities are also linear effects, and they are assumed to be tangential to the Gompertz curve for the long-term average 24-h avg O₃. To estimate the Gompertz model parameters, the effect estimates were fit to a derivative of the Gompertz model. Figure AX7-2 shows the fitted derivative curve using only communities with warm-season data (n = 40). The derivative model does not have the flexibility to estimate negative β (log relative risk per 1,000 ppb) estimates and can only estimate them with a value near zero. The area under the derivative curve is the Gompertz curve, which is shown in Figure 7-33 in Chapter 7.

The equation of the Gompertz model is as follows:

$$\begin{aligned} \% \text{ excess risk} &= 100 \times (e^{\beta} - 1) \\ \text{where } \beta &= b_1 \times \exp[-\exp(-b_2 (O_3 - EC_{0.05\%} - \log(\log(b_1 / 0,0005))))] \end{aligned} \quad (\text{AX7-8})$$

The estimated parameters of the Gompertz model are listed in Table AX7-9.

The result is a model with essentially a threshold at low concentrations and a flat curve at higher concentrations. The curve has shallower slopes above the median effective concentration (inflection point) than below that concentration point. The horizontal line is the 95% confidence interval on the long-term average 24-h avg O₃ associated with a 0.05% excess risk in mortality (EC_{0.05%}). The EC_{0.05%} is a risk that is believed to be low enough to be in the noise band. The upper 95% confidence limit on the EC_{0.05%} was 27.6 ppb, which may be considered the lowest concentration for which the data support a no-threshold association. The Gompertz model presents a threshold of effects at low concentrations and a flat curve at higher concentrations.

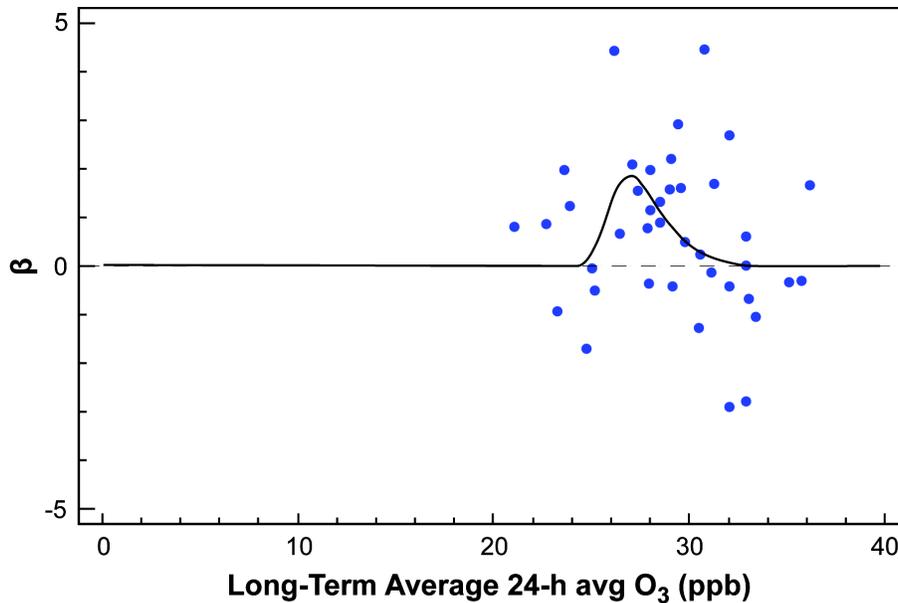


Figure AX7-2. Fitted derivative curve of the Gompertz model to the regression coefficients (β = log relative risk per 1,000 ppb) for the association between mortality and acute exposure to O₃ plotted against community-specific long-term average 24-h avg O₃ concentrations using data from the U.S. 95 communities study (Bell et al., 2004). Only the 40 communities with warm-season data are included.

Table AX7-9. Estimated Parameters of the Gompertz Model

Parameter	Estimate	SE	(95% CI)
$100 \times b_1$	0.63	0.21	(0.20, 1.06)
$EC_{0.05\%}$	25.8	0.9	(24.0, 27.6)
b_2	0.79	0.36	(0.06, 1.53)

The actual curve would not be flat indefinitely as the concentration increases, but there is no data to model what is probably a very complex portion of curve. To the extent that the estimated concentration associated with a 0.05% excess risk is realistic, the fit of the model supports the observed relationship between greater mortality risk at lower long-term O₃ concentrations.

The best method of estimating the $EC_{0.05\%}$ would be to estimate the Gompertz model directly from the pooled data from all the communities. Some of the disadvantages of estimating the $EC_{0.05\%}$ by using the community-specific regression coefficients are (1) other possibly important factors have not been used to adjust the estimate; (2) regression coefficients may not be tangents to the curve at the long-term average O_3 level, but rather have some other relationship; and (3) the data points represent a sampling of communities rather than individuals.

To compare O_3 levels from a 24-h avg to a 1-h max, one could multiply the x-axis by a factor of two as is done to obtain comparable incremental changes between the metrics (a 20 ppb increase in 24-h avg O_3 corresponds to a 40 ppb increase in 1-h max O_3). Many researchers believe that short spike exposures are more toxic than longer averages. However, the 24-h avg O_3 may be a more stable exposure estimate and still correlate with the shorter metrics of exposure.



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