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Integrated Science Assessment for Ozone and Related Photochemical Oxidants

National Center for Environmental Assessment-RTP Division
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC

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ACRONYMS AND ABBREVIATIONS

129	mouse strain (129S1/SvlmJ)
α	alpha, ambient exposure factor
α-ATD	alpha 1-antitrypsin deficiency
α-SMA	alpha-smooth muscle actin
α-tocopherol	alpha-tocopherol
α-TOH	alpha tocopherol
a	air exchange rate of the microenvironment
A2	climate scenario in IPCC
AADT	annual average daily traffic
A1B	climate scenario in IPCC
ABA	abscisic acid
ABI	abscisic acid insensitive
A1c	glycosylated hemoglobin blood test
Ach	acetylcholine
ACM	(Harvard University) Atmospheric Chemistry Modeling (Group)
ACS	American Cancer Society
ACS-CPSII	ACS Cancer Prevention Study II
ADC	arginine decarboxylase
ADSP	Adirondack State Park, NY
AER	air exchange rate
AH_2	ascorbic acid; ascorbate
AHR	airway(s) hyperresponsiveness, airway(s) hyperreactivity
AhR	aryl hydrocarbon receptor
AHSMOG	(California Seventh Day) Adventist Heath and Smog (Study)
AI	alveolar interstitial
AIC(s)	Akaike's information criterion
AIRS	Aerometric Information Retrieval System; Atmospheric Infrared Sounder (instrument)
A/J	mouse strain
Ala-9Val	genotype associated with Manganese superoxide dismutase (MnSOD) gene
AM	alveolar macrophage(s)
ANF	atrial natriuretic factor
AOT20	seasonal sum of the difference between an hourly concentration at the threshold value of 20 ppb, minus the threshold value of 20 ppb
AOT30	seasonal sum of the difference between an hourly concentration at the threshold value of 30 ppb, minus the threshold value of 30 ppb
AOT40	seasonal sum of the difference between an hourly concentration at the threshold value of 40 ppb, minus the threshold value of 40 ppb
AOT60	seasonal sum of the difference between an hourly concentration at the threshold value of 60 ppb, minus the threshold value of 60 ppb
AOTx	family of cumulative, cutoff concentration-based exposure indices
AP	activated protein
A2p	climate scenario in IPCC (preliminary version of A2)
APEX	Air Pollutants Exposure (model)
APHEA(2)	Air Pollution on Health: a European Approach (study)
APHENA	Air Pollution and Health: A European and North American Approach
ApoB	apolipoprotein B
ApoE	apolipoprotein E
APX	ascorbate peroxidase
aq	aqueous form: $(aq)O_3$
AQCD	Air Quality Criteria Document
AQI	Air Quality Index
AQS	(U.S. EPA) Air Quality System (database)
AR	acoustic rhinometry
AR4	Fourth Assessment Report (AR4) from the IPCC
AR5	Fifth Assessment Report (AR5) from the IPCC
ARG	arginase variants (ex., ARG1, ARG2, ARG1h4)
ARIC	Atherosclerosis Risk in Communities
ARIES	(Atlanta) Aerosol Research and Inhalation Epidemiology Study
atm	atmosphere
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase; adenosine triphosphate synthase
ATS	American Thoracic Society
avg	average
AVHRR	advanced very high resolution radiometer
β	beta, beta coefficient; regression coefficient; standardized coefficient; shape parameter; scale parameter
B	boron
B1	climate scenario in IPCC
B6	mouse strain (C57BL/6J)
BAL	bronchoalveolar lavage
BALB/c	mouse strain
BALF	bronchoalveolar lavage fluid
bb	bronchials

BB	bronchial airways
BC	black carbon
B cells	bone-marrow-derived lymphocytes; B lymphocytes
B6C3F1	mouse strain
BDNF	brain-derived neurotrophic factor
BEAS-2B	human bronchial epithelial cell line
BEIS	Biogenic Emissions Inventory System
BELD	Biogenic Emissions Landcover Database
BIPM	International Bureau of Weights and Measures
BM	basement membrane
BMI	body mass index
BNP	β -type natriuretic peptide
BP	blood pressure
BPD	biparietal diameter
bpm	breaths per minute
Br	bromine
BRFSS	Behavioral Risk Factor Surveillance System
BS	black smoke
BSA	bovine serum albumin
Bsp, BSP	black smoke particles
Bt, BT, bt	*Bacillus thuringiensis*; bacterium proteins used in pesticides (or genetically engineered plants produce Bt toxin)
BTEX	family of compounds (benzene, toluene, ethylbenzene, and xylene)
BW	body weight
C	carbon; concentration; ([vitamin] C, ascorbate)
ºC	degrees Celsius
^{13}C	carbon-13 isotope
C3	mouse strain (C3H/HEJ)
C3	plants that use only the Calvin cycle for fixing the carbon dioxide from the air
C4	plants that use the Hatch-Slack cycle for fixing the carbon dioxide from the air
C16:0	palmitic acid (saturated fatty acid)
C18:1	unsaturated fatty acid
Ca	calcium
C_a	ambient concentration
[Ca]	calcium concentration
Ca^{2+}	calcium ion
CA	Canada (ICD-10-CA)
CAA	Clean Air Act
CALINE4	California line source dispersion model for predicting air pollutant concentrations near roadways
CAM	plants that use crassulacean acid metabolism for fixing the carbon dioxide from the air
CAMP	Childhood Asthma Management Program
CAMx	Comprehensive Air Quality Model, with extensions
CAN	Canada
CAP(s)	concentrated ambient particles
CAR	centriacinar region
CASAC	Clean Air Scientific Advisory Committee
CASTNET	Clean Air Status and Trends Network
CAT	catalase
CB	carbon black; CMAQ mechanisms (ex., CB04, CB05, CB06)
C57BL/6	mouse strain
C57BL/6J	mouse strain
CBSA	core-based statistical area
C/C	carbon of total carbon
CCSP	Clara cell secretory protein
CD	cluster of differentiation (various receptors on T-cells: CD8+, CD44, etc.); criteria document (see AQCD)
CD-1	mouse strain
CDC	Centers for Disease Control and Prevention
CF	charcoal-filtered; carbon filtered air
CF2	twice-filtered air (particulate filter and activated charcoal filter)
C-fibers	afferent, slow, unmylenated nerves innervating the respiratory system
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CH_3	methyl group
CH_4	methane
C_2H_2	acetylene
C_2H_4	ethylene
C3H	mouse strain (C3H/HEJ or C3H/OuJ)
C_3H_6	propylene
CHAD	Consolidated Human Activity Database
CH_3Br	methyl bromide
CH_3-CHO	acetaldehyde
CH_3Cl	methyl chloride
CH_3-CO	acetyl radical(s)
CHD	coronary heart disease
CHF	congestive heart failure
C_2H_5–H	ethane
C3H/HeJ	mouse strain
CH_3I	methyl iodide
CHIP	Effects of Elevated Carbon Dioxide and Ozone on Potato Tuber Quality in the European Multiple Site Experiment
$CH_3O_2^{\bullet}$	methyl peroxy (radical)
CH_3OOH	acetic acid; methyl hydroperoxide
CHS	Child Health Study
CI	confidence interval(s)

C_j	airborne O_3 concentration at microenvironment j
Cl	chlorine
Cl^-	chlorine ion
Cl_2	chlorine gas
CLE	Current Legislation (climate scenario in IPCC)
CLM	chemiluminescence method
$ClNO_2$	nitryl chloride
cm	centimeter(s)
cm^2	square centimeters
CM	Clinical Modification (ICD-9-CM)
CMAQ	Community Multi-scale Air Quality modeling system
CN	constant atmospheric nitrogen deposition (in PnET-CN ecosystem model)
CNA	continental North America
CNS	central nervous system
CO	carbon monoxide; Cardiac output
CO_2	carbon dioxide
COD	coefficient of divergence; coefficient of determination
Col-0	(Arabidopsis ecotype) Columbia-0
COP	Conference of Parties (to the UNFCCC)
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase 2 enzyme
C-R	concentration-response
CRA	Centro di ricerca per la cerealicoltura (CRA) [The Centre for Cereal Research] – Unit 5: The Research Unit for Cropping Systems in Dry Environments in Bari, Italy (water-stressed conditions)
CRP	C-reactive protein
CS	corticosteroid
CSA	cross-sectional area; combined statistical area
csb, Csb	cockayne syndrome (cb) gene/protein group A
CSF	colony-stimulating factor
CST	central standard time
CSTR	continuous stirred tank reactor
CSV	comma-separated values (a spreadsheet format)
CT	computer tomography
CTM(s)	chemical transport model(s)
cum avg	cumulative average
CUOt	The cumulative stomatal uptake of O_3, using a constant O_3 uptake rate threshold (t) of nmol/m^2/s
CV, C.V.	coefficient of variation
cv, c.v.	cultivar
CVD	cardiovascular disease
CXC	chemokine family of cytokines, with highly conserved motif:cys-xxx-cys (CXC) amino acid group
CXCR2	CXC chemokine receptor 2 (CXCR2)
CXR	Chest (x-ray) radiograph(s)
CyS	protein cysteines
Cys-LT	cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4)
cyt	cytosolic-free
Δ, δ	delta, difference; change
ΔFEV_1	change in FEV_1
ΔV_D	change in dead space volume of the respiratory tract
2-D	two-dimensional
3-D	three-dimensional
DAHPS	3-deoxy-D-arabino-heptulosonat-7-phosphate synthase
DBP	diastolic blood pressure
DC(s)	dendritic cell(s)
DDM	direct decoupled method
DEP(s)	diesel exhaust particle(s)
df	degrees of freedom
DGGE	denaturing gradient gel electrophoresis
DHA	dehydroascorbate
DHAR	dehydroascorbate reductase
DHBA	2,3-dihydroxybenzoic acid
DLEM	Dynamic Land Ecosystem Model
dm^3	cubic decimeter(s)
DNA	deoxyribonucleic acid
DOAS	differential optical absorption spectroscopy
DOC	dissolved organic carbon
DR	type of human leukocyte antigens (HLA-DR)
dt	Portion of time-period spent in microenvironment *j*
DTH	delayed-type hypersensitivity
DU	Dobson unit(s)
DW	dry weight
E	embryonic day (ex., E15, E16, etc); [vitamin] E
E_a	exposure to pollutant of ambient origin
EBC	exhaled breath condensate (fluid)
EC	elemental carbon
ECE	endothelin converting enzyme(s) [i.e., ECE-1]
ECG	electrocardiogram
ECOPHYS	physiological process modeling to predict the response of aspen forest ecosystems (modeling growth and environmental stress in Populus)
ED	emergency department; embryonic day (ex., ED5, ED20)

EGEA	(The) Epidemiology (study on) Genetics and Environment of Asthma, (adults and children with asthma)
EGEA2	follow-up study on EGEA (adults with asthma only)
EHC-93	ambient PM reference sample (urban dust [air particles] collected in Ottawa Canada)
ELF	extracellular lining fluid
EMI	(U.S. EPA) Exposure Model for Individuals
E_{na}	exposure to pollutant of nonambient origin
ENA-78	epithelial cell-derived neutrophil-activating peptide 78
eNO	exhaled nitric oxide
eNOS	endothelial nitric oxide synthase
ENVISAT	(EAS) Earth Observation satellite
EOTCP	European Open Top Chamber Programme
EP	epithelial cells
EPA	U.S. Environmental Protection Agency
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	emergency room
ESA	European Space Agency
ET	extrathoracic; endothelin (i.e. ET-1)
ET_1	anterior nasal passages within the extrathoracic (ET) region
ET_2	oral airway and posterior nasal passages within the extrathoracic (ET) region
ETS	environmental tobacco smoke
EU	European Union
EUS	eastern U.S.
Φ	Phi; calculated efficiency
ΦPSII-max	maximum photochemical effective quantum yield of PSII
f	Fraction of the relevant time period
F	female
F344	Fischer 344 (rat strain)
F2a	8-isoprostane (major F2 prostaglandin [8 iso-PGF2a])
FA	filtered air
FACE	free-air−CO_2 enrichment (system)
FACES	Fresno Asthmatic Children's Environment Study
f_B	frequency of breathing
FC	fibrocartilaginous coat
FEF	forced expiratory flow
FEF_{25-75}	forced expiratory flow between the times at which 25% and 75% of the vital capacity is reached
FEFx	forced expiratory flow after (x)% vital capacity (e.g., after 25, 50, or 75% vital capacity)
FEM	Federal equivalent method
FeNO	exhaled nitric oxide fraction
FEV_1	forced expiratory volume in 1 second
FHM	(USDA Forest Service) Forest Health Monitoring Program
FIA	(USDA Forest Service) Forest Inventory and Analysis Program
F_{inf}	infiltration factor
$F_{inf,i}$	infiltration factor for indoor environment (i)
FLAG	Federal land managers' air quality related values workgroup
F_{LRT}	fractional uptake efficiency of the lower respiratory tract (LRT)
F_{nose}	fractional uptake efficiency via nasal absorption
F_o	fraction of time spent in outdoor microenvironments
FPM	Forest Pest Management
FR	Federal Register
FRAP	ferric reducing ability of plasma
FRC	functional residual capacity
FRM	Federal reference method
F_{RT}	fractional uptake efficiency of the respiratory tract (RT)
$Fst0_1$	flux cut off threshold
F_{URT}	fractional uptake efficiency of the upper respiratory tract (URT)
FVC	forced vital capacity
Fv/Fm	a ratio: a measure of the maximum efficiency of Photosystem II
FVI	fruits and vegetables index
γ	gamma
γ-TOH	gamma-tocopherol
g, mg, kg, µg, ng, pg	gram(s), milligram(s), kilogram(s), microgram(s), nanogram(s), picogram(s)
G	granulocyte; guanosine
g	gram(s); gaseous form: $(g)O_3$
GAM	generalized additive model(s)
g_{bs}	conductance through boundary layer and stomata
GCLC	(glutathione genetic variant) glutamate-cysteine ligase catalytic subunit
GCLM	(glutathione genetic variant) glutamate-cysteine ligase modifier subunit
G-CSF	granulocyte colony-stimulating factor (receptor)
GD	gestational day
GEE	generalized estimating equations
GEOS	(NASA) Goddard Earth Observing System model
GEOS5	GEOS version 5
GEOS-Chem	GEOS-Chemistry (tropospheric model)
GFAP	glial fibrillary acidic protein

GH	growth hormone
GHG	greenhouse gas
GLM(s)	generalized linear model(s)
GMAO	(NASA) Global Modeling and Assimilation Office
GM-CSF	granulocyte macrophage colony-stimulating factor
GOME	(ESA) Global Ozone Monitoring Experiment (spectrometer)
GOMOS	Global Ozone Monitoring by Occultation of Stars (ESA ENVISAT spectrometer measuring long-term trends in O_3)
G6P	glucose-6-phosphate
G6PD	glucose-6-phosphate dehydrogenase
GPP	gross primary production
G-proteins	GTPases
GPT	gas phase titration
GR	glutathione reductase
GSH	glutathione; reduced glutathione
GSO_3^-/GSO_3^{2-}	guanine sulfonates
GSR	glutathione reductase
GSS	glutathione synthetase
GSSG	glutathione disulfide
GST	glutathione S-transferase
GSTM1	glutathione S-transferase polymorphism M1 genotypes (GSTM1-null, -GSTM1-sufficient)
GSTP1	glutathione S-transferase polymorphism P1 genotypes
GTP	guanosine triphosphate
GTPases	G-proteins/enzymes
GWP	global warming potential
GxE	gene-environmental interaction
h	hour(s)
h/day	hour(s) per day
H; H+; H•	atomic hydrogen, hydrogen ion; hydrogen radical
^3H	radiolabeled hydrogen; tritium
H_2	molecular hydrogen
ha	hectare
HA	hyaluronic acid
HA(s)	hospital admission(s)
Hb	hemoglobin
HbA1c	glycosylated hemoglobin (blood test)
HC(s)	hydrocarbon(s)
HCFC(s)	hydrochlorofluorocarbon(s)
HCHO	formaldehyde
H_2CO	formaldehyde
HCO•	formyl (radical)
HDM	house dust mite
2HDM	second-highest daily maximum
HDMA	house dust mite allergen
^3He	non-radioactive isotope of helium
HeJ	O_3-resistant C3H mouse strain (C3H/HeJ)
HEPA	high efficiency particle air (filter)
HERO	Health and Environmental Research Online, NCEA Database System
12-HETE	12-Hydroxyeicosatetraenoic acid
HF	(HRV signal) high-frequency power
HFCs	hydrofluorocarbons
Hg	mercury
HHP-C9	1-hydroxy-1-hydroperoxynonane
HIST	histamine
HLA	human leukocyte antigen
HLA-DR	human leukocyte antigen receptor genes
HMOX	Heme oxygenase
HMOX-1	heme-oxygenase-1 (polymorphism)
HNE	4-hydroxynonenal
HNO_2	nitrous acid
HNO_3	nitric acid
HNO_4	pernitric acid
HO	hydroxyl; heme oxygenase
HO•	hydroxyl radical
HO-1	heme oxygenase 1
HO_2•	hydroperoxyl; hydroperoxy radical; protonated superoxide
HO_3•	protonated ozone radical
H_2O	water
H_2O_2	hydrogen peroxide
H_3O^+	hydronium ion
$HOCH_2OOH$	hydroxymethylhydroperoxide
HONO	nitrous acid
HO_2NO_2	peroxynitric acid
HOONO	pernitrous acid
HOX	hydrogen radical(s)
hPa	hectopascal
HPLC	high-pressure liquid chromatography
HPOT	13-hydroperoxide linolenic acid
HR	heart rate, hazard ratio
HR_{max}	maximum heart rate
HRP	horseradish peroxidase
HRV	heart rate variability
HSC	Houston Ship Channel (Texas)
hs-CRP	high-sensitivity C-reactive protein
H_2SO_4	sulfuric acid
HSP	high speed pellet (after centrifuge spin)
HSP70	heat shock protein 70
HSS	high speed supernatant (after centrifuge spin)
5-HT	5-hydroxytryptamine
hv	Energy per photon of electromagnetic energy at frequency v

HVAC	heating, ventilation, and air conditioning
Hz	hertz
I	iodine
IARC	International Agency for Research on Cancer
IAS	interalveolar septum
IBM	individual-based model or modeling
IC	inspiratory capacity; intracloud (lightning flash)
ICAM-1	intercellular adhesion molecule 1
ICARTT	International Consortium for Atmospheric Research on Transport and Transformation
ICAS	Inner City Asthma Study
ICC	intraclass correlation coefficient
ICD	implantable cardioverter defibrillator(s); International Classification of Diseases
ICD-9	International Classification of Disease 9th revision
ICD-10	International Classification of Disease 10th revision
ICEM	Indoor Chemistry and Exposure Model
ICNIRP	International Commission on Non-Ionizing Radiation Protection
ICP Forests	International Cooperative Programme on Assessment of Air Pollution Effects on Forests
ICU	Intensive Care Unit
ICVE	ischemic cerebrovascular events
IDW	inverse-distance-weighted
IFN	interferon (e.g., IFN-())
IFN-γ	interferon-gamma
Ig	immunoglobulin (e.g., IgE)
IgA	immunoglobulin A
IgE	immunoglobulin E
IGF-1	insulin-like growth factor 1
IgG	immunoglobulin G
IgM	immunoglobulin M
IHD	ischemic heart disease
IL	interleukin (e.g., IL-2, IL-4, IL-6, IL-8, etc.)
IL-1β	interleukin-1β
Ile	isoleucine
i.m.	intramuscular (route)
IMPACT	Interactive Modeling Project for Atmospheric Chemistry and Transport
IMPROVE	Interagency Monitoring of Protected Visual Environment
IN	intranasal
INF	interferon
inh	inhalation
iNKT	invariant (type I) natural killer T-cell
iNOS	inducible nitric oxide synthase
INRA	National agronomical research institute (INRA) in Thiverval-Grignon. France (adequately-watered conditions)
INTRASTAND	a stand-level model designed for hourly, daily and annual integration of forest carbon and water cycle fluxes
I/O	indoor-outdoor ratio
IOM	Institute of Medicine
i.p.	intraperitoneal (route)
IPCC	Intergovernmental Panel on Climate Change
IPCC-A2	Intergovernmental Panel on Climate Change 2nd Assessment Report
IPCC-AR4	Intergovernmental Panel on Climate Change 4th Assessment Report
IPCC-AR5	Intergovernmental Panel on Climate Change 5th Assessment Report
IPCC-TAR	Intergovernmental Panel on Climate Change Third Assessment Report
IPMMI	International Photolysis Frequency Measurement and Modeling Inter-comparison
IQR	interquartile range
IR	infrared
I/R	ischemia-reperfusion
IRIS	Integrated Risk Information System
IRP	Integrated Review Plan for the Ozone National Ambient Air Quality Standards
ISA	Integrated Science Assessment
ISCCP	International Satellite Cloud Climatology Project
ISO	International Standards Organization
8-iso-PGF	8-isoprostane
IT	intratracheal
IU	International Units
IUGR	intrauterine growth restriction
i.v.	intravenous (route)
IVF	in vitro fertilization
j	Microenvironment
JA	jasmonic acid
Jmax	maximum rate of electron transport (for regeneration of RuBP)
JNK	jun N-terminal kinase
JPL	Jet Propulsion Laboratory
κ	kappa
κB	kappa B
k	dissociation rate; root:shoot allometric coefficient; rate of O_3 loss in the microenvironment
K	potassium
K^+	potassium ion

K_a	intrinsic mass transfer coefficient/parameter
KC	keratinocyte-derived chemokine
kg	kilogram
K_g	mass transfer coefficient for gas phase
kHz	kilohertz
kJ	kilojoules
Kl	mass transfer coefficient for liquid phase
km	kilometer
KM	particle optical reflectance
KML	keyhole markup language
KMZ	zipped KML computer language
KO	knockout
Kr	reaction rate constant
KROFEX	Krauzberg Ozone Fumigation Experiment
L, dL, mL, µL	Liter, deciLiter, milliLiter, microLiter
L0	Lag (e.x., Lag 0, Lag 1, etc.)
LAI	leaf area index
LBL	Lawrence Berkeley Laboratory
LBLX	Lawrence Berkeley Laboratory model including airflow from natural ventilation
Lb(s)	pound(s)
LBW	low birth weight
LC_{50}	median lethal concentration
LCL	lower 95th% confidence limit
LDH	lactate dehydrogenase
LDL	low-density lipoprotein ; lower detectable level
LF	(HRV signal) low-frequency power
LFHFR	low frequency/high frequency (ratio)
LFT	lower free troposphere
LI	labeling index
LIDAR	Light Detection and Ranging (remote sensing system)
LIF	laser-induced fluorescence
LINKAGES	individual-based model of forest succession
LIS	lateral intercellular space
LLJ	low-level jet
L/min	liters per minute
Ln	Natural logarithm
LnRMSSD	natural log of RMSSD; measure of HRV
lnSDNN	natural log of the standard deviation of NN intervals in an EKG
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEL	lowest-observed-effect level
LOESS	locally weighted scatterplot smoothing
LOP	lipid ozonation products
LOSU	level of scientific understanding
LOWESS	locally weighted scatter plot smoother
LOX-1	Lipoxygenase; lectin-like oxidized low density lipoprotein receptor-1
LPS	lipopolysaccharide
LRS	lower respiratory symptoms
LRT	lower respiratory tract; lower airways; Long range transport
LST	local standard time
LT	leukotriene (e.g., LTB4 , LTC 4, LTD4 , LTE4); local time
LT-α	lymphotoxin-α
LTA	lymphotoxin-alpha
LUR	land use regression
LVEDD	left ventricular chamber dimensions at end diastole
LVEDP	left ventricular end diastolic pressure
LWC	liquid water content
µ	mu, micro
µeq	microequivalent
µg	microgram
$\mu g/m^3$	micrograms per cubic meter
µm	micrometer, micron
m, cm, µm, nm	meter(s), centimeter(s), micrometer/[micron](s), nanometer(s)
M	male
M, mM, µM, nM, pM	Molar, milliMolar, microMolar, nanoMolar, picoMolar
m^2	square meters
m^3	cubic meters
M#	Month (M1 Month1; M2 Month2; M3 Month3; M4 Month4)
M2	type of muscarinic receptor
M7	7-hour seasonal mean
M12	12-hour seasonal mean of O_3
ma	moving average
mAOT	modified accumulated exposure over threshold
MAP	mitogen-activated protein; mean arterial pressure
MAPK	mitogen-activated protein kinase(s), MAP kinase
MAQSIP	Multiscale Air Quality Simulation Platform (model)
MARAT	Mid-Atlantic Regional Assessment Team
MARCO	Macrophage receptor with collagenous structure
max	maximum
MBL	marine boundary layer
MCA	minimum cross-sectional area
MCCP	Mountain Cloud Chemistry Program
Mch; MCh	methacholine
MCM	master chemical mechanism

MCP-1	monocyte chemotactic protein 1
MDA	malondialdehyde
MDAR	monodehydroascorbate reductase
MDI	Mediterranean diet index
MDL	minimum detection level
MED	minimal erythema dose
$MEF_{50\%}$	maximal midexpiratory flow at 50% of forced vital capacity
MEGAN	model of emissions of gases and aerosols from nature
MeJA	methyl jasmonate
MENTOR	Modeling Environment for Total Risk Studies
METs	metabolic equivalent unit(s) [of work]
MFR	Maximum Feasible Reduction
Mg	magnesium
MGDG	monogalactosyldiacylglycerol
mg/m^3	milligrams per cubic meter
MHC	major histocompatibility complex
mi	mile(s)
MI	myocardial infarction, "heart attack"
MIESR	matrix isolation electron spin resonance (spectroscopy)
min	minute; minimum
MIP	macrophage inflammatory protein
MIP-2	macrophage inflammatory protein-2
mL	milliliter
mL/min	milliliter(s) per minute
MLN	mediastinal lymph node
Mm	megameter
mm	millimeter(s)
MM Mt.	Mt. Mitchell site
MM5	National Center for Atmospheric Research/Penn State Mesoscale Model (version 5)
MMAD	mass median aerodynamic diameter; mass median aerodynamic density
MMEF	maximal midexpiratory flow
mmHg	millimeters of mercury
MMMD	mean maximum mixing height depth
MMP-2	matrix metalloproteinase-2
MMP-3	matrix metalloproteinase-3
MMP-9	metalloproteinase-9
MMSP	Mount Mitchell State Park, NC
Mn	manganese
M/N	pooled data from mouth and nasal exposure
MnSOD	Manganese superoxide dismutase
mo	month(s)
MOA(s)	mode(s) of Action
MOBILE	(U.S. EPA) mobile vehicle emission factor model (on-road vehicles)
MOBILE6	vehicle emissions modeling software version 6; replaced by MOVES
MODNR	Missouri Department of Natural Resources
MONICA	Monitoring of Trends and Determinants in Cardiovascular Disease
MoOx	molybdenum oxides
MOSES	Met Office Surface Exchange Scheme
MOVES	Motor Vehicle Emission Simulator (replaced MOBILE6; for estimating emissions from cars, trucks, and motorcycles
MOZAIC	Measurement of Ozone and Water Vapor by Airbus In-Service Aircraft
MOZART	Model for Ozone and Related chemical Tracers
MPAN	peroxymethacryloyl nitrate; peroxy-methacrylic nitric anhydride
MPO	myeloperoxidase
MQL	Minimum quantification limit
MRI	magnetic resonance imaging; Midwest Research Institute; Meteorological Research Institute
mRNA	messenger RNA
ms	millisecond(s)
MS	mass spectrometry; Mt. Moosilauke site
MSA	Metropolitan Statistical Area; methane sulfonic acid
MSL	mean sea level
MS/MS	tandem mass spectrometry
MT	million ton(s); metric ton(s)
MT, Mt	metallothionein
MT1	mitochondria
MTBE	methyl-tertiary-butyl ether
mtDNA	mitochondrial DNA
Mtn	mountain
MV	minute volume
MW	molecular weight
MyD88	myeloid differentiation primary response gene 88
n, N	number; number of observations
N	nitrogen; North; nasal exposure by natural breathing
^{15}N	nitrogen-15, stable isotope of nitrogen
N_2	molecular nitrogen; nonreactive nitrogen
Na	sodium
NA	noradrenaline; North American
NA; N/A	not available; not applicable
Na^+	sodium ion
NAAQS	National Ambient Air Quality Standards
NAD	nicotinamide adenine nucleotide

NADH	reduced nicotinamide adenine dinucleotide; nicotinamide adenine dinucleotide dehydrogenase
NADP	National Atmospheric Deposition Program
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NADPH-CR	reduced nicotinamide adenine dinucleotide phosphate - cytochrome c reductase
NaE	sodium erythorbate
NAG	N-acetyl-glucosaminidase
Na-K-ATPase	sodium-potassium-dependent adenosine triphosphatase
NAMS	National Ambient Monitoring Stations
NAPAP	National Acid Precipitation Assessment Program
NAPBN	National Air Pollution Background Network
NARE	North Atlantic Regional Experiment
NARSTO	North American Regional Strategy for Tropospheric Ozone
NAS	National Academy of Sciences; Normative Aging Study
NASA	National Aeronautics and Space Administration
NBS	National Bureau of Standards
NBTH	3-methyl-2-benzothiazolinone acetone azine
NCEA	National Center for Environmental Assessment
NCEA-RTP	NCEA Division in Research Triangle Park, NC
NCHS	National Center for Health Statistics
NCICAS	National Cooperative Inner-City Asthma Study
NCLAN	National Crop Loss Assessment Network
NCore	National Core multi-pollutant monitoring network
NC-R	resistant clones of white clover
NC-S	sensitive clones of white clover
ND; n.d.	not detectable; not detected; no data
2ndHDM	second-highest daily maximum
NDF	neutral detergent fiber
NEE	net ecosystem CO_2 exchange
NEI	National Emissions Inventory
NEM	National Ambient Air Quality Standards Exposure Model
NEP	Net Ecosystem Production
NERL	National Exposure Research Laboratory
NESCAUM	Northeast States for Coordinated Air Use Management
NF	National Forest; non-filtered air
NF-κB	nuclear factor kappa B
ng	nanogram(s)
NGF	nerve growth factor
NH	northern hemisphere
NH_3	ammonia
NH_4^+	ammonium ion
NH_4HSO_4	ammonium bisulfate
$(NH_4)_2HSO_4$	ammonium sulfate
NHANES	National Health and Nutrition Examination Survey
NHANES III	National Health and Nutrition Examination Survey III
NHAPS	National Human Activity Pattern Survey
NHEERL	(U.S. EPA) National Health and Environmental Effects Research Laboratory
NHIS	National Health Interview Survey
$(NH_4)_2SO_4$	ammonium sulfate
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NK	natural killer cells; neurokinin
NKT	natural killer T cells
NL	nasal lavage
NLF	nasal lavage fluid
NM	National Monument
NMHC(s)	nonmethane hydrocarbon(s)
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NMOC(s)	nonmethane organic compound(s)
NMVOCs	nonmethane volatile organic compounds
NN	normal-to-normal (NN or RR) time interval between each QRS complex in the EKG
NNK	4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone
nNOS	neuronal nitric oxide synthase (NOS)
NO	nitric oxide
·NO	nitric oxide concentration (interpunct NO)
NO_2	nitrogen dioxide
NO_3; NO_3•	nitrate, nitrate radical
NO_3^-	nitrate, nitrate ion
N_2O	nitrous oxide
N_2O_5	dinitrogen pentoxide
NOAA	National Oceanic and Atmospheric Administration
NOAEL	no observed adverse effect level
NOS	nitric oxide synthase (types, NOS-1, NOS-2, NOS-3)
NO_X	nitrogen oxides, oxides of nitrogen (NO + NO2)
NO_Y	sum of NOX and NOZ; odd nitrogen species; total oxidized nitrogen

NO_Z	sum of all inorganic and organic reaction products of NO_X (HONO, HNO_3, HNO_4, organic nitrates, particulate nitrate, nitro-PAHs, etc.)
NP	National Park
NPP	net primary production
NPS	National Park Service, U.S. Department of the Interior
NQO1	NAD(P)H-quinone oxidoreductase (genotype)
NQO1wt	NAD(P)H-quinone oxidoreductase wild type (genotype)
NR	not reported
Nr	reactive nitrogen
NRC	National Research Council
Nrf-2	nuclear factor erythroid 2-related factor 2
Nrf2-ARE	NF-E2-related factor 2-antioxidant response element
NS; n.s.	nonsignificant; non-smoker; national seashore; natural spline
NSAID	non-steroidal anti-inflammatory agent
NSBR	nonspecific bronchial responsiveness
NSF	National Science Foundation
NTE	nasal turbinate epithelial (cells)
NTN	National Trends Network
NTP	National Toxicology Program
NTRMs	NIST Traceable Reference Materials
NTS	nucleus of the solitary tract (in brainstem)
NWR	national wildlife refuge
NWS	National Weather Service
NZW	New Zealand white (rabbit)
O	oxygen; horizon forest floor
^{18}O	oxygen-18, stable isotope of oxygen
O_2	molecular oxygen
O_2^-	superoxide
O_2•	superoxide radical
$^1O_2$	singlet oxygen
O_3	ozone
$^{18}O_3$	(oxygen-18 labeled) ozone
O_3*	electronically excited ozone
OAQPS	Office of Air Quality Planning and Standards
OAR	Office of Air and Radiation
OBMs	observationally based methods
OC	organic carbon
OD	outer diameter; optical density
$O(^1D)$	electronically excited oxygen atom
OH, OH•	hydroxyl group, hydroxyl radical
8-OHdG	8-hydroxy-2´-deoxyguanosine
OLS	ordinary least squares
OMI	Ozone Monitoring Instrument
ON	Ontario
$ONOO^-$	peroxynitrate ion
$O(^3P)$	ground-state oxygen atom
OPE	ozone production efficiency
OPECs	Outdoor Plant Environment Chambers
OR	odds ratio
ORD	Office of Research and Development
OSHA	Occupational Safety and Health Administration
OTC	open-top chamber
OuJ	O_3-sensitive C3H mouse strain (C3H/OuJ)
OVA	ovalbumin
OX	odd oxygen species; total oxidants
OxComp	oxidative capacity of the atmosphere
oz	ounce(s)
P	pressure in atmospheres; plants grown in pots; phosphorus; penetration fraction of O_3 into the microenvironment; pulmonary region
p	probability value
P450	cytochrome P450
p53	cell cycle protein gene
P90	90th percentile of the absolute difference in concentrations
PACF	partial autocorrelation function of the model residuals
PAD	peripheral arterial disease; pollutant-applied dose
PAF	platelet-activating factor; paroxysmal atrial fibrillation
PAH(s)	polycyclic aromatic hydrocarbon(s)
PAI-1	plasminogen activator fibrinogen inhibitor-1
PAL	phenylalanine ammonia lyase
PAMS	Photochemical Assessment Monitoring Stations network
PAN	peroxyacetyl nitrate
PaO_2	arterial oxygen pressure
PAPA	Public Health and Air Pollution in Asia
PAR	photosynthetically active radiation; proximal alveolar region
P_{atm}	Pressure in atmospheres
p-ATP	para-acetamidophenol
Pb	Lead
PBL	planetary boundary layer; peripheral blood lymphocytes
PBM	population-based model or modeling
PBN	C-phenyl N-tert-butyl nitrone
PBPK	physiologically based pharmacokinetic (model)
PBS	phosphate buffered saline
PC	phosphatidylchloline

PC_{20}	provocative concentration that produces a 20% decrease in forced expiratory volume in 1 second
$PC_{20}FEV_1$	provovative concentration that produces a 20% decrease in FEV_1
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-oxononononoyl)-sn-glycero-3-phosphocholine
PCD	programmed cell death
PCl	picryl chloride
pCNEM	Canadian version of National Ambient Air Quality Standards Exposure Model
PCO_2	Average partial pressure of O2 in lung capillaries
pCO_2	partial pressure of carbon dioxide
PCR	polymerase chain reaction
PCR-DGGE	PCR–denaturing gradient gel electrophoresis
PD	pregnancy day
PD_{20}	provocative dose that produces a 20% decrease in FEV_1
$PD_{20}FEV_1$	provocative dose that produces a 20% decrease in FEV_1
PD_{100}	provocative dose that produces a 100% increase in sRAW
$PD_{100}S_{Raw}$	provocative dose that produces a 100% increase in S_{Raw}
PDI	pain on deep inspiration
PE	post exposure, phosphatidylethanolamine
PEF	peak expiratory flow
$PEF_{0.75}$	peak expiratory flow in 0.75 second
PEFR	peak expiratory flow rate
PEFT	time to peak flow
PEG-CAT	polyethylene glycol-catalase
PEG-SOD	polyethylene glycol-superoxide dismutase
PEM(s)	personal exposure monitor(s)
Penh	enhanced pause
PEPc	phosphoenolpyruvate carboxylase
PFD	photosynthetic flux density
PFT	pulmonary function test
pg	picogram(s)
PG	prostaglandin (e.g., PGE2 ,PGF2); phosphatidylglycerol
6PGD	6-phosphogluconate dehydrogenase
PGE2	prostaglandin E2
PGF2α	prostaglandin F2-alpha
PGHS-2	prostaglandin endoperoxide G/H synthase 2
PGP	protein gene product (e.g., PGP9.5)
PGSM	Plant Growth Stress Model
pH	relative acidity; Log of the reciprocal of the hydrogen ion concentration
PHA	phytohemagglutinin A
PI	phosphatidylinositol; probability interval; posterior interval
PIF	peak inspiratory flow
PiZZ	respiratory phenotype
PK	pharmacokinetics
pKa	dissociation constant
PLFA	phospholipid fatty acid
PM	particulate matter
PM_X	Particulate matter of a specific size range not defined for regulatory use. Usually X refers to the 50% cut point, the aerodynamic diameter at which the sampler collects 50% of the particles and rejects 50% of the particles. The collection efficiency, given by a penetration curve, increases for particles with smaller diameters and decreases for particles with larger diameters. The definition of PM_X is sometimes abbreviated as “particles with a nominal aerodynamic diameter less than or equal to X µm” although X is usually a 50% cut point.
$PM_{2.5}$	In general terms, particulate matter with an aerodynamic diameter less than or equal to a nominal 2.5 µm; a measurement of fine particles in regulatory terms, particles with an upper 50% cut-point of 2.5 µm aerodynamic diameter (the 50% cut point diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) and a penetration curve as measured by a reference method based on Appendix L of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53, by an equivalent method designated in accordance with 40 CFR Part 53, or by an approved regional method designated in accordance with Appendix C of 40 CFR Part 58.

PM_{10}	In general terms, particulate matter with an aerodynamic diameter less than or equal to a nominal 10 µm; a measurement of thoracic particles (i.e., that subset of inhalable particles thought small enough to penetrate beyond the larynx into the thoracic region of the respiratory tract) in regulatory terms, particles with an upper 50% cut-point of 10± 0.5 µm aerodynamic diameter (the 50% cut point diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) and a penetration curve as measured by a reference method based on Appendix J of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53 or by an equivalent method designated in accordance with 40 CFR Part 53.
$PM_{10-2.5}$	In general terms, particulate matter with an aerodynamic diameter less than or equal to a nominal 10 µm and greater than a nominal 2.5 µm; a measurement of thoracic coarse particulate matter or the coarse fraction of PM10 in regulatory terms, particles with an upper 50% cut-point of 10 µm aerodynamic diameter and a lower 50% cut-point of 2.5 µm aerodynamic diameter (the 50% cut point diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) as measured by a reference method based on Appendix O of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53 or by an equivalent method designated in accordance with 40 CFR Part 53.
PM_{10C}	The $PM_{10-2.5}$ concentration of $PM_{10-2.5}$ measured by the 40 CFR Part 50 Appendix O reference method which consists of currently operated, co-located low-volume (16.7 Lpm) PM_{10} and $PM_{2.5}$ reference method samplers.
p38MAPK	p38 mitogen-activated protein kinase(s)
PM-CAMx	Comprehensive Air Quality Model with extensions and with particulate matter chemistry
PMN(s)	polymorphonuclear leukocyte(s)
PMT	photomultiplier tube
PND	post natal day
pNEM	probabilistic National Exposure Model
PnET	Photosynthetic EvapoTranspiration model
PNN	proportion of interval differences of successive normal-beat intervals in EKG
PNN50	proportion of interval differences of successive normal-beat intervals greater than 50 ms in EKG
PO_2	partial pressure of oxygen
POC	particulate organic carbon
POD	peroxidase
polyADPR	poly(adenosinediphosphate-ribose)
POMS	Portable Ozone Monitoring Systems
ppb	parts per billion
ppb-h	parts per billion per hour
ppbv	parts per billion by volume
pphm	parts per hundred million
ppm	parts per million
ppm-h	parts per million hours; weighted concentration values based on hourly concentrations: usually summed over a certain number of hours, day(s), months, and/or season.
ppmv	parts per million by volume
PPN	peroxypropionyl nitrate; peroxypropionic nitric anhydride
PPPs	power plant plumes
ppt	parts per trillion
pptv	parts per trillion by volume
PQH2	plastoquinone
PR	pathogenesis-related (protein)
PR-1	promoter region 1
PRB	policy-relevant background
preproET-1	pre-protein form of ET-1 mRNA
PRYL	predicted relative yield (biomass) loss
PS	penalized spline
PS	paradoxical sleep
PS II	Photosystem II: enzyme that uses light to obtain electrons from water (for photosynthesis).
PSA	picryl sulfonic acid
PSC	polar stratospheric clouds
PTB	preterm birth
PTR-MS	proton-transfer-reaction mass spectroscopy
PU, PUL	pulmonary
PUFA(s)	polyunsaturated fatty acid(s)
PV	potential vorticity
PVCD	peripheral vascular and cerebrovascular disease
PVD	peripheral vascular disease
PVOCs	photochemical volatile organic compounds
PWM	pokeweed mitogen
PWTES	(left ventricular) posterior wall thickness at end systole
Pxase	peroxidase
QA	Quality Assurance
QC	quality control

QCE	quasi continuous exercise
qNP	non-photochemical quenching
q_{NP}	non-photochemical quenching
qP	photochemical quenching
QRS	A complex of three distinct electrocardiogram waves which represent the beginning of ventricular contraction
QT	interval measure of the time interval between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	corrected QT interval
r	Pearson correlation coefficient
R, r	correlation coefficient
r^2	correlation coefficient
R^2	multiple regression correlation coefficient
R^2, r^2	coefficient of determination
RACM	Regional Atmospheric Chemistry Mechanism
RADM	Regional Acid Deposition Model
rALP	recombinant antileukoprotease
RAMS	Regional Atmospheric Modeling System
RANTES	regulated upon activation, normal T cell expressed and secreted (cells)
Raw	airway resistance
RB	respiratory bronchiole
RBC(s)	red blood cell(s); erythrocyte(s)
rbcL	Rubisco large subunit
rbcS	Rubisco small subunit
R′CO acyl	acyl carrier protein
$R'C(O)–O_2$	acyl peroxy
rcd1	Arabidopsis mutant radical induced cell death
RCD3	rod-cone dysplasia 3
RCP	Representative Concentration Pathways
RDBMS	Relational Database Management Systems
Re	Reynolds number
REHEX	Regional Human Exposure Model
RER	rough endoplasmic reticulum; Respiratory exchange ratio
RF	radiative forcing
RGR	relative growth rate
RH	relative humidity
RIOPA	Relationship of Indoor, Outdoor, and Personal Air (study)
RL	total pulmonary resistance
RLKs	receptor-like/Pelle kinase group
RMNP	Rocky Mountain National Park, Colorado
RMR	resting metabolic rate
rMSSD	root mean squared differences between adjacent normal-to-normal heartbeat intervals
Rn	nasal resistance
RNA	ribonucleic acid
RO_2	organic peroxyl; organic peroxy
ROG	reactive organic gases
ROI	reactive oxygen intermediate/superoxide anion
$RONO_2$	organic nitrate
ROOH	organic peroxides
$ROONO_2$, RO_2NO_2	peroxy nitrate
ROS	reactive oxygen species
RPD	relative percent difference
RR	normal-to-normal (NN or RR) time interval between each QRS complex in the EKG; risk ratio; relative risk; respiratory rate
RRMS	relatively remote monitoring sites
RT	respiratory tract
RT	transepithelial resistance
RTLF	respiratory tract lining fluid
RuBisCO; Rubisco	ribulose-1,5-bisphosphate carboxylase/oxygenase
RuBP	ribulose bisphosphate
σ	sigma, standard deviation
σg	sigma-g; (geometric standard deviation)
s	second
S	Short; smoker; sulfur; South
s.c.	subcutaneous (route)
SA	salicylic acid
SAB	Science Advisory Board
SAC	Staphylococcus aureus Cowan 1 strain
SAG21	senescence
SAI	Systems Applications International
S-allele	short-allele
SAMD	S-adenosyl methionine decarboxylase
SaO_2	oxygen saturation of arterial blood
SAPALDIA	Study of Air Pollution and Lung Diseases in Adults
SAPRC	Stratospheric Processes and their Role in Climate; Statewide Air Pollution Research Center, University of California, Riverside
SAR	systemic acquired resistance
SAROAD	Storage and Retrieval of Aerometric Data (U.S. EPA centralized database; superseded by Aerometric Information Retrieval System [AIRS])
SAWgrp	small airway function group
SBNF	San Bernardino National Forest, California
SBP	systolic blood pressure
SBUV	Solar Backscatter Ultraviolet Spectrometer
SC	stratum corneum
Sc	scandium

SCAQS	Southern California Air Quality Study
SCE(s)	sister chromatid exchange(s)
SD	standard deviation; Sprague-Dawley rat
SDNN	standard deviation normal-to-normal (NN or RR) time interval between each QRS complex in the EKG
SE	standard error
SEBAS	Social Environment and Biomarkers of Aging Study
sec	second
Sess.	session
SEM	simultaneously extracted metal; standard error of the mean; scanning electron microscopy
SENP	Sequoia National Park, California
SES	socioeconomic status
SF	San Francisco Bay Area
SF6	sulfur hexafluoride (tracer gas)
SGA	small for gestational age
sRaw	specific airway conductance
SH	Shenandoah National Park site
SHEDS	Stochastic Human Exposure and Dose Simulation
SHEN	Shenandoah National Park
sICAM-1	soluble intercellular adhesion molecule
SIDS	sudden infant death syndrome
SIGMOID	sigmoid weighted summed concentration
SINIC	Simple Nitrogen Cycle model
SIP	State Implementation Plan
SIPK	salicylic acid (SA) induced protein kinase
SK	shikimate kinase
SLA	specific leaf area
SLAC1	(protein) slow anion channel associated 1
SLAMS	State and Local Air Monitoring Stations
SM	smooth muscle
SMD	soil moisture deficit
SME	soybean oil methyl ester
SMNP	Great Smoky Mountain National Park (North Carolina and Tennessee)
SMOKE	Spare-Matrix Operator Kernel Emissions
S_N	normalized slope of the alveolar plateau
SNAAQS	Secondary National Ambient Air Quality Standards
SNP(s)	single-nucleotide polymorphism
SO_2	sulfur dioxide
SO_4^{2-}	sulfate
SOA	secondary organic aerosol
SOC	soil organic carbon
SOD	superoxide dismutase
SOS	Southern Oxidant Study
SO_X	sulfur oxides
SoyFACE	Soybean Free Air gas Concentration Enrichment (Facility)
SP	surfactant protein (e.g., SPA, SPD); substance P
SP-A	surfactant protein-A
SPF	specific pathogen free
SPMs	special purpose monitors
SP-NK	substance P – neurokinin receptor complex
sRaw,	specific airway resistance
SRBC	sheep red blood cell
SRES	Special Report on Emissions Scenarios
SRM	standard reference method
SRP	standard reference photometers
SSCP	single-strand conformation polymorphism
129S1/SvlmJ	mouse strain
STE	stratosphere-troposphere exchange
STEP	Stratospheric-Tropospheric-Exchange Project
STN	speciation trends network
sTNFR1	soluble tumor necrosis factor receptor 1
STP	standard temperature and pressure
STPD	standard temperature and pressure, dry
STRF	Spatio-Temporal Random Field (theory)
subscript i	Index of indoor microenvironments
subscript o	Index of outdoor microenvironments
subscript o,i	Index of outdoor microenvironments adjacent to a given indoor microenvironment *i*
SUM00	sum of all hourly average concentrations
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
SVE	supraventricular ectopy
S-W	square-wave
SWS	slow wave sleep
SZA	solar zenith angle
τ	tau, photochemical lifetime; atmospheric lifetime
t	t-test statistical value; t statistic
T	time; duration of exposure

T cell(s)	T lymphocyte(s), thymus-dependent lymphocytes
T1	first trimester
T2	second trimester
T_3	triiodothyronine
T3	third trimester
T_4	thyroxine
TAR	IPCC Third Assessment Report
TAR WGI	IPCC Third Assessment Report of Working Group I
TB	tracheobronchial; terminal bronchioles; tuberculosis
TBA	thiobarbituric acid
TBARS	thiobarbituric acid reactive substances
TC	total carbon
^{99m}Tc	Technetium-99m
T-cells	T-lymphocytes, Thymus-derived lymphocytes
^{99m}Tc-DTPA	99mTc-diethylenetriaminepentaacetic acid
Tco	core temperature
TDLAS	Tunable Diode Laser Absorption Spectrometer
Te	expiratory time
TEM	transmission electron microscopy; Terrestrial Ecosystem Model
TES	Tropospheric Emission Spectrometer
TexAQS	Texas Air Quality Field Study
Tg	teragram(s)
TGF	transforming growth factor
TGF β	transforming growth factor beta
Th	T helper cell type
Th2	T helper cell type 2
THC	Total hydrocarbon content
tHcy	total homocysteine
Ti	inspiratory time
Ti	titanium
TIA	transient ischemic attack
TIMP-2	tissue inhibitor of matrix metalloprotease-2
TiO_2	titanium dioxide
TLC	total lung capacity
TLNISE	two-level normal independent sampling estimation
Tlr	toll-like receptor gene
TLR	Toll-like receptor protein (ex., TLR2, TLR4)
TMPO	tetramethylphrrolise 1-oxide
TNC	total nonstructural carbohydrate
TNF	tumor necrosis factor (e.g., TNF-α)
TNF-308	tumor necrosis factor genotype
TNF-α	tumor necrosis factor alpha
TNFR	tumor necrosis factor receptor
TOMS	Total Ozone Mapping/Monitoring Satellite; total ozone mapping spectrometer
TOPSE	Tropospheric Ozone Production About the Spring Equinox
tPA	tissue plasminogen activator
TPLIF	two-photon laser-induced fluorescence
TRAMP	TexAQS-II Radical and Aerosol Measurement Project
TREGRO	Tree Growth Model
TRIFFID	Top-down Representation of Interactive Foliage and Flora Including Dynamics
TRIM	Total Risk Integrated Methodology (model)
TRIM.Expo	Total Risk Integrated Methodology Exposure Event (model)
TRP	transient receptor potential (ion channel[s], ex., TRP-A1, TRP-V1, TRP-M8)
TSH	thyroid stimulating hormone
TSP	total suspended particles
TTFMS	two-tone frequency-modulated spectroscopy
TWA	time-weighted average
TX	thromboxane (e.g., TXB_2)
TXB_2	thromboxane B2
UA	uric acid; Urate
UAM	Urban Airshed Model
UCL	upper 95th% confidence limit
UDGT	UDP -galactose-1,2,-diacylglycerol galactosyltransferase
UDP	uridine diphosphate
U.K.	United Kingdom
UNECE	United Nations Economic Commission for Europe
UNEP	United Nations Environmental Programme
UNFCCC	United Nations Framework Convention on Climate Change
U-O	epioxides formed from uric acid
$U\text{-}O_2^-$	peroxides formed from uric acid
$U\text{-}O_3^-$	ozonides formed from uric acid
URI	upper respiratory infection
URS	upper respiratory symptoms
URT	upper respiratory tract; upper airways
U.S.	United States (of America)
USC; U.S.C.	U.S. Code
USDA	U.S. Department of Agriculture
USFS	U.S. Forest Service
USGCRP	U.S. Global Change Research Program
USGS	U.S. Geological Survey
UV	ultraviolet radiation
UV-A	ultraviolet radiation at wavelengths of 320 to 400 nm

UV-B	ultraviolet radiation at wavelengths of 280 to 320 nm
UV-C	ultraviolet radiation at wavelengths of 200 to 280 nm
UV-DIAL	Ultraviolet Differential Absorption Lidar
V	vanadium
V, mV, µV	volt, millivolt, microvolt
VA	alveolar ventilation
Val	valine
VC	vital capacity
VCAM	vascular cell adhesion molecule
V_d	deposition rate, deposition velocity (cm/s)
V_D	volume of the anatomic or physiological dead space
V_E	ventilation rate; minute ventilation; ventilatory volume
VEGF	vascular endothelial growth factor
$V_E$max	maximum minute ventilation
Vmax	maximum velocity
$Vmax_{25\%}$	maximum expiratory flow at 25% of the vital capacity
$Vmax_{50\%}$	maximum expiratory flow at 50% of the vital capacity
$Vmax_{75\%}$	maximum expiratory flow at 75% of the vital capacity
VMD	volume median diameter
Vn	nasal volume
VO_2	oxygen consumption
VO_2max	maximum volume per time, of oxygen (maximal oxygen consumption, maximal oxygen uptake or aerobic capacity)
VOC(s)	volatile organic compound(s)
VP	volumetric penetration
$VP_{50\%}$	volume at which 50% of an inhaled bolus is absorbed
VPD	vapor pressure deficit; Vehicles per day; Ventricular premature depolarization
VT	tidal volume
VTB	terminal bronchiole region volume
VTmax	maximum tidal volume
VUA	volume of the upper airways
vWF	von Willebrand factor
W	width; wilderness; week(s)
W126	cumulative integrated exposure index with a sigmoidal weighting function
W95	cumulative integrated exposure index with a sigmoidal weighting function
WBC	white blood cell
WBGT	wet bulb globe temperature
wc	sigmoidal weighting of hourly O_3 concentration
WCB	warm conveyor belt
WED	(U.S. EPA NHEERL) Western Ecology Division
WF, WFM	White Face Mountain site
WHI	Women's Health Initiative
WHO	World Health Organization
wk(s)	week(s)
W/m^2, $W\ m^{-2}$	watts per square meter
WMO	World Meteorological Organization
WMO/UNEP	World Meteorological Organization/United Nations Environment Program
WRF	Weather Research and Forecasting model
Ws	Wassilewskija Arabidopsis ecotype
WS	wood smoke
WT	wild type; White Top Mountain site
wt %	percent by weight
WUS	western U.S.
w/v	weight per volume
Y	three parameter Weibull model
yr	year
Z	Airway generation
ZAPS	Zonal Air Pollution System
ZELIG	a forest succession simulation model
Zn	zinc

PREAMBLE

Process of ISA Development

This preamble outlines the general process for developing an Integrated Science Assessment (ISA) including the framework for evaluating weight of evidence and drawing scientific conclusions and causal judgments. The ISA provides a concise review, synthesis, and evaluation of the most policy-relevant science to serve as a scientific foundation for the review of the National Ambient Air Quality Standards (NAAQS). The general process for NAAQS reviews is described at http://www.epa.gov/ttn/naaqs/review.html; information for individual NAAQS reviews is available at www.epa.gov/ttn/naaqs. This preamble is a general discussion of the basic steps and criteria used in developing an ISA; for each ISA, specific details and considerations are included in the introductory section for that assessment.

The fundamental process for developing an ISA includes:

- literature searches;
- study selection;
- evaluation and integration of the evidence; and
- development of scientific conclusions and causal judgments.

An initial step in this process is publication of a call for information in the Federal Register that invites the public to provide information relevant to the assessment, such as new publications on health or welfare[1] effects of the pollutant, or from atmospheric and exposure sciences fields. EPA maintains an ongoing literature search process for identification of relevant scientific studies published since the last review of the NAAQS. Search strategies are designed for pollutants and scientific disciplines and iteratively modified to optimize identification of pertinent publications. Papers are identified for inclusion in several additional ways: specialized searches on specific topics; independent review of tables of contents for journals in which relevant papers may be published; independent identification of relevant literature by expert scientists; review of citations in previous assessments and identification by the public and CASAC during the external review process. Publications considered for inclusion in the ISA are added to the Health and Environmental Research Online (HERO) database developed by EPA (http://hero.epa.gov/); the references in the ISA include a hyperlink to the database.

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

Studies that have undergone scientific peer review and have been published or accepted for publication and reports that have undergone review are considered for inclusion in the ISA. Analyses conducted by EPA using publicly available data are also considered for inclusion in the ISA. All relevant epidemiologic, controlled human exposure, toxicological, and ecological and welfare effects studies published since the last review are considered, including those related to exposure-response relationships, mode(s) of action (MOA), and potentially at-risk populations and lifestages. Studies on atmospheric chemistry, environmental fate and transport, dosimetry, toxicokinetics and exposure are also considered for inclusion in the document, as well as analyses of air quality and emissions data. References that were considered for inclusion in a specific ISA can be found using the HERO website (http://hero.epa.gov).

Each ISA builds upon the conclusions of previous assessments for the pollutant under review. EPA focuses on peer reviewed literature published following the completion of the previous review and on any new interpretations of previous literature, integrating the results of recent scientific studies with previous findings. Important older studies may be discussed in detail to reinforce key concepts and conclusions or for reinterpretation in light of newer data. Older studies also are the primary focus in some areas of the document where research efforts have subsided, or if these older studies remain the definitive works available in the literature.

Selection of studies for inclusion in the ISA is based on the general scientific quality of the study, and consideration of the extent to which the study is informative and policy-relevant. Policy relevant and informative studies include those that provide a basis for or describe the relationship between the criteria pollutant and effects, including studies that offer innovation in method or design and studies that reduce uncertainty on critical issues, such as analyses of confounding or effect modification by copollutants or other variables, analyses of concentration-response or dose-response relationships, or analyses related to time between exposure and response. Emphasis is placed on studies that examine effects associated with pollutant concentrations relevant to current population and ecosystem exposures, and particularly those pertaining to concentrations currently found in ambient air. Other studies are included if they contain unique data, such as a previously unreported effect or MOA for an observed effect, or examine multiple concentrations to elucidate exposure-response relationships. In general, in assessing the scientific quality and relevance of health and welfare effects studies, the following considerations have been taken into account when selecting studies for inclusion in the ISA.

- Are the study populations, subjects, or animal models adequately selected, and are they sufficiently well defined to allow for meaningful comparisons between study or exposure groups?

- Are the statistical analyses appropriate, properly performed, and properly interpreted? Are likely covariates adequately controlled or taken into account in the study design and statistical analysis?
- Are the air quality data, exposure, or dose metrics of adequate quality and sufficiently representative of information regarding ambient conditions?
- Are the health, ecological or welfare effect measurements meaningful, valid and reliable?
- Do the analytical methods provide adequate sensitivity and precision to support conclusions?

Considerations specific to particular disciplines include the following. In selecting epidemiologic studies, EPA considers whether a given study: (1) presents information on associations with short- or long-term pollutant exposures at or near ambient conditions; (2) addresses potential confounding by other pollutants; (3) assesses potential effect modifiers; (4) evaluates health endpoints and populations not previously extensively researched; and (5) evaluates important methodological issues related to interpretation of the health evidence (e.g., lag or time period between exposure and effects, model specifications, thresholds, mortality displacement).

Considerations for the selection of research evaluating controlled human exposure or animal toxicological studies includes a focus on studies conducted using relevant pollutant exposures. For both types of studies, relevant pollutant exposures are considered to be those generally within one or two orders of magnitude of ambient concentrations. Studies in which higher doses were used may also be considered if they provide information relevant to understanding MOA or mechanisms, as noted below.

Evaluation of controlled human exposure studies focuses on those that approximated expected human exposure conditions in terms of concentration and duration. Studies should include control exposures to filtered air, as appropriate. In the selection of controlled human exposure studies, emphasis is placed on studies that: (1) investigate potentially at-risk populations and lifestages such as people with asthma or cardiovascular diseases, children or older adults; (2) address issues such as concentration-response or time-course of responses; and (3) have sufficient statistical power to assess findings.

Review of the animal toxicological evidence focuses on studies that approximate expected human dose conditions, which vary depending on the dosimetry, toxicokinetics and biological sensitivity of the particular laboratory animal species or strains studied. Emphasis is placed on studies that: (1) investigate animal models of disease that can provide information on populations potentially at increased risk of effects; (2) address

issues such as concentration-response or time-course of responses; and (3) have sufficient statistical power to assess findings. Due to resource constraints on exposure duration and numbers of animals tested, animal studies typically utilize high-concentration exposures to acquire data relating to mechanisms and assure a measurable response. Emphasis is placed on studies using doses or concentrations generally within 1-2 orders of magnitude of current levels. Studies with higher concentration exposures or doses are considered to the extent that they provide useful information to inform our understanding of interspecies differences and potential differences between healthy and susceptible human populations. Results from in vitro studies may also be included if they provide mechanistic insight or further support for results demonstrated in vivo.

These criteria provide benchmarks for evaluating various studies and for focusing on the policy-relevant studies in assessing the body of health, ecological and welfare effects evidence. As stated initially, the intent of the ISA is to provide a concise review, synthesis, and evaluation of the most policy-relevant science to serve as a scientific foundation for the review of the NAAQS, not extensive summaries of all health, ecological and welfare effects studies for a pollutant. Of most relevance for inclusion of studies is whether they provide useful qualitative or quantitative information on exposure-effect or exposure-response relationships for effects associated with pollutant exposures at doses or concentrations relevant to ambient conditions that can inform decisions on whether to retain or revise the standards.

In developing an ISA, EPA reviews and summarizes the evidence from: studies of atmospheric sciences and exposure; the health effects evidence from toxicological, controlled human exposure and epidemiologic studies; and ecological and welfare effects evidence. In the process of developing the first draft ISA, EPA may convene a public workshop in which EPA and non-EPA experts review the scientific content of preliminary draft materials to ensure that the ISA is up to date and focused on the most policy-relevant findings, and to assist EPA with integration of evidence within and across disciplines.

EPA integrates the evidence from across scientific disciplines or study types and characterizes the weight of evidence for relationships between the pollutant and various outcomes. The integration of evidence on health, and ecological or welfare effects, involves collaboration between scientists from various disciplines. As an example, an evaluation of health effects evidence would include the integration of the results from epidemiologic, controlled human exposure, and toxicological studies, and application of the causal framework (described below) to draw conclusions. Using the causal framework described in the following section, EPA scientists consider aspects such as strength, consistency, coherence, and biological plausibility of the evidence, and develop

draft causality determinations on the nature of the relationships. Causality determinations often entail an iterative process of review and evaluation of the evidence. Two drafts of the ISA are typically released for review by the CASAC and the public, and comments received on the characterization of the science as well as the implementation of the causal framework are carefully considered in revising and completing the final ISA.

EPA Framework for Causal Determination

EPA has developed a consistent and transparent basis to evaluate the causal nature of air pollution-related health or welfare effects for use in developing ISAs. The framework described below establishes uniform language concerning causality and brings more specificity to the findings. This standardized language was drawn from sources across the federal government and wider scientific community, especially the National Academy of Sciences (NAS) Institute of Medicine (IOM) document, *Improving the Presumptive Disability Decision-Making Process for Veterans* (2008), a comprehensive report on evaluating causality. This framework:

- describes the kinds of scientific evidence used in establishing a general causal relationship between exposure and health effects;
- characterizes the evidence necessary to reach a conclusion about the existence of a causal relationship;
- identifies issues and approaches related to uncertainty; and
- provides a framework for classifying and characterizing the weight of evidence in support of a general causal relationship.

Approaches to assessing the separate and combined lines of evidence (e.g., epidemiologic, controlled human exposure, and animal toxicological studies) have been formulated by a number of regulatory and science agencies, including the IOM of the NAS (2008), International Agency for Research on Cancer (2006), *EPA Guidelines for Carcinogen Risk Assessment* (2005), and Centers for Disease Control and Prevention (2004). Causal inference criteria have also been described for ecological effects evidence (U.S. EPA, 1998; Fox, 1991). These formalized approaches offer guidance for assessing causality. The frameworks are similar in nature, although adapted to different purposes, and have proven effective in providing a uniform structure and language for causal determinations.

Evaluating Evidence for Inferring Causation

The 1964 Surgeon General's report defined "cause" as a "significant, effectual relationship between an agent and an associated disorder or disease in the host" (HEW); more generally, a cause is defined as an agent that brings about an effect or a result. An association is the statistical relationship among variables; alone, however, it is insufficient proof of a causal relationship between an exposure and a health outcome. Unlike an association, a causal claim supports the creation of counterfactual claims, that is, a claim about what the world would have been like under different or changed circumstances (Samet and Bodurow, 2008).

Many of the health and environmental outcomes reported in these studies have complex etiologies. Diseases such as asthma, coronary heart disease (CHD) or cancer are typically initiated by multiple agents. Outcomes depend on a variety of factors, such as age, genetic susceptibility, nutritional status, immune competence, and social factors (Samet and Bodurow, 2008; Gee and Payne-Sturges, 2004). Effects on ecosystems are often also multifactorial with a complex web of causation. Further, exposure to a combination of agents could cause synergistic or antagonistic effects. Thus, the observed risk may represent the net effect of many actions and counteractions.

In estimating the causal influence of an exposure on health or environmental effects, it is recognized that scientific findings incorporate uncertainty. "Uncertainty" can be defined as having limited knowledge to exactly describe an existing state or future outcome, e.g., the lack of knowledge about the correct value for a specific measure or estimate. Uncertainty analysis may be qualitative or quantitative in nature. In many cases, the analysis is qualitative, and can include professional judgment or inferences based on analogy with similar situations. Quantitative uncertainty analysis may include use of simple measures (e.g., ranges) and analytical techniques. Quantitative uncertainty analysis might progress to more complex measures and techniques, if needed for decision support. Various approaches to evaluating uncertainty include classical statistical methods, sensitivity analysis, or probabilistic uncertainty analysis, in order of increasing complexity and data requirements. However, data may not be available for all aspects of an assessment and those data that are available may be of questionable or unknown quality. Ultimately, the assessment is based on a number of assumptions with varying degrees of uncertainty. The ISA generally evaluates uncertainties qualitatively in assessing the evidence from across studies; in some situations quantitative analysis approaches, such as meta-regression, may be used.

Publication bias is a source of uncertainty regarding the magnitude of health risk estimates. It is well understood that studies reporting non-null findings are more likely to be published than reports of null findings, and publication bias can also result in

overestimation of effect estimate sizes (Ioannidis, 2008). For example, effect estimates from single-city epidemiologic studies have been found to be generally larger than those from multicity studies (Bell et al., 2005).

Consideration of evidence from scientific disciplines

Moving from association to causation involves the elimination of alternative explanations for the association. The ISA focuses on evaluation of the findings from the body of evidence, drawing upon the results of all studies determined to meet the criteria described previously. Causality determinations are based on the evaluation and synthesis of evidence from across scientific disciplines. The relative importance of different types of evidence varies by pollutant or assessment, as does the availability of different types of evidence for causality determination. Three general types of studies inform consideration of human health effects: controlled human exposure, epidemiologic and toxicological studies. Evidence on ecological or welfare effects may be drawn from a variety of experimental approaches (e.g., greenhouse, laboratory, field) and numerous disciplines (e.g., community ecology, biogeochemistry and paleological/historical reconstructions).

The most direct evidence of a causal relationship between pollutant exposures and human health effects comes from controlled human exposure studies. Controlled human exposure studies experimentally evaluate the health effects of administered exposures in human volunteers under highly controlled laboratory conditions. Also referred to as human clinical studies, these experiments allow investigators to expose subjects to known concentrations of air pollutants under carefully regulated environmental conditions and activity levels. In some instances, controlled human exposure studies can also be used to characterize concentration-response relationships at pollutant concentrations relevant to ambient conditions. Controlled human exposures are typically conducted using a randomized crossover design, with subjects exposed both to the pollutant and a clean air control. In this way, subjects serve as their own controls, effectively controlling for many potential confounders. However, controlled human exposure studies are limited by a number of factors, including small sample size and short exposure time. For example, exposure patterns relevant to understanding real-world exposures, especially long-term exposures, are generally not practical to replicate in a laboratory setting. In addition, although subjects do serve as their own controls, personal exposure to pollutants in the hours and days preceding the controlled exposures may vary significantly between and within individuals. Finally, controlled human exposure studies require investigators to adhere to stringent health criteria for subjects included in the study, and therefore the results cannot necessarily be generalized to an entire population. Although some controlled human exposure studies have included health-compromised individuals such as those with respiratory or cardiovascular disease, these individuals must also be

relatively healthy and may not represent the most sensitive individuals in the population. In addition, the study design is limited to exposures and endpoints that are not expected to result in severe health outcomes. Thus, not observing an effect in controlled human exposure studies does not necessarily mean that a causal relationship does not exist. While controlled human exposure studies provide important information on the biological plausibility of associations observed in epidemiologic studies, observed effects in these studies may underestimate the response in certain populations.

Epidemiologic studies provide important information on the associations between health effects and exposure of human populations to ambient air pollution. In epidemiologic or observational studies of humans, the investigator generally does not control exposures or intervene with the study population. Broadly, observational studies can describe associations between exposures and effects. These studies fall into several categories: e.g., cross-sectional, prospective cohort, panel and time-series studies. "Natural experiments" offer the opportunity to investigate changes in health related to a change in exposure, such as closure of a pollution source.

In evaluating epidemiologic studies, consideration of many study design factors and issues must be taken into account to properly inform their interpretation. One key consideration is evaluation of the potential contribution of the pollutant to a health outcome when it is a component of a complex air pollutant mixture. Reported effect estimates in epidemiologic studies may reflect: independent effects on health outcomes; effects of the pollutant acting as an indicator of a copollutant or a complex ambient air pollution mixture; effects resulting from interactions between that pollutant and copollutants.

In the evaluation of epidemiologic evidence, one important consideration is potential confounding. Confounding is "… a confusion of effects. Specifically, the apparent effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect (which may be null)" (Rothman and Greenland, 1998). One approach to remove spurious associations due to possible confounders is to control for characteristics that may differ between exposed and unexposed persons; this is frequently termed "adjustment." Scientific judgment is needed to evaluate likely sources and extent of confounding, together with consideration of how well the existing constellation of study designs, results, and analyses address this potential threat to inferential validity. A confounder is associated with both the exposure and the effect; for example, confounding can occur between correlated pollutants that are associated with the same effect.

Several statistical methods are available to detect and control for potential confounders, with none of them being completely satisfactory. Multivariable regression models

constitute one tool for estimating the association between exposure and outcome after adjusting for characteristics of participants that might confound the results. The use of multipollutant regression models has been the prevailing approach for controlling potential confounding by copollutants in air pollution health effects studies. Finding the likely causal pollutant from multipollutant regression models is made difficult by the possibility that one or more air pollutants may be acting as a surrogate for an unmeasured or poorly measured pollutant or for a particular mixture of pollutants. In addition, more than one pollutant may exert similar health effects, resulting in independently observed associations for multiple pollutants. The number and degree of diversity of covariates, as well as their relevance to the potential confounders, remain matters of scientific judgment. Despite these limitations, the use of multipollutant models is still the prevailing approach employed in most air pollution epidemiologic studies and provides some insight into the potential for confounding or interaction among pollutants.

Confidence that unmeasured confounders are not producing the findings is increased when multiple studies are conducted in various settings using different subjects or exposures, each of which might eliminate another source of confounding from consideration. For example, multicity studies which use a consistent method to analyze data from across locations with different levels of covariates can provide insight on potential confounding in associations. Intervention studies, because of their quasi-experimental nature, can be particularly useful in characterizing causation.

Another important consideration in the evaluation of epidemiologic evidence is effect modification, which occurs when the effect differs between subgroups or strata; for example, effect estimates that vary by age group or potential risk factor. “Effect-measure modification differs from confounding in several ways. The main difference is that, whereas confounding is a bias that the investigator hopes to prevent or remove from the effect estimate, effect-measure modification is a property of the effect under study . . . In epidemiologic analysis one tries to eliminate confounding but one tries to detect and estimate effect-measure modification” (Rothman and Greenland, 1998). When a risk factor is a confounder, it is the true cause of the association observed between the exposure and the outcome; when a risk factor is an effect modifier, it changes the magnitude of the association between the exposure and the outcome in stratified analyses. For example, the presence of a preexisting disease or indicator of low socioeconomic status may be an effect modifier in causing increased risk of effects related to air pollution exposure. It is often possible to stratify the relationship between health outcome and exposure by one or more of these potential effect modifiers. For variables that modify the association, effect estimates in each stratum will be different from one another and different from the overall estimate, indicating a different exposure-response relationship may exist in populations represented by these variables.

Another key consideration for epidemiologic evidence is exposure measurement error. There are several components that contribute to exposure measurement error in epidemiologic studies, including the difference between true and measured ambient concentrations, the difference between average personal exposure to ambient pollutants and ambient concentrations at central monitoring sites, and the use of average population exposure rather than individual exposure estimates.

The third main type of health effects evidence, animal toxicological studies, provides information on the pollutant's biological action under controlled and monitored exposure circumstances. Taking into account physiological differences of the experimental species from humans, these studies inform characterization of health effects of concern, exposure-response relationships and MOAs. Further, animal models can inform determinations of at-risk or susceptible populations. These studies evaluate the effects of exposures to a variety of pollutants in a highly controlled laboratory setting and allow exploration of toxicological pathways or mechanisms by which a pollutant may cause effects. Understanding the biological mechanisms underlying various health outcomes can prove crucial in establishing or negating causality. In the absence of human studies data, extensive, well-conducted animal toxicological studies can support determinations of causality, if the evidence base indicates that similar responses are expected in humans under ambient exposure conditions.

Interpretations of animal toxicological studies are affected by limitations associated with extrapolation between animal and human responses. The differences between humans and other species have to be taken into consideration, including metabolism, hormonal regulation, breathing pattern, and differences in lung structure and anatomy. Also, in spite of a high degree of homology and the existence of a high percentage of orthologous genes across humans and rodents (particularly mice), extrapolation of molecular alterations at the gene level is complicated by species-specific differences in transcriptional regulation. Given these differences, there are uncertainties associated with quantitative extrapolations of observed pollutant-induced pathophysiological alterations between laboratory animals and humans, as those alterations are under the control of widely varying biochemical, endocrine, and neuronal factors.

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

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

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

Application of Framework for Causal Determination

In its evaluation of the scientific evidence on health or welfare effects of criteria pollutants, EPA determines the weight of evidence in support of causation and characterizes the strength of any resulting causal classification. EPA also evaluates the quantitative evidence and draws scientific conclusions, to the extent possible, regarding the concentration-response relationships and the loads to ecosystems, exposure doses or concentrations, duration and pattern of exposures at which effects are observed.

To aid judgment, various "aspects"[2] of causality have been discussed by many philosophers and scientists. The 1964 Surgeon General's report on tobacco smoking discussed criteria for the evaluation of epidemiologic studies, focusing on consistency, strength, specificity, temporal relationship, and coherence (HEW, 1964). Sir Austin Bradford Hill (1965) articulated aspects of causality in epidemiology and public health that have been widely used (Samet and Bodurow, 2008; IARC, 2006; U.S. EPA, 2005; HHS, 2004). These aspects (Hill, 1965) have been modified (Table I) for use in causal

[2] The "aspects" described by Hill (1965) have become, in the subsequent literature, more commonly described as "criteria." The original term "aspects" is used here to avoid confusion with "criteria" as it is used, with different meaning, in the Clean Air Act.

Table I Aspects to aid in judging causality

Consistency of the observed association	An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.
Coherence	An inference of causality from one line of evidence (e.g., epidemiologic, clinical or animal studies) may be strengthened by other lines of evidence that support a cause-and-effect interpretation of the association. Evidence on ecological or welfare effects may be drawn from a variety of experimental approaches (e.g., greenhouse, laboratory, and field) and subdisciplines of ecology (e.g., community ecology, biogeochemistry and paleological/historical reconstructions). The coherence of evidence from various fields greatly adds to the strength of an inference of causality. In addition, there may be coherence in demonstrating effects across multiple study designs or related health endpoints within one scientific line of evidence.
Biological plausibility.	An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms. A proposed mechanistic linking between an effect and exposure to the agent is an important source of support for causality, especially when data establishing the existence and functioning of those mechanistic links are available.
Biological gradient (exposure-response relationship)	A well-characterized exposure-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g., increasing effects observed following longer exposure times).
Strength of the observed association	The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. However, it is noted that a small magnitude in an effect estimate may represent a substantial effect in a population.
Experimental evidence	Strong evidence for causality can be provided through “natural experiments” when a change in exposure is found to result in a change in occurrence or frequency of health or welfare effects.
Temporal relationship of the observed association	Evidence of a temporal sequence between the introduction of an agent, and appearance of the effect, constitutes another argument in favor of causality.
Specificity of the observed association	Evidence linking an exposure to a specific outcome can provide a strong argument for causation. However, it must be recognized that rarely, if ever, does exposure to a pollutant invariably predict the occurrence of an outcome, and that a given outcome may have multiple causes.
Analogy	Structure activity relationships and information on the agent’s structural analogs can provide insight into whether an association is causal. Similarly, information on mode of action for a chemical, as one of many structural analogs, can inform decisions regarding likely causality.

determinations specific to health and welfare effects for pollutant exposures (U.S. EPA, 2009d).[3] Although these aspects provide a framework for assessing the evidence, they do not lend themselves to being considered in terms of simple formulas or fixed rules of evidence leading to conclusions about causality (Hill, 1965). For example, one cannot simply count the number of studies reporting statistically significant results or

[3] The Hill aspects were developed for interpretation of epidemiologic results. They have been modified here for use with a broader array of data, i.e., epidemiologic, controlled human exposure, ecological, and animal toxicological studies, as well as in vitro data, and to be more consistent with EPA’s Guidelines for Carcinogen Risk Assessment.

statistically nonsignificant results and reach credible conclusions about the relative weight of the evidence and the likelihood of causality. Rather, these aspects are taken into account with the goal of producing an objective appraisal of the evidence, informed by peer and public comment and advice, which includes weighing alternative views on controversial issues. In addition, it is important to note that the aspects in Table I cannot be used as a strict checklist, but rather to determine the weight of the evidence for inferring causality. In particular, not meeting one or more of the principles does not automatically preclude a determination of causality [see discussion in (HHS, 2004)].

Determination of Causality

In the ISA, EPA assesses the body of relevant literature, building upon evidence available during previous NAAQS reviews, to draw conclusions on the causal relationships between relevant pollutant exposures and health or environmental effects. ISAs use a five-level hierarchy that classifies the weight of evidence for causation[4]. In developing this hierarchy, EPA has drawn on the work of previous evaluations, most prominently the IOM's *Improving the Presumptive Disability Decision-Making Process for Veterans* (Samet and Bodurow, 2008), EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), and the U.S. Surgeon General's smoking report (HHS, 2004). This weight of evidence evaluation is based on various lines of evidence from across the health and environmental effects disciplines. These separate judgments are integrated into a qualitative statement about the overall weight of the evidence and causality. The five descriptors for causal determination are described in Table II.

Determination of causality involves the evaluation of evidence for different types of health, ecological or welfare effects associated with short- and long-term exposure periods. In making determinations of causality, evidence is evaluated for major outcome categories and then conclusions are drawn based upon the integration of evidence from across disciplines and also across the spectrum of related endpoints. In making causal judgments, the ISA focuses on major outcome categories (e.g., respiratory effects, vegetation growth), by evaluating the coherence of evidence across a spectrum of related endpoints (e.g., health effects ranging from inflammatory effects to respiratory mortality) to draw conclusions regarding causality. In discussing the causal determination, EPA characterizes the evidence on which the judgment is based, including strength of evidence for individual endpoints within the major outcome category.

[4] It should be noted that the Center for Disease Control (CDC) and IOM frameworks use a four-category hierarchy for the strength of the evidence. A five-level hierarchy is used here to be consistent with the EPA Guidelines for Carcinogen Risk Assessment and to provide a more nuanced set of categories.

Table II Weight of evidence for causal determination

	Health Effects	Ecological and Welfare Effects
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (i.e., doses or exposures generally within one to two orders of magnitude of current levels). That is, the pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example: a) controlled human exposure studies that demonstrate consistent effects; or b) observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g., animal studies or mode of action information). Evidence includes replicated and consistent high-quality studies by multiple investigators.	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures i.e., doses or exposures generally within one to two orders of magnitude of current levels). That is, the pollutant has been shown to result in effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. Controlled exposure studies (laboratory or small- to medium-scale field studies) provide the strongest evidence for causality, but the scope of inference may be limited. Generally, determination is based on multiple studies conducted by multiple research groups, and evidence that is considered sufficient to infer a causal relationship is usually obtained from the joint consideration of many lines of evidence that reinforce each other.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures, but important uncertainties remain. That is, the pollutant has been shown to result in health effects in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. For example: a) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or b) animal toxicological evidence from multiple studies from different laboratories that demonstrate effects, but limited or no human data are available. Evidence generally includes replicated and high-quality studies by multiple investigators.	Evidence is sufficient to conclude that there is a likely causal association with relevant pollutant exposures. That is, an association has been observed between the pollutant and the outcome in studies in which chance, bias and confounding are minimized, but uncertainties remain. For example, field studies show a relationship, but suspected interacting factors cannot be controlled, and other lines of evidence are limited or inconsistent. Generally, determination is based on multiple studies in multiple research groups.
Suggestive of a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited. For example, (a) at least one high-quality epidemiologic study shows an association with a given health outcome but the results of other studies are inconsistent; or (b) a well-conducted toxicological study, such as those conducted in the National Toxicology Program (NTP), shows effects in animal species.	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows an effect, but the results of other studies are inconsistent.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an effect.	The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence is suggestive of no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations, are mutually consistent in not showing an effect at any level of exposure.	Several adequate studies, examining relationships with relevant exposures, are consistent in failing to show an effect at any level of exposure.

In drawing judgments regarding causality for the criteria air pollutants, the ISA focuses on evidence of effects in the range of relevant pollutant exposures or doses, and not on determination of causality at any dose. Emphasis is placed on evidence of effects at doses (e.g., blood lead concentration) or exposures (e.g., air concentrations) that are relevant to, or somewhat above, those currently experienced by the population. The extent to which studies of higher concentrations are considered varies by pollutant and major outcome

category, but generally includes those with doses or exposures in the range of one to two orders of magnitude above current or ambient conditions. Studies that use higher doses or exposures may also be considered to the extent that they provide useful information to inform our understanding of mode of action, interspecies differences or factors that may increase risk of effects for a population. Thus, a causality determination is based on weight of evidence evaluation for health, ecological or welfare effects, focusing on the evidence from exposures or doses generally ranging from current levels to one or two orders of magnitude above current levels.

In addition, EPA evaluates evidence relevant to understand the quantitative relationships between pollutant exposures and health, ecological or welfare effects. This includes evaluation of the form of concentration-response or dose-response relationships and, to the extent possible, drawing conclusions on the levels at which effects are observed. The ISA also draws scientific conclusions regarding important exposure conditions for effects and populations that may be at greater risk for effects, as described in the following section.

Quantitative relationships: Effects on Human Populations

Once a determination is made regarding the causal relationship between the pollutant and outcome category, important questions regarding quantitative relationships include:

- What is the concentration-response, exposure-response, or dose-response relationship in the human population?
- What is the interrelationship between incidence and severity of effect?
- What exposure conditions (dose or exposure, duration and pattern) are important?
- What populations and lifestages appear to be differentially affected (i.e., more at risk of experiencing effects)?

To address these questions, the entirety of quantitative evidence is evaluated to characterize pollutant concentrations and exposure durations at which effects were observed for exposed populations, including populations and lifestages potentially at increased risk. To accomplish this, evidence is considered from multiple and diverse types of studies, and a study or set of studies that best approximates the concentration-response relationships between health outcomes and the pollutant may be identified. Controlled human exposure studies provide the most direct and quantifiable exposure-response data on the human health effects of pollutant exposures. To the extent available, the ISA evaluates results from across epidemiologic studies that use various methods to

characterize the form of relationships between the pollutant and health outcomes and draws conclusions on the shape of these relationships. Animal data may also inform evaluation of concentration-response relationships, particularly relative to MOAs and characteristics of susceptible populations.

An important consideration in characterizing the public health impacts associated with exposure to a pollutant is whether the concentration-response relationship is linear across the range of concentrations or if nonlinear relationships exist along any part of this range. Of particular interest is the shape of the concentration-response curve at and below the level of the current standards. Various sources of variability and uncertainty, such as low data density in the lower concentration range, possible influence of exposure measurement error, and variability between individuals in susceptibility to air pollution health effects, tend to smooth and "linearize" the concentration-response function, and thus can obscure the existence of a threshold or nonlinear relationship. Since individual thresholds vary from person to person due to individual differences such as genetic level susceptibility or preexisting disease conditions (and even can vary from one time to another for a given person), it can be difficult to demonstrate that a threshold exists in a population study. These sources of variability and uncertainty may explain why the available human data at ambient concentrations for some environmental pollutants (e.g., particulate matter [PM], O_3, lead [Pb], environmental tobacco smoke [ETS], radiation) do not exhibit thresholds for cancer or noncancer health effects, even though likely mechanisms include nonlinear processes for some key events. These attributes of human population dose-response relationships have been extensively discussed in the broader epidemiologic literature (Rothman and Greenland, 1998).

Finally, identification of the population groups or lifestages that may be at greater risk of health effects from air pollutant exposures contributes to an understanding of the public health impact of pollutant exposures. In the ISA, the term "at-risk population" is used to encompass populations variously described as susceptible, vulnerable, or sensitive. "At-risk populations" is defined here as those populations or lifestages that have a greater likelihood of experiencing health effects related to exposure to an air pollutant due to a variety of factors. These factors may be intrinsic, such as genetic or developmental factors, race, gender, lifestage, or the presence of preexisting diseases, or they may be extrinsic, such as socioeconomic status (SES), activity pattern and exercise level, reduced access to health care, low educational attainment, or increased pollutant exposures (e.g., near roadways). Epidemiologic studies can help identify populations potentially at increased risk of effects by evaluating health responses in the study population. Examples include testing for interactions or effect modification by factors such as gender, age group, or health status. Experimental studies using animal models of susceptibility or

disease can also inform the extent to which health risks are likely greater in specific population groups.

Quantitative relationships: Effects on Ecosystems or Public Welfare

Key questions for understanding the quantitative relationships between exposure (or concentration or deposition) to a pollutant and risk to ecosystems or the public welfare include:

- What elements of the ecosystem (e.g., types, regions, taxonomic groups, populations, functions, etc.) appear to be affected, or are more sensitive to effects? Are there differences between locations or materials in welfare effects responses, such as impaired visibility or materials damage?
- Under what exposure conditions (amount deposited or concentration, duration and pattern) are effects seen?
- What is the shape of the concentration-response or exposure-response relationship?

Evaluations of causality generally consider the probability of quantitative changes in ecological and welfare effects in response to exposure. A challenge to the quantification of exposure-response relationships for ecological effects is the great regional and local variability in ecosystems. Thus, exposure-response relationships are often determined for a specific ecological system and scale, rather than at the national or even regional scale. Quantitative relationships therefore are available site by site and may differ greatly between ecosystems.

Concepts in Evaluating Adversity of Health Effects

In evaluating health evidence, a number of factors can be considered in delineating between adverse and nonadverse health effects resulting from exposure to air pollution. Some health outcomes, such as hospitalization for respiratory or cardiovascular diseases, are clearly considered adverse. It is more difficult to determine the extent of change that constitutes adversity in more subtle health measures. These include a wide variety of responses, such as alterations in markers of inflammation or oxidative stress, changes in pulmonary function or heart rate variability, or alterations in neurocognitive function measures. The challenge is determining the magnitude of change in these measures when there is no clear point at which a change become adverse; for example, what percentage change in a lung function measure represents an adverse effect. What constitutes an

adverse health effect may vary between populations. Some changes that may not be considered adverse in healthy individuals would be potentially adverse in more susceptible individuals.

For example, the extent to which changes in lung function are adverse has been discussed by the American Thoracic Society (ATS) in an official statement titled *What Constitutes an Adverse Health Effect of Air Pollution?* (2000b). An air pollution-induced shift in the population distribution of a given risk factor for a health outcome was viewed as adverse, even though it may not increase the risk of any one individual to an unacceptable level. For example, a population of asthmatics could have a distribution of lung function such that no identifiable individual has a level associated with significant impairment. Exposure to air pollution could shift the distribution such that no identifiable individual experiences clinically relevant effects. This shift toward decreased lung function, however, would be considered adverse because individuals within the population would have diminished reserve function and therefore would be at increased risk to further environmental insult. The committee also observed that elevations of biomarkers, such as cell number and types, cytokines and reactive oxygen species, may signal risk for ongoing injury and clinical effects or may simply indicate transient responses that can provide insights into mechanisms of injury, thus illustrating the lack of clear boundaries that separate adverse from nonadverse effects.

It is important to recognize that the more subtle health outcomes may be connected mechanistically to health events that are clearly adverse. For example, air pollution may affect markers of transient myocardial ischemia such as ST-segment abnormalities and onset of exertional angina. These effects may not be apparent to the individual, yet may still increase the risk of a number of cardiac events, including myocardial infarction and sudden death. Thus, small changes in physiological measures may not appear to be clearly adverse when considered alone, but contribute to a coherent and biologically plausible group of related health outcomes, including responses that are very clearly adverse.

Concepts in Evaluating Adversity of Ecological Effects

Adversity of ecological effects can be understood in terms ranging in scale from the cellular level to the individual organism and to the population, community and ecosystem levels. In the context of ecology, a population is a group of individuals of the same species, and a community is an assemblage of populations of different species interacting with one another that inhabit an area. An ecosystem is the interactive system formed from all living organisms and their abiotic (physical and chemical) environment within a given area (IPCC, 2007a). The boundaries of what could be called an ecosystem are somewhat

arbitrary, depending on the focus of interest or study. Thus, the extent of an ecosystem may range from very small spatial scales to, ultimately, the entire Earth (IPCC, 2007a).

Effects on an individual organism are generally not considered to be adverse, however if effects occur to enough individuals within a population, communities and ecosystems may be disrupted. Changes to populations, communities and ecosystems can in turn result in an alteration of ecosystem processes. Ecosystem processes are defined as the metabolic functions of ecosystems including energy flow, elemental cycling, and the production, consumption and decomposition of organic matter (U.S. EPA, 2002). Growth, reproduction, and mortality are species-level endpoints that can be clearly linked to community and ecosystem effects and are considered to be adverse when negatively affected. Other endpoints such as changes in behavior and physiological stress can decrease ecological fitness of an organism, but are harder to link unequivocally to effects at the population, community and ecosystem level. The degree to which pollutant exposure is considered adverse may also depend on the location and its intended use (i.e. city park, commercial cropland). Support for consideration of adversity beyond the species level by making explicit the linkages between stress-related effects at the species and effects at the ecosystem level is found in *A Framework for Assessing and Reporting on Ecological Condition: an SAB report* (U.S. EPA, 2002). Additionally, the National Acid Precipitation Assessment Program (NAPAP) uses the following working definition of *adverse ecological effects* in the preparation of reports to Congress mandated by the Clean Air Act: "any injury (i.e. loss of chemical or physical quality or viability) to any ecological or ecosystem component, up to and including at the regional level, over both long and short terms."

On a broader scale, ecosystem services may provide indicators for ecological impacts. Ecosystem services are the benefits that people obtain from ecosystems (UNEP, 2003). According to the Millennium Ecosystem Assessment, ecosystem services include: "provisioning services such as food and water; regulating services such as regulation of floods, drought, land degradation, and disease; supporting services such as soil formation and nutrient cycling; and cultural services such as recreational, spiritual, religious and other nonmaterial benefits." For example, a more subtle ecological effect of pollution exposure may result in a clearly adverse impact on ecosystem services if it results in a population decline in a species that is recreationally or culturally important.

PREFACE

Legislative Requirements for the NAAQS Review

Two sections of the Clean Air Act (CAA) govern the establishment and revision of the National Ambient Air Quality Standards (NAAQS). Section 108 (42 USC §7408) directs the Administrator to identify and list certain air pollutants and then to issue air quality criteria for those pollutants. The Administrator is to list those air pollutants that in her "judgement; cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare" and whose "presence…in the ambient air results from numerous or diverse mobile or stationary sources" (CAA, 1990a). Air quality criteria are intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in ambient air . . . [42 USC §7408(b)].

Section 109 (CAA, 1990b) directs the Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants for which air quality criteria have been issued. Section 109(b)(1) defines a primary standard as one "the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health."[5] A secondary standard, as defined in section 109(b)(2), must "specify a level of air quality the attainment and maintenance of which, in the judgment of the Administrator, based on such criteria, is required to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air."[6]

The requirement that primary standards include an adequate margin of safety was intended to address uncertainties associated with inconclusive scientific and technical information available at the time of standard setting. It was also intended to provide a reasonable degree of protection against hazards that research has not yet identified. See Lead Industries Association v. EPA, 647 F.2d 1130, 1154 (D.C. Cir 1980), cert. denied, 449 U.S. 1042 (1980); American Petroleum Institute v. Costle, 665 F.2d 1176, 1186 (D.C. Cir. 1981), cert. denied, 455 U.S. 1034 (1982). Both kinds of uncertainties are components of the risk associated with pollution at levels below

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

[6] Welfare effects as defined in section 302(h) include, but are not limited to, "effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being" (CAA, 2005).

those at which human health effects can be said to occur with reasonable scientific certainty. Thus, in selecting primary standards that include an adequate margin of safety, the Administrator is seeking not only to prevent pollution levels that have been demonstrated to be harmful but also to prevent lower pollutant levels that may pose an unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree.

In selecting a margin of safety, the EPA considers such factors as the nature and severity of the health effects involved, the size of the sensitive population(s) at risk, and the kind and degree of the uncertainties that must be addressed. The selection of any particular approach to providing an adequate margin of safety is a policy choice left specifically to the Administrator's judgment. See Lead Industries Association v. EPA, supra, 647 F.2d at 1161-1162.

In setting standards that are "requisite" to protect public health and welfare, as provided in Section 109(b), EPA's task is to establish standards that are neither more nor less stringent than necessary. In so doing, EPA may not consider the costs of implementing the standards. [See generally Whitman v. American Trucking Associations, 531 U.S. 457, 465-472, 475-76.]

Section 109(d)(1) requires that "not later than December 31, 1980, and at 5-year intervals thereafter, the Administrator shall complete a thorough review of the criteria published under section 108 and the national ambient air quality standards … and shall make such revisions in such criteria and standards and promulgate such new standards as may be appropriate…" Section 109(d)(2) requires that an independent scientific review committee "shall complete a review of the criteria … and the national primary and secondary ambient air quality standards … and shall recommend to the Administrator any new . . . standards and revisions of existing criteria and standards as may be appropriate …" Since the early 1980s, this independent review function has been performed by CASAC.

History of the NAAQS for Ozone

Tropospheric (ground-level) O_3 is the indicator for the mix of photochemical oxidants (e.g., peroxyacetyl nitrate, hydrogen peroxide) formed from biogenic and anthropogenic precursor emissions. Naturally occurring O_3 in the troposphere can result from biogenic organic precursors reacting with naturally occurring nitrogen oxides (NO_X) and by stratospheric O_3 intrusion into the troposphere. Anthropogenic precursors of O_3, especially NO_X, and volatile organic compounds (VOCs), originate from a wide variety of stationary and mobile sources. Ambient O_3 concentrations

produced by these emissions are directly affected by temperature, solar radiation, wind speed, and other meteorological factors.

NAAQS are comprised of four basic elements: indicator, averaging time, level, and form. The indicator defines the pollutant to be measured in the ambient air for the purpose of determining compliance with the standard. The averaging time defines the time period over which air quality measurements are to be obtained and averaged or cumulated, considering evidence of effects associated with various time periods of exposure. The level of a standard defines the air quality concentration used (i.e., an ambient concentration of the indicator pollutant) in determining whether the standard is achieved. The form of the standard specifies the air quality measurements that are to be used for compliance purposes (e.g., the annual fourth-highest daily maximum 8-hour concentration, averaged over 3 years), and whether the statistic is to be averaged across multiple years. These four elements taken together determine the degree of public health and welfare protection afforded by the NAAQS.

Table III Summary of primary and secondary NAAQS promulgated for ozone during the period 1971-2008

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

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

EPA first established primary and secondary NAAQS for photochemical oxidants in 1971 . Both primary and secondary standards were set at a level of 0.08 parts per million (ppm), 1-h avg, total photochemical oxidants, not to be exceeded more than 1 hour per year. The standards were based on scientific information contained in the 1970 AQCD.

In 1977, EPA announced the first periodic review of the 1970 AQCD in accordance with Section 109(d)(1) of the Clean Air Act. In 1978, EPA published an AQCD.

Based on the 1978 AQCD, EPA published proposed revisions to the original NAAQS in 1978 (U.S. EPA, 1978b) and final revisions in 1979 (U.S. EPA, 1979a). The level of the primary and secondary standards was revised from 0.08 to 0.12 ppm; the indicator was revised from photochemical oxidants to O_3; and the form of the standards was revised from a deterministic to a statistical form, which defined attainment of the standards as occurring when the expected number of days per calendar year with maximum hourly average concentration greater than 0.12 ppm is equal to or less than one.

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

In August 1992, EPA announced plans to initiate the third periodic review of the air quality criteria and O_3 NAAQS (U.S. EPA, 1992). On the basis of the scientific evidence contained in the 1996 O_3 AQCD and the 1996 Staff Paper (U.S. EPA, 1996e), and related technical support documents, linking exposures to ambient O_3 to adverse health and welfare effects at levels allowed by the then existing standards, EPA proposed to revise the primary and secondary O_3 standards on December 13, 1996 (U.S. EPA, 1996d). The EPA proposed to replace the then existing 1-hour primary and secondary standards with 8-h avg O_3 standards set at a level of 0.08 ppm (equivalent to 0.084 ppm using standard rounding conventions). The EPA also proposed, in the alternative, to establish a new distinct secondary standard using a biologically based cumulative seasonal form. The EPA completed the review on July

18, 1997 by setting the primary standard at a level of 0.08 ppm, based on the annual fourth-highest daily maximum 8-h avg concentration, averaged over 3 years, and setting the secondary standard identical to the revised primary standard (U.S. EPA, 1997).

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

EPA initiated the next periodic review if the air quality criteria and O_3 standards in September 2000 with a call for information (U.S. EPA, 2000). The schedule for completion of that rulemaking later became governed by a consent decree resolving a lawsuit filed in March 2003 by a group of plaintiffs representing national environmental and public health organizations. Based on the 2006 O_3 AQCD (U.S. EPA, 2006b) published in March 2006, the Staff Paper (U.S. EPA, 2007b) and related technical support documents, the proposed decision was published in the Federal Register on July 11, 2007 (U.S. EPA, 2007a). The EPA proposed to revise the level of

the primary standard to a level within the range of 0.075 to 0.070 ppm. Two options were proposed for the secondary standard: (1) replacing the current standard with a cumulative, seasonal standard, expressed as an index of the annual sum of weighted hourly concentrations cumulated over 12 daylight hours during the consecutive 3-month period within the O_3 season with the maximum index value, set at a level within the range of 7 to 21 ppm-h; and (2) setting the secondary standard identical to the revised primary standard. The EPA completed the rulemaking with publication of a final decision on March 27, 2008 (U.S. EPA, 2008e), revising the level of the 8-hour primary O_3 standard from 0.08 ppm to 0.075 ppm and revising the secondary standard to be identical to the primary standard.

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1 EXECUTIVE SUMMARY

1.1 Introduction

This Integrated Science Assessment (ISA) is a synthesis and evaluation of the most policy-relevant science that forms the scientific foundation for the review of the primary (health-based) and secondary (welfare-based) national ambient air quality standard (NAAQS) for ozone (O_3) and related photochemical oxidants. The current primary O_3 standard includes an 8-hour average standard set in 2008 at 75 parts per billion (ppb). The secondary standard for O_3 is equal to the primary standard. The current primary NAAQS protects against respiratory health effects incurred after short-term exposure to O_3, while the secondary NAAQS protects against damage to vegetation and ecosystems.

1.2 Scope

EPA has developed an extensive and robust process for evaluating the scientific evidence and drawing conclusions regarding air pollution-related health and welfare effects. This ISA is focused on health and welfare effects resulting from current ambient concentrations of O_3. This review builds upon the findings of previous assessments, and evaluates the relevant results pertaining to the atmospheric science of O_3; short- and long-term exposure to ambient O_3; health effects due to ambient O_3 exposure as characterized in epidemiologic, controlled human exposure, and toxicological studies; and ecological or welfare effects; as well as O_3 exposure-response relationships, mode(s) of action (MOA), and populations at increased risk for O_3-related health effects. In this ISA, the conclusions and key findings from previous reviews provide the foundation for the consideration of evidence from recent studies. Conclusions are drawn based on the synthesis of evidence from recent studies and building upon the extensive evidence presented in previous reviews.

EPA has developed a consistent and transparent approach to evaluate the causal nature of air pollution-related health and environmental effects for use in developing ISAs; the framework for causal determinations is described in the Preamble to this document. Causality determinations are based on the evaluation and synthesis of evidence from across scientific disciplines; the type of evidence that is most important for such determinations will vary by pollutant or assessment. EPA assesses the entire body of relevant literature, building upon evidence available during the previous NAAQS reviews, to draw conclusions on the causal relationships between relevant pollutant exposures and health or welfare effects. EPA also evaluates the quantitative evidence and

draws scientific conclusions, to the extent possible, regarding the concentration-response relationships and the loads to ecosystems, exposure doses or concentrations, duration and pattern of exposures at which effects are observed. This ISA uses a five-level hierarchy that classifies the weight of evidence for causation, not just association. This weight of evidence evaluation is based on various lines of evidence from across the health and environmental effects disciplines. These separate judgments are integrated into a qualitative statement about the overall weight of the evidence and causality. The causal determinations are:

- Causal relationship
- Likely to be a causal relationship
- Suggestive of a causal relationship
- Inadequate to infer a causal relationship
- Not likely to be a causal relationship

1.3 Atmospheric Chemistry and Ambient Concentrations

Ozone is naturally present in the stratosphere, where it serves the beneficial role of blocking harmful ultraviolet radiation from the Sun and preventing the majority of this radiation from reaching the surface of the Earth. However, in the troposphere, O_3 acts as a powerful oxidant and can harm living organisms and materials. Tropospheric O_3 is present not only in polluted urban air, but throughout the globe.

Ozone in the troposphere originates from both anthropogenic (i.e., man-made) and natural source categories. Ozone attributed to anthropogenic sources is formed in the atmosphere by photochemical reactions involving sunlight and precursor pollutants including volatile organic compounds, nitrogen oxides, and carbon monoxide. Ozone attributed to natural sources is formed through the same photochemical reactions involving natural emissions of precursor pollutants from vegetation, microbes, animals, biomass burning, lightning, and geogenic sources. A schematic overview of the major photochemical cycles influencing O_3 in the troposphere and the stratosphere is shown in the figure to the right.

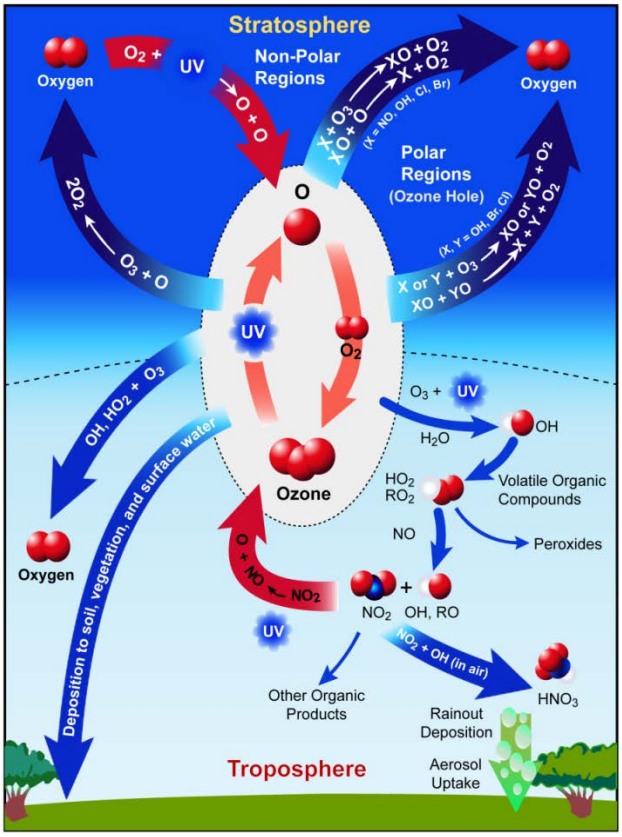


Figure 1-1 Schematic overview of photochemical processes influencing stratospheric and tropospheric ozone.

Ozone in rural areas is produced from emissions of O_3 precursors emitted directly within the rural areas and from emissions in urban areas that are processed during transport. Because O_3 is produced downwind of urban source areas and O_3 tends to persist longer in rural than in urban areas as a result of lower chemical scavenging, the result is substantial cumulative exposures for humans and vegetation in rural areas, that are often higher than cumulative exposures in urban areas.

On a smaller scale, O_3 can be influenced by local meteorological conditions, circulation patterns, emissions, and topographic barriers, resulting in heterogeneous concentrations across an individual urban area. On a larger scale, O_3 persists in the atmosphere long enough that it can be transported from continent to continent and around the globe. The degree of influence from intercontinental transport varies greatly by location and time.

Background concentrations of O_3 have been given various definitions in the literature over time. In the context of a review of the NAAQS, it is useful to define background O_3 concentrations in a way that distinguishes between concentrations that result from

precursor emissions that are relatively less directly controllable from those that are relatively more directly controllable through U.S. policies. For this document, we have focused on the sum of those background concentrations from natural sources everywhere in the world and from anthropogenic sources outside the U.S., Canada and Mexico, i.e., North American background. Since North American background is a construct that cannot be measured, the range of North American background O_3 concentrations is estimated using chemistry transport models. Model-predicted annual average North American background estimates are typically less than 50 ppb across the country with highest concentrations in the Intermountain West during the spring and the Southwest during the summer.

1.4 Human Exposure

Ozone is ubiquitous throughout the environment, originating from both natural and anthropogenic sources, although few indoor sources exist. As such, people are routinely exposed to O_3 as they participate in normal day-to-day activities. A number of factors affect the pattern of personal O_3 exposure. These include: the variation in O_3 concentrations at various spatial and temporal scales; individual's activity patterns, particularly time spent outdoors, which may involve changes in personal behavior to avoid known high exposure to O_3; and infiltration of ambient O_3 into indoor microenvironments, which is driven by air exchange rate.

Several approaches have been used to measure or quantify exposure to ambient O_3, giving an indication of the impact of some of the factors that affect the pattern of human exposure to O_3. These approaches include characterizing the correlation and ratio between personal exposure and ambient O_3 concentrations, determining the ratio between indoor and outdoor concentrations, and using models to estimate exposure to O_3 based on ambient concentrations. The factors affecting the pattern of personal exposure, as well as the types of approaches used for quantification of exposure, may have implications for epidemiologic studies.

1.5 Dosimetry and Modes of Action

When O_3 is inhaled, the amount of O_3 that is absorbed is affected by a number of factors including the shape and size of the respiratory tract, route of breathing (nose or mouth), as well as how quickly and deeply a person is breathing. Another factor involves the reaction of O_3 with compounds present in the lung lining fluid to produce secondary

oxidation products. On a breath-by-breath basis, humans at rest absorb between 80 and 95% of inhaled O_3. The site of the greatest O_3 dose to the lung tissue is the junction of the conducting airway and the gas exchange region, in the deeper portion of the respiratory tract. Additionally, the primary site of O_3 uptake moves deeper into the respiratory tract during exercise when breathing becomes faster and the breathing route begins to move from the nose only to oronasal breathing (i.e., through the nose and mouth).

Once O_3 has been inhaled, there are several key events in the toxicity pathway of O_3 in the respiratory tract that lead to O_3-induced health effects. These include formation of secondary oxidation products in the lung, activation of neural reflexes, initiation of inflammation, alterations of epithelial barrier function, sensitization of bronchial smooth muscle, modification of innate and adaptive immunity, and airway remodeling. Another key event, systemic inflammation and vascular oxidative/nitrosative stress, may be critical to the extrapulmonary effects of O_3.

Table 1-1 Summary of ozone causal determinations by exposure duration and health outcome

Health Outcome	Conclusions from Previous Review	Conclusions from 2011 2nd Draft ISA
Short-Term Exposure to O_3		
Respiratory effects	The overall evidence supports a causal relationship between acute ambient O_3 exposures and increased respiratory morbidity outcomes.	Causal Relationship
Cardiovascular effects	The limited evidence is highly suggestive that O_3 directly and/or indirectly contributes to cardiovascular-related morbidity, but much remains to be done to more fully substantiate the association.	Suggestive of a Causal Relationship
Central nervous system effects	Toxicological studies report that acute exposures to O_3 are associated with alterations in neurotransmitters, motor activity, short and long term memory, sleep patterns, and histological signs of neurodegeneration.	Suggestive of a Causal Relationship
Mortality	The evidence is highly suggestive that O_3 directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality.	Likely to be a Causal Relationship
Long-term Exposure to O_3		
Respiratory effects	The current evidence is suggestive but inconclusive for respiratory health effects from long-term O_3 exposure.	Likely to be a Causal Relationship
Cardiovascular Effects	No studies from previous review.	Suggestive of a Causal Relationship
Reproductive and developmental effects	Limited evidence for a relationship between air pollution and birth-related health outcomes, including mortality, premature births, low birth weights, and birth defects, with little evidence being found for O_3 effects.	Suggestive of a Causal Relationship
Central nervous system effects	Evidence regarding chronic exposure and neurobehavioral effects was not available.	Suggestive of a Causal Relationship
Cancer	Little evidence for a relationship between chronic O_3 exposure and increased risk of lung cancer.	Inadequate to infer a Causal Relationship
Mortality	There is little evidence to suggest a causal relationship between chronic O_3 exposure and increased risk for mortality in humans.	Suggestive of a Causal Relationship

1.6 Integration of Ozone Health Effects

This ISA evaluates and integrates the evidence from short-term (i.e., hours, days, weeks) or long-term (i.e., months to years) exposure studies across scientific disciplines (i.e., controlled human exposure studies, toxicology, and epidemiology) in interpreting the health effects evidence that spans all lifestages, and varies in severity from minor subclinical effects to death. The results from the health studies evaluated in combination with the evidence from atmospheric chemistry and exposure assessment studies contribute to the causal determinations made for the health outcomes discussed in this ISA. The conclusions from the previous NAAQS review and the causality determinations from this review are summarized in the table below. Additional details are provided here for respiratory health effects and mortality, for which there is the strongest evidence of an effect from O_3, and for additional health effects for which there is emerging evidence of an association with O_3; details for all health effects are provided in the ISA.

1.6.1 Respiratory Effects

The clearest evidence for health effects associated with exposure to O_3 is provided by studies of respiratory effects. Collectively, a very large amount of evidence spanning several decades supports the causal association between exposure to O_3 and a continuum of respiratory effects (See figure below). The majority of this evidence is derived from studies investigating short-term exposure (i.e., hours to weeks) to O_3, although animal toxicological studies and recent epidemiologic evidence demonstrate that long-term exposure (i.e., months to years) may also be detrimental to the respiratory system.

The last review concluded that there was clear, consistent evidence of a causal relationship between short-term exposure to O_3 and respiratory health effects. This causal association was substantiated in this ISA by the coherence of effects observed across controlled human exposure, epidemiologic, and toxicological studies indicating associations of short-term O_3 exposures with a range of respiratory health endpoints from respiratory tract inflammation to respiratory emergency department (ED) visits and hospital admissions (HA). Across disciplines, short-term O_3 exposures induced or were associated with statistically significant declines in lung function. An equally strong body of evidence from controlled human exposure and toxicological studies demonstrated O_3-induced inflammatory responses, increased epithelial permeability, and airway hyperresponsiveness. Toxicological studies provided additional evidence for O_3-induced impairment of host defenses. Combined, these findings from experimental studies provided support for epidemiologic evidence, in which short-term O_3 exposure was

consistently associated with increases in respiratory symptoms and asthma medication use in asthmatic children, respiratory-related hospital admissions, and asthma-related ED visits. Although O_3 was consistently associated with nonaccidental and cardiopulmonary mortality, the contribution of respiratory causes to these findings was uncertain. The combined evidence across disciplines **supports a causal relationship between short-term O_3 exposure and respiratory effects**.

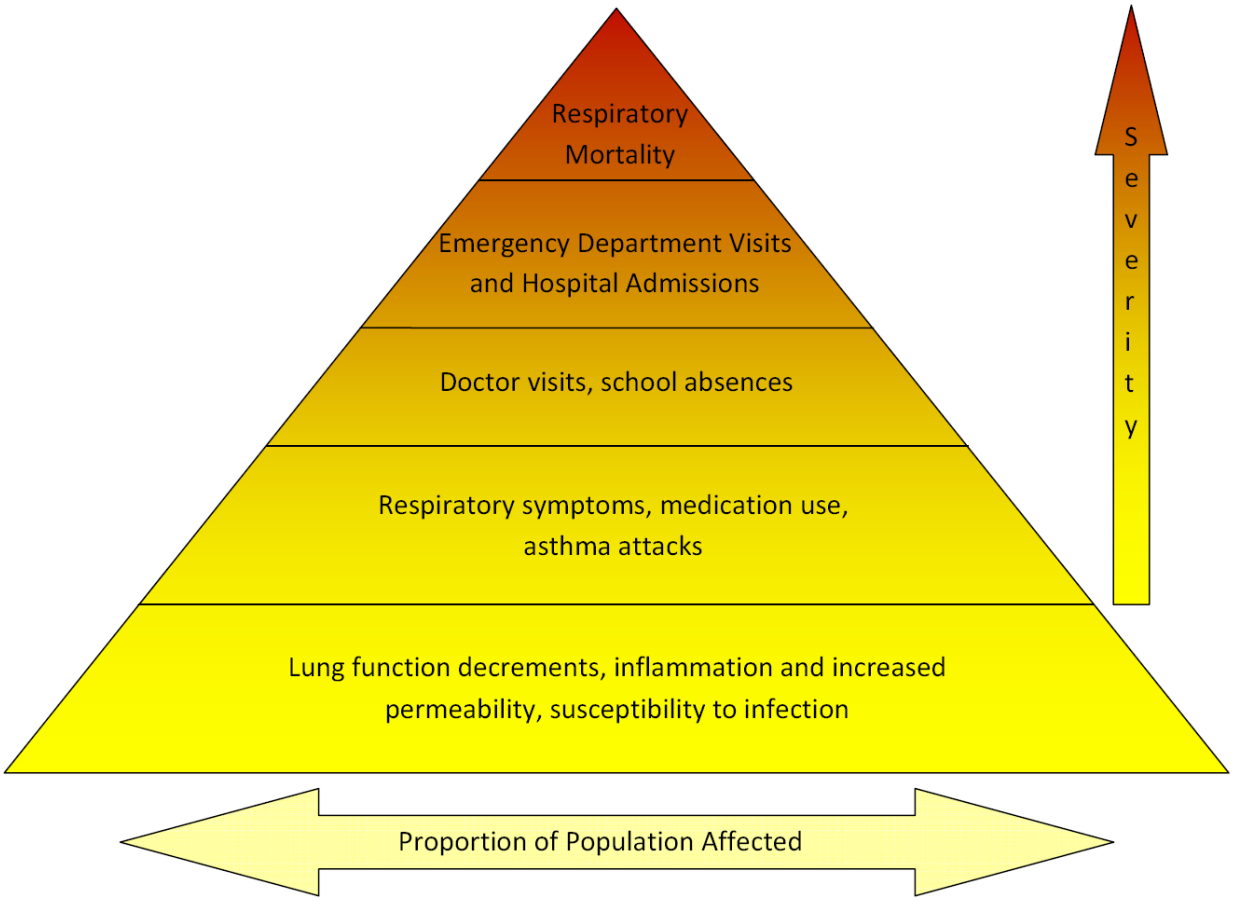


Figure 1-2 The continuum of respiratory effects, noting increases in severity but decreases in the proportion of the population affected moving up the pyramid.

Recent evidence for a relationship between long-term O_3 exposure and respiratory morbidity comes from a single cohort demonstrating associations between long-term measures of O_3 exposure and new-onset asthma in children and increased respiratory

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

1.6.2 Mortality Effects

The last review concluded that the overall body of evidence was highly suggestive that short-term exposure to O_3 directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality; but that additional research was needed to more fully establish underlying mechanisms by which such effects occur. The evaluation of new multicity studies that have examined the association between short-term O_3 exposure and mortality found evidence which supports the conclusions of the last review. These recent studies reported consistent positive associations between short-term O_3 exposure and total (nonaccidental) mortality, with associations being stronger during the warm season. They also added support for associations between O_3 exposure and cardiovascular mortality being similar to or stronger than those between O_3 exposure and respiratory mortality. Additionally, these new studies examined previously identified areas of uncertainty in the O_3-mortality relationship, and provide evidence that continues to support an association between short-term O_3 exposure and mortality. The body of evidence indicates that **there is likely to be a causal relationship between short-term exposures to O_3 and mortality.**

1.6.3 Emerging Evidence

In the last review, completed in 2006, there were a number of health effects for which an insufficient amount of evidence existed to adequately characterize the relationships with exposure to O_3. However, recent evidence indicates that O_3 may impart health effects

through exposure durations and biological mechanisms not previously considered. This includes:

- Toxicological studies provide evidence for cardiovascular morbidity, while epidemiologic studies provide evidence for cardiovascular mortality, and together, this evidence **is suggestive of a causal relationship for both relevant short- and long-term exposures to O_3 and cardiovascular effects.**
- Recent toxicological studies add to earlier evidence that short- and long-term exposures to O_3 can produce a range of effects on the central nervous system and behavior. The single epidemiologic study conducted showed that long-term exposure to O_3 affects memory in humans as well. Together the evidence from studies of short- and long-term exposure to **O_3 is suggestive of a causal relationship between O_3 exposure and adverse central nervous system effects.**
- There is limited though positive toxicological evidence for O_3-induced developmental effects. Limited epidemiologic evidence exists for an association with O_3 concentration and decreased sperm concentration and associations with reduced birth weight and restricted fetal growth. Overall, the evidence **is suggestive of a causal relationship between long-term exposures to O_3 and reproductive and developmental effects**.
- Several recent studies provide evidence of an association between long-term exposure to O_3 and mortality, especially respiratory mortality. Collectively, the evidence **is suggestive of a causal relationship between long-term O_3 exposures and mortality**.

1.6.4 Populations at Increased Risk

The examination of populations potentially at increased risk for O_3 exposure allows for the NAAQS to provide an adequate margin of safety for both the general population and for sensitive populations. Some studies attempt to identify populations that are at increased risk for O_3-related health effects; these studies do so by examining groups within the study population, such as those with an underlying health condition or genetic polymorphism; categories of age, race, or sex; or by developing animal models that mimic the conditions associated with an adverse health effect. Such studies have identified a multitude of factors that could potentially contribute to whether an individual is at increased risk for O_3-related health effects. The populations identified that are most at risk for O_3-related health effects are individuals with influenza/infection, individuals with asthma, and older age groups. Other potential factors, including preexisting

conditions such as chronic obstructive pulmonary disease and cardiovascular disease, young age, sex, and variations in multiple genes (such as *GSTM1, GSTP1, HMOX-1, NQO1,* and *TNF-α*), appear related to susceptibility, but further evidence is needed.

1.6.5 Ozone Concentration-Response Relationship

An important consideration in characterizing the association of O_3 with morbidity and mortality is the shape of the concentration-response relationship across the O_3 concentration range. In this ISA, studies have been identified that attempt to characterize the shape of the O_3 concentration-response curve along with possible O_3 "thresholds" (i.e., O_3 levels which must be exceeded in order to elicit a physiological response). These studies have indicated a generally linear concentration-response function with no indication of a threshold for O_3 concentrations greater than 30 or 40 ppb, thus if a threshold exists, it is likely at the lower end of the range of ambient O_3 concentrations.

1.7 Integration of Effects on Vegetation and Ecosystems

The ISA presents the most policy-relevant information pertaining to the review of the NAAQS for the effects of O_3 on vegetation and ecosystems. It integrates key findings about plant physiology, biochemistry, whole plant biology, ecosystems and exposure-response relationships. The welfare effects of O_3 can be observed across spatial scales, starting at the cellular and subcellular level, then the whole plant and finally, ecosystem-level processes. Ozone effects at small spatial scales, such as the leaf of an individual plant, can result in effects at a continuum of larger spatial scales. These effects include altered rates of leaf gas exchange, growth and reproduction at the individual plant level and can result in changes in ecosystems, such as productivity, C storage, water cycling, nutrient cycling, and community composition. The conclusions from the previous NAAQS review and the causality determinations from this review are summarized in the table below. Further discussion of these conclusions is provided below for visible foliar injury, growth, productivity, and carbon storage, reduced yield and quality of agricultural crops, water cycling, below-ground processing, community composition, and O_3 exposure-response relationships; discussion for all relevant welfare effects is provided in the ISA.

Table 1-2 Summary of ozone causal determination for welfare effects

Vegetation and Ecosystem Effects	Conclusions from Previous Review	Conclusions from 2011 2nd Draft ISA
Visible Foliar Injury Effects on Vegetation	Data published since the 1996 O_3 AQCD strengthen previous conclusions that there is strong evidence that current ambient O_3 concentrations cause impaired aesthetic quality of many native plants and trees by increasing foliar injury.	Causal Relationship
Reduced Vegetation Growth	Data published since the 1996 O_3 AQCD strengthen previous conclusions that there is **strong evidence that current ambient O_3 concentrations cause decreased growth and biomass accumulation** in annual, perennial and woody plants, including agronomic crops, annuals, shrubs, grasses, and trees.	Causal Relationship
Reduced Productivity in Terrestrial Ecosystems	There is **evidence that O_3 is an important stressor of ecosystems** and that the effects of O_3 on individual plants and processes are scaled up through the ecosystem, affecting net primary productivity.	Causal Relationship
Reduced Carbon (C) Sequestration in Terrestrial Ecosystems	**Limited studies** from previous review	Likely to be a Causal Relationship
Reduced Yield and Quality of Agricultural Crops	Data published since the 1996 O_3 AQCD strengthen previous conclusions that there is **strong evidence that current ambient O_3 concentrations cause decreased yield and/or nutritive quality** in a large number of agronomic and forage crops.	Causal Relationship
Alteration of Terrestrial Ecosystem Water Cycling	Ecosystem **water quantity may be affected by O_3 exposure** at the landscape level.	Likely to be a Causal Relationship
Alteration of Below-ground Biogeochemical Cycles	Ozone-sensitive species have **well known responses to O_3 exposure**, including altered C allocation to below-ground tissues, and altered rates of leaf and root production, turnover, and decomposition. These shifts can affect overall C and N loss from the ecosystem in terms of respired C, and leached aqueous dissolved organic and inorganic C and N.	Causal Relationship
Alteration of Terrestrial Community Composition	Ozone may be affecting above- and below -ground community composition through impacts on both growth and reproduction. **Significant changes in plant community composition resulting directly from O_3 exposure** have been demonstrated.	Likely to be a Causal Relationship

1.7.1 Visible Foliar Injury

Visible foliar injury resulting from exposure to O_3 has been well characterized and documented over several decades on many tree, shrub, herbaceous and crop species. Ozone-induced visible foliar injury symptoms on certain plant species are considered diagnostic of exposure to O_3, as experimental evidence has clearly established a consistent association, with greater exposure often resulting in greater and more prevalent injury. Additional sensiptive species showing visible foliar injury continue to be identified from field surveys and verified in controlled exposure studies. **Overall, evidence is sufficient to conclude that there is a causal relationship between ambient O_3 exposure and the occurrence of O_3-induced visible foliar injury on sensitive vegetation across the U.S.**

1.7.2 Growth, Productivity, Carbon Storage and Agriculture

Ambient O_3 concentrations have long been known to cause decreases in photosynthetic rates and plant growth. The O_3-induced effects at the plant scale may translate to the ecosystem scale, and cause changes in productivity and C storage. The effects of O_3 exposure on photosynthesis, growth, biomass allocation, ecosystem production and ecosystem C sequestration were reviewed for natural ecosystems, and crop productivity and crop quality were reviewed for agricultural ecosystems. There is strong and consistent evidence that ambient concentrations of O_3 decrease plant photosynthesis and growth in numerous plant species across the U.S. Studies conducted during the past four decades have also demonstrated unequivocally that O_3 alters biomass allocation and plant reproduction. Studies at the leaf and plant scales showed that O_3 reduced photosynthesis and plant growth, providing coherence and biological plausibility for the reported decreases in ecosystem productivity. In addition to primary productivity, other indicators such as net ecosystem CO_2 exchange and C sequestration were often assessed by modeling studies. Model simulations consistently found that O_3 exposure caused negative impacts on those indicators, but the severity of these impacts was influenced by multiple interactions of biological and environmental factors. Although O_3 generally causes negative effects on ecosystem productivity, the magnitude of the response varies among plant communities. **Overall, evidence is sufficient to conclude that there is a causal relationship between O_3 exposure and reduced plant growth and productivity, and a likely causal relationship between O_3 exposure and reduced carbon sequestration in terrestrial ecosystems.**

The detrimental effect of O_3 on crop production has been recognized since the 1960's, and current O_3 concentrations across the U.S. are high enough to cause yield loss for a variety of agricultural crops including, but not limited to, soybean, wheat, potato, watermelon, beans, turnip, onion, lettuce, and tomato. Continued increases in O_3 concentration may further decrease yield in these sensitive crops while also initiating yield losses in less sensitive crops. Research has linked increasing O_3 concentration to decreased photosynthetic rates and accelerated senescence, which are related to yield. **Evidence is sufficient to conclude that there is a causal relationship between O_3 exposure and reduced yield and quality of agricultural crops.**

1.7.3 Water Cycling

Ozone can affect water use in plants and ecosystems through several mechanisms including damage to stomatal functioning and loss of leaf area. Possible mechanisms for

O_3 exposure effects on stomatal functioning include the build-up of CO_2 in the substomatal cavity, impacts on signal transduction pathways and direct O_3 impact on guard cells. Regardless of the mechanism, O_3 exposure has been shown to alter stomatal performance, which may affect plant and stand transpiration and therefore may affect hydrological cycling. Although the direction of the response differed among studies, **the evidence is sufficient to conclude that there is likely to be a causal relationship between O_3 exposure and the alteration of ecosystem water cycling.**

1.7.4 Below Ground Processes

Below-ground processes are tightly linked with above-ground processes. The responses of above-ground process to O_3 exposure, such as reduced photosynthetic rates, increased metabolic cost, and reduced root C allocation, have provided biologically plausible mechanisms for the alteration of below-ground processes. These include altered quality and quantity of C input to soil, microbial community composition, and C and nutrient cycling. **The evidence is sufficient to conclude that there is a causal relationship between O_3 exposure and the alteration of below-ground biogeochemical cycles.**

1.7.5 Community Composition

Ozone exposure changes competitive interactions and leads to loss of O_3-sensitive species or genotypes. Studies at the plant level found that the severity of O_3 damage to growth, reproduction and foliar injury varied among species, which provided the biological plausibility for the alteration of community composition. For example, there is a tendency for O_3 exposure to shift the biomass of grass-legume mixtures in favor of grass species. Ozone exposure not only altered community composition of plant species, but also microorganisms: research since the last review has shown that O_3 can also alter community composition and diversity of soil microbial communities. Shifts in community composition of bacteria and fungi have been observed in both natural and agricultural ecosystems, although no general patterns could be identified. **The evidence is sufficient to conclude that there is likely a causal relationship between O_3 exposure and the alteration of community composition.**

1.7.6 Ozone Exposure-Response Relationships

Previous reviews of the NAAQs have included exposure-response functions for the yield of many crop species, and for the biomass accumulation of tree species. They were based

on large-scale experiments designed to obtain clear exposure-response data, and are updated in this ISA by using the W126 metric to quantify exposure. In recent years, extensive exposure-response data obtained in more naturalistic settings have become available for yield of soybean and growth of aspen. This ISA validates the exposure-response median functions based on previous data by comparing their predictions with the newer observations. The functions supply very accurate predictions of effects in naturalistic settings. Recent meta-analyses of large sets of crop and tree studies do not give rise to exposure-response functions, but their results are consistent with the functions presented in the ISA. It is important to note that although these median functions provide reliable models for groups of species or group of genotypes within a species, the original data and recent results consistently show that some species, and within species and some genotypes within species are much more severely affected by exposure to O_3.

1.8 The Role of Tropospheric Ozone in Climate Change and UV-B Effects

Atmospheric O_3 plays an important role in the Earth's energy budget by interacting with incoming solar radiation and outgoing infrared radiation. Tropospheric O_3 makes up only a small portion of the total column of O_3, but it has important incremental effects on the overall radiation budget. Therefore, perturbations in tropospheric O_3 concentrations can have direct effects on climate and indirect effects on health, ecology and welfare by shielding the earth's surface from solar ultraviolet (UV) radiation.

Ozone is an important greenhouse gas, and increases in its abundance in the troposphere may contribute to climate change. Models calculate that the global burden of tropospheric O_3 has doubled since the preindustrial era, while observations indicate that in some regions O_3 may have increased by factors as great as 4 or 5. These increases are tied to the rise in emissions of O_3 precursors from human activity, mainly fossil fuel consumption and agricultural processes.

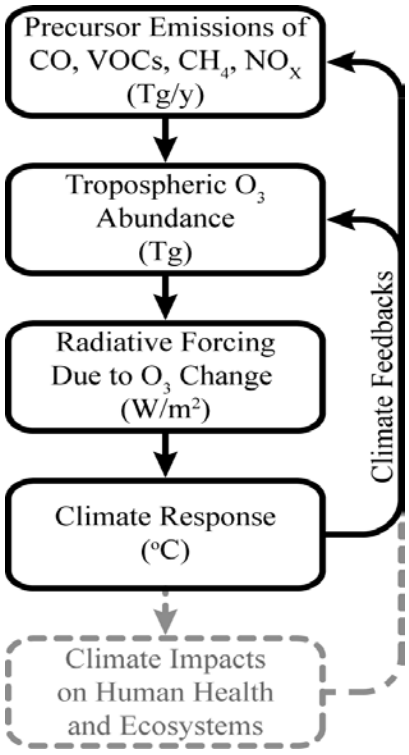


Figure 1-3 Schematic illustrating the effects of tropospheric O_3 on climate.

Figure 1-3 shows the main steps involved in the influence of tropospheric O_3 on climate. Emissions of O_3 precursors lead to production of tropospheric O_3. A change in the abundance of tropospheric O_3 perturbs the radiative balance of the atmosphere, an effect quantified by the radiative forcing (RF) metric. The earth-atmosphere-ocean system responds to the radiative forcing with a climate response, typically expressed as a change in surface temperature. Finally, the climate response causes downstream climate-related health and ecosystem impacts. Feedbacks from both the climate response and downstream impacts can, in turn, affect the abundance of tropospheric O_3 and O_3 precursors through multiple feedback mechanisms as indicated in the figure.

UV radiation emitted from the Sun contains sufficient energy when it reaches the Earth to have damaging effects on living organisms and materials. Atmospheric O_3 plays a crucial role in reducing exposure to UV radiation at the Earth's surface. Ozone in the stratosphere is responsible for the majority of this shielding, but O_3 in the troposphere provides supplemental shielding of UV radiation in the mid-wavelength range (UV-B), thereby influencing human and ecosystem health.

The conclusions from the previous NAAQS review and the causality determinations from this review relating climate change and UV-B effects are summarized in the table below, with details provided in the ISA.

Table 1-3 Summary of ozone causal determination for climate change and UV-B effects

Effects	Conclusions from Previous Review	Conclusions from 2011 2nd Draft ISA
Radiative Forcing	Climate forcing by O_3 at the regional scale may be its most important impact on climate.	Causal Relationship
Climate Change	While more certain estimates of the overall importance of global-scale forcing due to tropospheric O_3 await further advances in monitoring and chemical transport modeling, the overall body of scientific evidence **suggests** that high concentrations of O_3 on the regional scale **could have a discernable** influence on climate, leading to surface temperature and hydrological cycle changes.	Likely to be a Causal Relationship
UV-B Related Health and Welfare Effects	UV-B has **not been studied in sufficient detail** to allow for a credible health benefits assessment. In conclusion, the effect of changes in surface-level O_3 concentrations on UV-induced health outcomes cannot yet be critically assessed within reasonable uncertainty.	Inadequate to Determine if a Causal Relationship Exists

1.9 Conclusion

The clearest evidence for human health effects associated with exposure to O_3 is provided by studies of respiratory effects. Collectively, there is a very large amount of evidence spanning several decades in support of a causal association between exposure to O_3 and a continuum of respiratory effects. The majority of this evidence is derived from studies investigating short-term O_3 exposure (i.e., hours to weeks), although animal toxicological studies and recent epidemiologic evidence demonstrate that long-term exposure (i.e., months to years) may also be detrimental to the respiratory system. Additionally, consistent positive associations between short-term O_3 exposure and total (nonaccidental) mortality have helped to resolve previously identified areas of uncertainty in the O_3-mortality relationship, indicating that there is likely to be **a causal relationship between short-term exposures to O_3 and all-cause mortality.** Recent evidence is suggestive of a **causal relationship between long-term O_3 exposures and mortality**. The evidence for these health effects indicates that the relationship between concentration and response is linear within concentrations present in the U.S., with no indication of a threshold of O_3 concentrations under which no effect would be observed. The populations identified as being most at risk for O_3-related health effects are individuals with influenza/infection, individuals with asthma, and older age groups.

There has been over 40 years of research on the effects of O_3 exposure on vegetation and ecosystems. The best evidence for effects is from controlled exposure studies. These studies have clearly shown that exposure to O_3 is causally linked to visible foliar injury, decreased photosynthesis, changes in reproduction, and decreased growth. Recently, studies at larger spatial scales support the results from controlled studies and indicate that ambient O_3 exposures can affect ecosystem productivity, crop yield, water cycling, and ecosystem community composition. And on a global scale, tropospheric O_3 is the third most important greenhouse gas, playing an important role in climate change.

2 INTEGRATIVE SUMMARY

This Integrated Science Assessment (ISA) forms the scientific foundation for the review of the national ambient air quality standards (NAAQS) for ozone (O_3). The ISA is a concise evaluation and synthesis of the most policy-relevant science, and it communicates critical science judgments relevant to the review of the NAAQS for O_3. The ISA accurately reflects "the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health which may be expected from the presence of [a] pollutant in ambient air" (CAA, 1990a). Key information and judgments contained in prior Air Quality Criteria Documents (AQCD) for O_3 are incorporated into this assessment. Additional details of the pertinent scientific literature published since the last review, as well as selected older studies of particular interest, are included. This ISA thus serves to update and revise the evaluation of the scientific evidence available at the time of the completion of the 2006 O_3 AQCD. The current primary O_3 standard includes an 8-hour (h) average (avg) standard set at 75 parts per billion (ppb). The secondary standard for O_3 is set equal to the primary standard. Further information on the legislative and historical background for the O_3 NAAQS is contained in the Preface to this ISA.

This chapter summarizes and synthesizes the newly available scientific evidence and is intended to provide a concise synopsis of the ISA conclusions and findings that best inform consideration of the policy-relevant questions that frame this assessment (presented in Section 2.1). It includes:

- An integration of the evidence on the health effects associated with short- and long-term exposure to O_3, discussion of important uncertainties identified in the interpretation of the scientific evidence, and an integration of health evidence from the different scientific disciplines and exposure durations.
- An integration of the evidence on the ecological and welfare effects associated with exposure to O_3, and discussion of important uncertainties identified in the interpretation of the scientific evidence.
- Discussion of policy-relevant considerations, such as potentially at-risk populations and concentration-response relationships.

2.1 Policy-Relevant Questions for O_3 NAAQS Review

The draft *Integrated Review Plan for the Ozone National Ambient Air Quality Standards* (IRP) (U.S. EPA, 2009c) identified key policy-relevant questions that provide a framework for this assessment of the scientific evidence. These questions frame the entire

review of the NAAQS for O_3 and thus are informed by both science and policy considerations. The ISA organizes, presents, and integrates the scientific evidence which is considered along with findings from risk analyses and policy considerations to help the U.S. Environmental Protection Agency (EPA) address these questions during the NAAQS review. In evaluating the health evidence, the focus of this assessment is on scientific evidence that is most relevant to the following questions taken directly from the Integrated Review Plan:

- To what extent has new scientific information become available that alters or substantiates our understanding of the health effects associated with various time periods of exposure to ambient O_3, including short-term (1-3 hours), prolonged (6-8 hours), and chronic (months to years) exposures?
- To what extent has new scientific information become available that alters or substantiates our understanding of the health effects of O_3 on at-risk populations, including those with potentially increased susceptibility such as children and disadvantaged populations?
- To what extent has new scientific information become available that alters or substantiates conclusions from previous reviews regarding the plausibility of adverse health effects caused by O_3 exposure?
- At what levels of O_3 exposure are health effects observed? Is there evidence of effects at exposure levels lower than those previously observed, and what are the important uncertainties associated with that evidence? What is the nature of the exposure-response relationships of O_3 for the various health effects evaluated?
- To what extent has new scientific information become available that alters or substantiates our understanding of non-O_3-exposure factors that might influence the associations between O_3 levels and health effects being considered (e.g., weather-related factors; behavioral factors such as heating/air conditioning use; driving patterns; and time-activity patterns)?
- To what extent do risk and/or exposure analyses suggest that exposures of concern for O_3-related health effects are likely to occur with current ambient levels of O_3 or with levels that just meet the O_3 standard? Are these risks/exposures of sufficient magnitude such that the health effects might reasonably be judged to be important from a public health perspective? What are the important uncertainties associated with these risk/exposure estimates?
- To what extent have important uncertainties identified in the last rulemaking been addressed and/or have new uncertainties emerged?

In evaluating the welfare evidence, the available scientific evidence will focus on key policy-relevant issues by addressing a series of questions including the following:

- To what extent has new scientific information become available that alters or substantiates our understanding of the effects on vegetation and other welfare effects following exposures to levels of O_3 found in the ambient air?
- To what extent has new scientific information become available to inform our understanding of the nature of the exposures that are associated with such effects in terms of biologically relevant cumulative, seasonal exposure indices?
- To what extent has new scientific information become available that alters or substantiates our understanding of the effects of O_3 on sensitive plant species, ecological receptors, or ecosystem processes?
- To what extent has new scientific information become available that alters or substantiates our understanding of exposure factors other than O_3 that might influence the associations between O_3 levels and welfare effects being considered (e.g., site specific features such as elevation, soil moisture level, presence of co-occurring competitors, pests, pathogens, other pollutant stressors, weather-related factors)?
- To what extent has new scientific information become available that alters or substantiates conclusions regarding the occurrence of adverse welfare effects at levels of O_3 as low as or lower than those observed previously? What is the nature of the exposure-response relationships of O_3 for the various welfare effects evaluated?
- Given recognition in the last review that the significance of O_3-induced effects to the public welfare depends in part on the intended use of the plants or ecosystems on which those effects occurred, to what extent has new scientific evidence become available to suggest additional locations where the vulnerability of sensitive species or ecosystems would have special significance to the public welfare and should be given increased focus in this review?
- To what extent do risk and/or exposure analyses suggest that exposures of concern for O_3-related welfare effects are likely to occur with current ambient levels of O_3 or with levels that just meet the O_3 standard? Are these risks/exposures of sufficient magnitude such that the welfare effects might reasonably be judged to be important from a public welfare perspective? What are the important uncertainties associated with these risk/exposure estimates?

- To what extent have important uncertainties identified in the last review been addressed and/or have new uncertainties emerged?
- To what extent does newly available information reinforce or call into question any of the basic elements of the current O_3 standard?

2.2 ISA Development and Scope

EPA has a developed a robust, consistent, and transparent process for evaluating the scientific evidence and drawing conclusions and causal judgments regarding air pollution-related health and environmental effects. The ISA development process includes literature search strategies, criteria for selecting and evaluating studies, approaches for evaluating weight of the evidence, and a framework for making causality determinations. The process and causality framework are described in more detail in the Preamble to the ISA [website]. This section provides a brief overview of the process for development of this ISA.

EPA initiated the current review of the NAAQS for O_3 on September 29, 2008, with a call for information from the public (U.S. EPA, 2008f). Literature searches were conducted routinely to identify studies published since the last review, focusing on studies published from 2005 (close of previous scientific assessment) through July 2011. References that were considered for inclusion in this ISA can be found using the HERO website (http://hero.epa.gov/ozone). This site contains HERO links to lists of references that are cited in the ISA, as well as those that were considered for inclusion, but not cited in the ISA, with bibliographic information and abstracts.

This review has endeavored to evaluate all relevant data published since the last review pertaining to the atmospheric science of O_3, human exposure to ambient O_3, epidemiologic, controlled human exposure, toxicological, and ecological or welfare effects studies, including studies related to exposure-response relationships, mode(s) of action (MOA), and understanding of at-risk or susceptible populations for effects of O_3 exposure. Added to the body of research were EPA's analyses of air quality and emissions data, studies on atmospheric chemistry, transport, and fate of these emissions, as well as issues related to exposure to O_3.

Previous AQCDs (U.S. EPA, 2006b, 1996a, b, 1984, 1978a) have included an extensive body of evidence on both health and ecological effects of O_3 exposure, as well as an understanding of the atmospheric chemistry of O_3 (U.S. EPA, 2006b). In this ISA, the conclusions and key findings from previous reviews are summarized at the beginning of each section, to provide the foundation for consideration of evidence from recent studies.

Results of key studies from previous reviews are included in discussions or tables and figures, as appropriate, and conclusions are drawn based on the synthesis of evidence from recent studies with the extensive literature summarized in previous reviews.

The Preamble discusses the general framework for conducting the science assessment and developing an ISA, including criteria for evaluating studies and developing scientific conclusions. For selection of epidemiologic studies in the O_3 ISA, particular emphasis is placed on those studies most relevant to the review of the NAAQS. Studies conducted in the United States (U.S.) or Canada are discussed in more detail than those from other geographical regions, and particular emphasis is placed on: (1) recent multicity studies that employ standardized analysis methods for evaluating effects of O_3 and that provide overall estimates for effects, based on combined analyses of information pooled across multiple cities; (2) studies that help understand quantitative relationships between exposure concentrations and effects; (3) new studies that provide evidence on effects in susceptible populations; and (4) studies that consider and report O_3 as a component of a complex mixture of air pollutants. In evaluating toxicological and controlled human exposure studies, emphasis is placed on studies using concentrations or doses that are within about an order of magnitude of ambient O_3 concentrations. Consideration of issues important for evaluation of human exposure to ambient O_3 include the relationship between O_3 measured at central site monitors and personal exposure to ambient O_3 environments, since penetration of O_3 into indoor environments may be limited.

This ISA uses a five-level hierarchy that classifies the weight of evidence for causation:

- Causal relationship
- Likely to be a causal relationship
- Suggestive of a causal relationship
- Inadequate to infer a causal relationship
- Not likely to be a causal relationship

Beyond judgments regarding causality are questions relevant to quantifying health or environmental risks based on our understanding of the quantitative relationships between pollutant exposures and health or welfare effects. Once a determination is made regarding the causal relationship between the pollutant and outcome category, important questions regarding quantitative relationships include:

- What is the concentration-response or dose-response relationship?
- Under what exposure conditions (dose or concentration, duration and pattern) are effects observed?

- What populations appear to be differentially affected i.e., more susceptible to effects?
- What elements of the ecosystem (e.g., types, regions, taxonomic groups, populations, functions, etc.) appear to be affected or are more sensitive to effects?

This chapter summarizes and integrates the newly available scientific evidence that best informs consideration of the policy-relevant questions that frame this assessment. Section 2.3 discusses the trends in ambient concentrations and sources of O_3 and provides a brief summary of ambient air quality for short- and long-term exposure durations. Section 2.4 presents the evidence regarding personal exposure to ambient O_3 in outdoor and indoor microenvironments, and it discusses the relationship between ambient O_3 concentrations and personal exposure to O_3 from ambient sources. Section 2.5 provides a discussion of the dosimetry and mode of action evidence for O_3 exposure. Section 2.6 integrates the evidence for studies that examine the health effects associated with short- and long-term exposure to O_3 and discusses important uncertainties identified in the interpretation of the scientific evidence. Section 2.7 provides a discussion of policy-relevant considerations, such as potentially at-risk populations, lag structure, and the O_3 concentration-response relationship. Section 2.8 integrates the health evidence from the different scientific disciplines and exposure durations. Finally, Section 2.9 summarizes the evidence for welfare effects related to O_3 exposure, and Section 2.10 reviews the literature on the influence of tropospheric O_3 on climate and exposure to solar ultraviolet radiation.

2.3 Atmospheric Chemistry and Ambient Concentrations

2.3.1 Physical and Chemical Processes

Ozone in the troposphere originates from both anthropogenic (i.e., man-made) and natural source categories. Ozone attributed to anthropogenic sources is formed in the atmosphere by photochemical reactions involving sunlight and precursor pollutants including volatile organic compounds (VOCs), nitrogen oxides (NO_X), and carbon monoxide (CO). Ozone attributed to natural sources is formed through the same photochemical reactions involving natural emissions of precursor pollutants from vegetation, microbes, animals, biomass burning, lightning, and geogenic sources. A schematic overview of the major photochemical cycles influencing O_3 in the troposphere and the stratosphere is shown in Figure 2-1. The processes depicted in this figure are fairly well understood, and were covered in detail in the previous O_3 AQCD. The

formation of O_3, other oxidants, and oxidation products from these precursors is a complex, nonlinear function of many factors including: (1) the intensity and spectral distribution of sunlight; (2) atmospheric mixing; (3) concentrations of precursors in the ambient air and the rates of chemical reactions of these precursors; and (4) processing on cloud and aerosol particles.

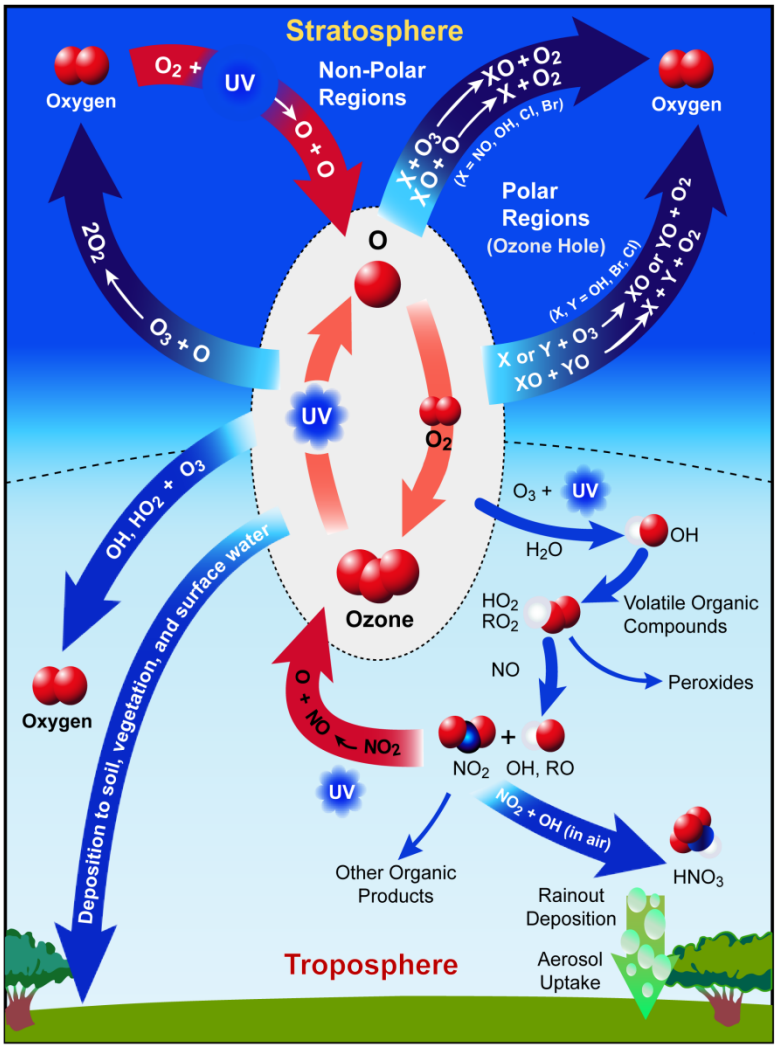


Figure 2-1 Schematic overview of photochemical processes influencing stratospheric and tropospheric ozone.

Ozone is present not only in polluted urban atmospheres but throughout the troposphere, even in remote areas of the globe. The same basic processes involving sunlight-driven reactions of NO_X, VOCs and CO contribute to O_3 formation throughout the troposphere.

These processes also lead to the formation of other photochemical products, such as peroxyacetyl nitrate, nitric acid, and sulfuric acid, and to other compounds, such as formaldehyde and other carbonyl compounds. In urban areas, NO_X, VOCs and CO are all important for O_3 formation. In nonurban vegetated areas, biogenic VOCs emitted from vegetation tend to be the most important precursor to O_3 formation. In the remote troposphere, methane – structurally the simplest VOC – and CO are the main carbon-containing precursors to O_3 formation. Throughout the troposphere, O_3 is subsequently lost through a number of gas phase reactions and deposition to surfaces as shown in Figure 2-1.

Convective processes and turbulence transport O_3 and other pollutants both upward and downward throughout the planetary boundary layer and the free troposphere. In many areas of the U.S., O_3 and its precursors can be transported over long distances, aided by vertical mixing. The transport of pollutants downwind of major urban centers is characterized by the development of urban plumes. Meteorological conditions, small-scale circulation patterns, localized chemistry, and mountain barriers can influence mixing on a smaller scale, resulting in frequent heterogeneous O_3 concentrations across an individual urban area.

Furthermore, the mean tropospheric lifetime of O_3 is long enough that it can be transported from continent to continent and latitudinally around the globe. The degree of influence from intercontinental transport varies greatly by location and time. For instance, high elevation sites are most susceptible to the intercontinental transport of pollution, particularly during spring. Given the nonlinear chemistry involving O_3 formation, the task of isolating the influence of intercontinental transport of O_3 and O_3 precursors on regional air quality is quite complex and the topic of the next section.

2.3.2 Atmospheric Modeling of Background Ozone Concentrations

Background concentrations of O_3 have been given various definitions in the literature over time. In the context of a review of the NAAQS, it is useful to define background O_3 concentrations in a way that distinguishes between concentrations that result from precursor emissions that are relatively less directly controllable from those that are relatively more directly controllable through U.S. policies. North American (NA) background O_3 can include contributions that result from emissions from natural sources (e.g., stratospheric intrusion, biogenic methane and more short-lived VOC emissions), emissions of pollutants that contribute to global concentrations of O_3 (e.g., anthropogenic methane) from countries outside North America. In previous NAAQS reviews, a specific definition of background concentrations was used and referred to as policy relevant

background (PRB). In those previous reviews, PRB concentrations were defined by EPA as those concentrations that would occur in the U.S. in the absence of anthropogenic emissions in continental North America (CNA), defined here as the U.S., Canada, and Mexico. For this document, we have focused on the sum of those background concentrations from natural sources everywhere in the world and from anthropogenic sources outside CNA. North American background concentrations so defined facilitate separation of pollution that can be controlled directly by U.S. regulations or through international agreements with neighboring countries from that which would require more comprehensive international agreements, such as are being discussed as part of the United Nations sponsored Convention on Long Range Transboundary Air Pollution Task Force on Hemispheric Air Pollution. There is no chemical difference between background O_3 and O_3 attributable to CNA anthropogenic sources, and background concentrations can contribute to the risk of health effects. However, to inform policy considerations regarding the current or potential alternative standards, it is useful to understand how total O_3 concentrations can be attributed to different source.

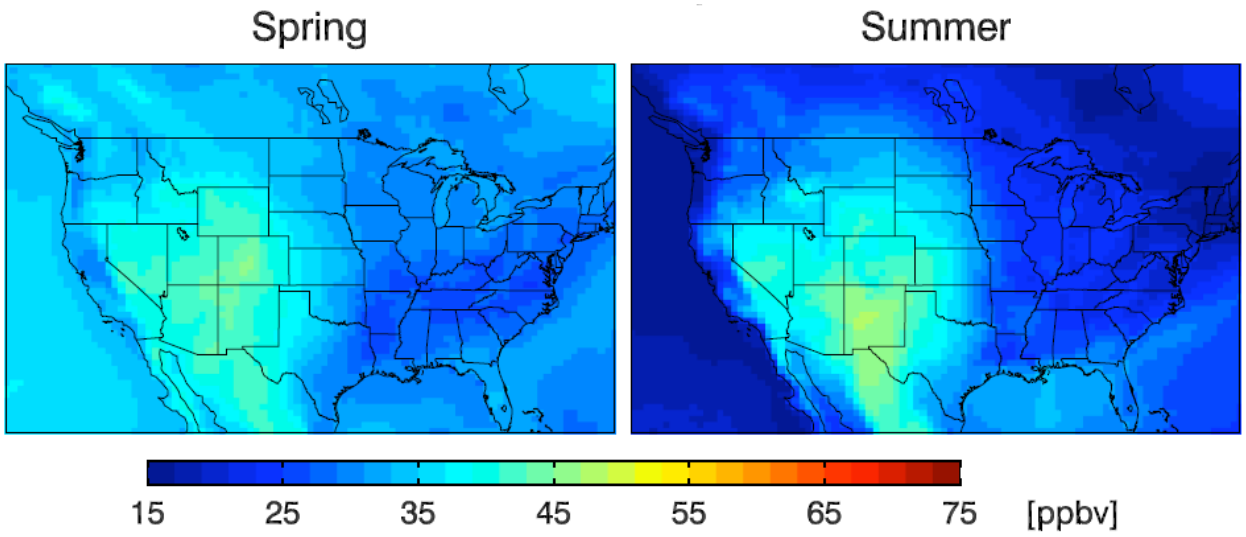
Since North American background as defined above is a construct that cannot be directly measured, the range of background O_3 concentrations are estimated using chemistry transport models (CTMs). The 2006 O_3 AQCD provided regional estimates of PRB O_3 concentrations based on a coarse resolution (2°×2.5°, or ~200 km×200 km) GEOS-Chem model. For the current assessment, updated results from a finer resolution (0.5°×0.667°, or ~50 km×50 km) GEOS-Chem model were used. Base-case model performance evaluations comparing 2006 predicted to observed mean O_3 concentrations from March to August showed general agreement to within ~5 ppb at most (26 out of 28) sites investigated. Exceptions included over-prediction of mean O_3 during the summer at a site on the Atlantic coast of Florida and under-prediction of mean O_3 year-round at a site in Yosemite NP. The finer resolution GEOS-Chem model agrees more closely with observations in the intermountain West than earlier versions.

The GEOS-Chem model-predicted North American O_3 seasonal mean concentrations for spring and summer, 2006 are shown in Figure 2-2. As can be seen, North American background concentrations are generally higher in spring than in summer across the U.S., with exception in the Southwest where predictions peak in the summer. Highest estimates are found in the Intermountain West during the spring (less than 47 ppb) and in the Southwest during the summer (less than 49 ppb). Lowest estimates occur over the East in the spring (greater than 23 ppb) and over the Northeast in the summer (greater than 15 ppb).

2.3.3 Monitoring

The federal reference method (FRM) for O_3 measurement is based on the detection of chemiluminescence resulting from the reaction of O_3 with ethylene gas. However, almost all of the state and local air monitoring stations (SLAMS) that reported data to the EPA's Air Quality System (AQS) database from 2005 to 2009 used the federal equivalence method (FEM) UV absorption photometer. More than 96% of O_3 monitors met precision and bias goals during this period.

In 2010, there were 1250 SLAMS O_3 monitors reporting data to AQS. Ozone is required to be monitored at SLAMS during the local "ozone season" which varies by state. In addition, National Core (NCore) is a new multipollutant monitoring network implemented to meet multiple monitoring objectives and each state is required to operate at least one NCore site. The NCore network consists of 60 urban and 20 rural sites nationwide (See Figure 3-16). The densest concentrations of O_3 sites are located in California and the eastern half of the U.S.



Source: Zhang et al. (In Press)

Figure 2-2 GEOS-Chem modeled U.S. policy relevant background seasonal-mean surface ozone concentrations in spring (left) and summer (right), 2006.

The Clean Air Status and Trends Network (CASTNET) is a regional monitoring network established to assess trends in acidic deposition and also provides concentration

measurements of O_3. CASTNET O_3 monitors operate year round and are primarily located in rural areas; in 2010, there were 80 CASTNET sites reporting O_3 data to AQS. The National Park Service (NPS) operates 23 CASTNET sites in national parks and other Class-I areas, and provided data to AQS from 20 additional Portable Ozone Monitoring Systems (POMS) in 2010 (See Figure 3-17). Compared to urban-focused monitors, rural-focused monitors are relatively scarce across the U.S.

2.3.4 Ambient Concentrations

Ozone is the only photochemical oxidant other than NO_2 that is routinely monitored and for which a comprehensive database exists. Other photochemical oxidants are typically only measured during special field studies. Therefore, the concentration analyses in Chapter 3 are limited to widely available O_3 data obtained directly from AQS for the period from 2007 to 2009. The median 24-h average, 8-h daily maximum, and 1-h daily maximum O_3 concentrations across all U.S. sites reporting data to AQS between 2007 and 2009 were 29, 40, and 44 ppb, respectively.

To investigate O_3 variability in urban areas across the U.S., 20 combined statistical areas (CSAs) were selected for closer analysis based on their importance in O_3 epidemiology studies and on their location. Several CSAs had relatively little spatial variability in 8-h daily maximum O_3 concentrations (e.g., inter-monitor correlations ranging from 0.61 to 0.96 in the Atlanta CSA) while other CSAs exhibited considerably more variability in O_3 concentrations (e.g., inter-monitor correlations ranging from -0.06 to 0.97 in the Los Angeles CSA). As a result, caution should be observed in using data from the network of ambient O_3 monitors to approximate community-scale exposures.

To investigate O_3 variability in rural settings across the U.S., six focus areas were selected for closer analysis based on the impact of O_3 or O_3 precursor transport from upwind urban areas. The selected rural focus area with the largest number of available AQS monitors was Great Smoky Mountain National Park where the May-September median 8-h daily maximum O_3 concentration ranged from 47 ppb at the lowest elevation (564 m) site to 60 ppb at the highest elevation (2,021 m) site. Correlations between sites within each rural focus area ranged from 0.78 to 0.92. Ozone in rural areas is produced from emissions of O_3 precursors emitted directly within the rural areas, from emissions in urban areas that are processed during transport, and from occasional stratospheric intrusions. Factors contributing to variations observed within these rural focus areas include proximity to local O_3 precursor emissions, local scale circulations related to topography, and possibly stratospheric intrusions as a function of elevation. In addition, O_3 tends to persist longer in rural than in urban areas as a result of less chemical

scavenging. This results in a more uniform O_3 concentration throughout the day and night without the typical nocturnal decrease in O_3 concentration observed in urban areas. Persistently high O_3 concentrations observed at many of the rural sites investigated here indicate that cumulative exposures for humans and vegetation in rural areas can be substantial and often higher than cumulative exposures in urban areas.

According to the 2010 National Air Quality Status and Trends report (U.S. EPA, 2010e), O_3 concentrations have declined over the last decade; with the majority of this decline occurring before 2004. A noticeable decrease in O_3 between 2003 and 2004 coincides with NO_X emissions reductions resulting from implementation of the NO_X SIP Call rule, which began in 2003 and was fully implemented in 2004. This rule was designed to reduce NO_X emissions from power plants and other large combustion sources in the eastern U.S. As noted in the 2006 O_3 AQCD, trends in national parks and rural areas are similar to nearby urban areas, reflecting the regional nature of O_3 pollution.

Since O_3 is a secondary pollutant, it is not expected to be highly correlated with primary pollutants such as CO and NO_X. Furthermore, O_3 formation is strongly influenced by meteorology, entrainment, and transport of both O_3 and O_3 precursors, resulting in a broad range in correlations with other pollutants which can vary substantially with season. Correlations between 8-h daily maximum O_3 and other criteria pollutants exhibit mostly negative correlations in the winter and mostly positive correlations in the summer. The median seasonal correlations are modest at best with the highest positive correlation at 0.52 for $PM_{2.5}$ in the summer and the highest negative correlation at -0.38 for $PM_{2.5}$ in the winter. As a result, statistical analyses that may be sensitive to correlations between copollutants need to take seasonality into consideration, especially when O_3 is being investigated.

2.4 Human Exposure

Ozone is ubiquitous throughout the environment, originating from both natural and anthropogenic sources. As such, people are routinely exposed to O_3 as they participate in normal day-to-day activities. A number of factors affect the pattern of personal O_3 exposure. These include: the variation in O_3 concentrations at various spatial and temporal scales; individuals' activity patterns, particularly time spent outdoors, which may involve changes in personal behavior to avoid exposure to O_3; and infiltration of ambient O_3 into indoor microenvironments, which is driven by air exchange rate. Similarly, several approaches have been used to measure or quantify exposure to ambient O_3, giving an indication of the impact of these factors. These approaches include characterizing the correlation and ratio between personal exposure and ambient O_3

concentration, determining the ratio between indoor and outdoor concentrations, and using models to estimate exposure to O_3 based on ambient concentrations. Both the factors affecting the pattern of exposure as well as the type of approaches used for quantification of exposure may have implications for epidemiologic studies.

Variations in O_3 concentrations occur over multiple spatial and temporal scales. Near roadways, O_3 concentrations are reduced due to reaction with NO and other species (Section 4.3.4.2). Over spatial scales of a few kilometers and away from roads, O_3 may be somewhat more homogeneous due to its formation as a secondary pollutant, while over scales of tens of kilometers, additional atmospheric processing can result in higher concentrations downwind of an urban area. Although local-scale variability impacts the magnitude of O_3 concentrations, O_3 formation rates are influenced by factors that vary over larger spatial scales, such as temperature (Section 3.2), suggesting that urban monitors may track one another temporally but miss small-scale variability. This variation in concentrations changes the pattern of exposure people experience as they move through different microenvironments and affects the magnitude of exposures in different locations within an urban area.

Another factor that may influence the pattern of exposure is the tendency for people to avoid O_3 exposure by altering their behavior (e.g., reducing time spent outdoors) on high-O_3 days. Activity pattern has a substantial effect on ambient O_3 exposure, with time spent outdoors contributing to increased exposure (Section 4.4.2). Air quality alerts and public health recommendations induce reductions in outdoor activity on high-O_3 days among some populations, particularly for children, older adults, and people with respiratory problems. Such effects are less pronounced in the general population, possibly due to the opportunity cost of behavior modification. Preliminary epidemiologic evidence reports increased asthma hospital admissions among children and older adults when O_3 alert days were excluded from the analysis of daily hospital admissions and O_3 concentrations (presumably thereby eliminating averting behavior based on high O_3 forecasts). The lower rate of admissions observed when alert days were included in the analysis suggests that estimates of health effects based on dose-response functions which do not account for averting behavior may be biased towards the null.

Personal exposure to O_3 is moderately correlated with ambient O_3 concentration, as indicated by studies reporting correlations generally in the range of 0.3-0.8 (Table 4-2). To the extent that relative changes in central-site monitor concentration are associated with relative changes in exposure concentration, this indicates that ambient monitor concentrations are representative of day-to-day changes in average total personal exposure and in personal exposure to ambient O_3. The ratio between personal exposure and ambient concentration varies widely depending on activity patterns, housing

characteristics, and season. Personal-ambient ratios are typically 0.1-0.3, although individuals spending substantial time outdoors (e.g., outdoor workers) have shown much higher ratios (0.5-0.9) (Table 4-3). Thus, applying personal-ambient ratios for outdoor workers to the general population or susceptible populations spending substantial time indoors can result in overestimates of the magnitude of personal exposure for these groups. Some studies report much lower personal-ambient correlations, a result attributable in part to low air exchange rate and O_3 concentrations below the sampler detection limit, conditions often encountered during wintertime. Low correlations may also occur for individuals or populations spending increased time indoors. Since there are relatively few indoor sources of O_3, indoor O_3 concentrations are often substantially lower than outdoor concentrations due to reactions of O_3 with indoor surfaces and airborne constituents (Section 4.3.2). The lack of indoor sources also suggests that fluctuations in ambient O_3 may be primarily responsible for changes in personal exposure, even under low-ventilation, low-concentration conditions.

The factors affecting exposure patterns and quantification of exposure result in uncertainty which may contribute to exposure measurement error in epidemiologic studies. Low personal-ambient correlations are a source of exposure error for epidemiologic studies, tending to obscure the presence of thresholds, bias effect estimates toward the null, and widen confidence intervals, and this impact may be more pronounced among populations spending substantial time indoors. The impact of this exposure error may tend more toward widening confidence intervals than biasing effect estimates, since epidemiologic studies evaluating the influence of monitor selection indicate that effect estimates are similar across different spatial averaging scales and monitoring sites.

2.5 Dosimetry and Mode of Action

Upon inspiration, O_3 uptake in the respiratory tract is affected by a number of factors including respiratory tract morphology, and breathing route, frequency, and volume. Additionally, physicochemical properties of O_3 itself and how it is transported, as well as the physical and chemical properties of the extracellular lining fluid (ELF) and tissue layers in the respiratory tract can influence O_3 uptake. Experimental studies and models have suggested that there are differences between the total absorption of O_3 from the inhaled air and the O_3 dose reaching the respiratory tract tissues. The total O_3 absorption gradually decreases with distal progression into the respiratory tract. In contrast, the primary site of O_3 delivery to the lung epithelium is believed to be the centriacinar region or the junction of the conducting airways with the gas exchange region.

Ozone uptake efficiency is sensitive to a number of factors including tidal volume, minute volume, breathing frequency, O_3 concentration, and exposure time. However, the greatest source of variability in uptake efficiency is interindividual variability, primarily due to differences in tracheobronchial volume and thus surface area. An increase in tidal volume and breathing frequency are both associated with increased physical activity. These changes and a switch to oronasal breathing during exercise result in deeper penetration of O_3 into the lung with a higher absorbed fraction in the upper respiratory tract, tracheobronchial, and alveolar airways. For these reasons, increased physical activity acts to move the maximum tissue dose of O_3 distally in the respiratory tract and into the alveolar region.

The ELF is a complex mixture of lipids, proteins, and antioxidants that serves as the first barrier and target for inhaled O_3 (see Figure 5-8). Distinct products with diverse reactivity (i.e., secondary oxidation products), are formed by reactions of O_3 with soluble ELF components or plasma membranes. The thickness of the ELF and that of the mucus layer, within the ELF, are important determinants of the dose of O_3 to the tissues; a thicker ELF generally results in a lower dose of O_3 to the tissues. Additionally, the quenching ability and the concentrations of antioxidants and other ELF components are determinants of the formation of secondary oxidation products. These reactions appear to limit interaction of O_3 with underlying tissues and to prevent penetration of O_3 distally into the respiratory tract.

In addition to contributing to the driving force for O_3 uptake, formation of secondary oxidation products contributes to oxidative stress which may lead to cellular injury and altered cell signaling in the respiratory tract. Secondary oxidation products initiate pathways (See Figure 5-9) that provide the mechanistic basis for short- and long-term health effects described in detail in Chapters 6 and 7. Other key events involved in the mode of action of O_3 in the respiratory tract include the activation of neural reflexes, initiation of inflammation, alterations of epithelial barrier function, sensitization of bronchial smooth muscle, modification of innate and adaptive immunity, and airway remodeling. Another key event, systemic inflammation and vascular oxidative/nitrosative stress, may be critical to the extrapulmonary effects of O_3.

Secondary oxidation products can transmit signals to respiratory tract cells resulting in the activation of neural reflexes. Nociceptive sensory nerves mediate the involuntary truncation of respiration, resulting in decreases in lung function (i.e., FVC, FEV_1, and tidal volume), and pain upon deep inspiration. Studies implicate TRPA1 receptors on bronchial C-fibers in this reflex. Another neural reflex involves vagal sensory nerves, which mediate a mild increase in airways obstruction (i.e., bronchoconstriction)

following exposure to O_3 via parasympathetic pathways. Substance P release from bronchial C-fibers and the SP-NK receptor pathway may also contribute to this response.

Secondary oxidation products also initiate the inflammatory cascade following exposure to O_3. Studies have implicated eicosanoids, chemokines and cytokines, vascular endothelial adhesion molecules, and tachykinins in mediating this response. Inflammation is characterized by airways neutrophilia as well as the influx of other inflammatory cell types. Recent studies demonstrate a later phase of inflammation characterized by increased numbers of macrophages, which is mediated by hyaluronan. Inflammation further contributes to O_3-induced oxidative stress.

Alteration of the epithelial barrier function of the respiratory tract also occurs as a result of O_3-induced secondary oxidation product formation. Increased epithelial permeability may lead to enhanced sensitization of bronchial smooth muscle, resulting in airways hyperresponsiveness (AHR). Neurally-mediated sensitization also occurs and is mediated by cholinergic postganglionic pathways and bronchial C-fiber release of substance P. Recent studies implicate hyaluronan and toll-like receptor 4 (TLR4) signaling in bronchial smooth muscle sensitization, while older studies demonstrate roles for eicosanoids, cytokines, and chemokines.

Evidence is accumulating that exposure to O_3 modifies innate and adaptive immunity through effects on macrophages, monocytes, and dendritic cells. Enhanced antigen presentation, adjuvant activity, and altered responses to endotoxin have been demonstrated. TLR4 signaling contributes to some of these responses. Effects on innate and adaptive immunity may result in both short- and longer-term consequences related to the exacerbation and/or induction of asthma and to alterations in host defense.

Airway remodeling has been demonstrated following chronic and/or intermittent exposure to O_3 by mechanisms which are not well understood. However, the TGF-β signaling pathway has recently been implicated in O_3-induced deposition of collagen in the airways wall. These studies were conducted in adult animal models and their relevance to effects in humans is unknown.

Evidence is also accumulating that O_3 exposure results in systemic inflammation and vascular oxidative/nitrosative stress. The release of diffusible mediators from the O_3-exposed lung into the circulation may initiate or propagate inflammatory responses in the vascular or in systemic compartments. This may provide a mechanistic basis for extrapulmonary effects, such as vascular dysfunction.

Both dosimetric and mechanistic factors contribute to the understanding of inter-individual variability in response. Inter-individual variability is influenced by variability in respiratory tract volume and thus surface area, breathing route, certain genetic

polymorphisms, pre-existing conditions and disease, nutritional status, lifestages, attenuation, and coexposures. In particular, functional genetic polymorphisms of genes associated with antioxidant defense have been implicated in O_3-mediated health effects. Pre-existing asthma, allergic airways disease, and obesity modulate immune and inflammatory responses to O_3. Older adults exhibit diminished spirometric responses to O_3 compared with younger adults. Very young individuals may be sensitive to developmental effects of O_3 since studies in animal models demonstrated altered development of lung and other organ systems.

Some of these factors are also influential in understanding species homology and sensitivity. Qualitatively, animal models exhibit a similar pattern of tissue dose distribution for O_3 with the largest tissue dose delivered to the centriacinar region. However, due to anatomical and biochemical respiratory tract differences, the actual O_3 dose delivered differs between humans and animal models. Animal data obtained in resting conditions underestimates the dose to the respiratory tract relative to exercising humans. Further, it should be noted that, with the exception of airways remodeling, the mechanistic pathways discussed above have been demonstrated in both animals and human subjects in response to the inhalation of O_3. Even though interspecies differences limit quantitative comparison between species, the short- and long-term functional responses of laboratory animals to O_3 appear qualitatively homologous to those of the human making them a useful tool in determining mechanistic and cause-effect relationships with O_3 exposure.

2.6 Integration of Ozone Health Effects

This section evaluates the evidence from toxicological, controlled human exposure, and epidemiologic studies that examined the health effects associated with short- and long-term exposure to O_3, and summarizes the main conclusions of this assessment regarding the health effects of O_3 and the concentrations at which those effects are observed. The conclusions from the previous NAAQS review and the causality determinations from this review are summarized in Table 2-1. The results from the health studies evaluated in combination with the evidence from atmospheric chemistry and exposure assessment studies contribute to the causal determinations made for the health outcomes discussed in this assessment (See Preamble to this document). In the following sections a discussion of the causal determinations will be presented by exposure duration (i.e., short-term [i.e., hours, days, weeks] or long-term [i.e., months to years] exposure) for the health effects for which sufficient evidence was available to conclude a causal, likely to be causal or suggestive relationship. This section also integrates the evidence from short- and long-term exposure studies across scientific disciplines (i.e., controlled human exposure

studies, toxicology, and epidemiology) in interpreting the health effects evidence that spans from prenatal development to death.

Table 2-1 Summary of evidence from epidemiologic, controlled human exposure, and animal toxicological studies on the health effects associated with short- and long-term exposure to ozone

Health Outcome	Conclusions from 2006 O_3 AQCD	Conclusions from 2011 2nd Draft ISA
Short-Term Exposure to O_3		
Respiratory effects	The overall evidence supports a causal relationship between acute ambient O_3 exposures and increased respiratory morbidity outcomes.	Causal relationship
Lung function	Results from controlled human exposure studies and animal toxicological studies provide clear evidence of causality for the associations observed between acute (≤ 24 h) O_3 exposure and relatively small, but statistically significant declines in lung function observed in numerous recent epidemiologic studies. Declines in lung function are particularly noted in children, asthmatics, and adults who work or exercise outdoors.	Recent controlled human exposure studies demonstrate group mean decreases in FEV_1 in the range of 2 to 3% with 6.6 h exposures to as low as **60 ppb** O_3. The collective body of epidemiologic evidence demonstrates associations between short-term ambient O_3 exposure and decrements in lung function, particularly in asthmatics, children, and adults who work or exercise outdoors.
Airway hyperresponsiveness	Evidence from human clinical and animal toxicological studies clearly indicate that acute exposure to O_3 can induce airway hyperreactivity, thus likely placing atopic asthmatics at greater risk for more prolonged bouts of breathing difficulties due to airway constriction in response to various airborne allergens or other triggering stimuli.	A limited number of studies have observed airway hyperresponsiveness in rodents and guinea pigs after exposure to less than **300 ppb** O_3. As previously reported in the 2006 O_3 AQCD, increased airway responsiveness has been demonstrated at **80 ppb** in young, health adults, and at **50 ppb** in certain strains of rats, suggesting a genetic component.
Pulmonary inflammation, injury and oxidative stress	The extensive human clinical and animal toxicological evidence, together with the limited available epidemiologic evidence, is clearly indicative of a causal role for O_3 in inflammatory responses in the airways.	Epidemiologic studies provided new evidence for associations of ambient O_3 with mediators of airway inflammation and oxidative stress and indicate that higher antioxidant levels may reduce pulmonary inflammation associated with O_3 exposure. Generally, these studies had mean 8-h max O_3 concentrations less than **73 ppb**.
Respiratory symptoms and medication use	Young healthy adult subjects exposed in clinical studies to O_3 concentrations ≥ 80 ppb for 6 to 8 h during moderate exercise exhibit symptoms of cough and pain on deep inspiration. The epidemiologic evidence shows significant associations between acute exposure to ambient O_3 and increases in a wide variety of respiratory symptoms (e.g., cough, wheeze, production of phlegm, and shortness of breath) and medication use in asthmatic children.	The collective body of epidemiologic evidence demonstrates positive associations between short-term exposure to ambient O_3 and respiratory symptoms (e.g., cough, wheeze, production of phlegm, and shortness of breath) in asthmatic children. Generally, these studies had mean 8-h max O_3 concentrations less than **69 ppb**.
Lung host defenses	Toxicological studies provided extensive evidence that acute O_3 exposures as low as 80 to 500 ppb can cause increases in susceptibility to infectious diseases due to modulation of lung host defenses. A single controlled human exposure study found decrements in the ability of alveolar macrophages to phagocytose microorganisms upon exposure to 80 to 100 ppb O_3.	Recent studies in human subjects demonstrate the increased expression of cell surface markers and alterations in sputum leukocyte markers related to innate adaptive immunity with short-term O_3 exposures of **80-400 ppb**. Recent studies demonstrating altered immune responses and natural killer cell function build on prior evidence that O_3 can affect multiple aspects of innate and acquired immunity with short-term O_3 exposures as low as **80 ppb**.

Health Outcome	Conclusions from 2006 O_3 AQCD	Conclusions from 2011 2nd Draft ISA
Allergic and asthma related responses	Previous toxicological evidence indicated that O_3 exposure skews immune responses toward an allergic phenotype, and enhances the development and severity of asthma-related responses such as AHR.	Recent studies in human subjects demonstrate enhanced allergic cytokine production in atopic individuals and asthmatics, increased IgE receptors in atopic asthmatics, and enhanced markers of innate immunity and antigen presentation in health subjects or atopic asthmatics with short-term exposure to **80-400 ppb** O_3, all of which may enhance allergy and/or asthma. Further evidence for O_3-induced allergic skewing is provided by a few recent studies in rodents using exposure concentrations as low as **200 ppb**.
Hospital admissions, ED visits, and physician visits	Aggregate population time-series studies observed that ambient O_3 concentrations are positively and robustly associated with respiratory-related hospitalizations and asthma ED visits during the warm season.	Strong evidence demonstrated associations of ambient O_3 with respiratory hospital admissions and ED visits in the U.S., Europe, and Canada with supporting evidence from single city studies. Generally, these studies had mean 8-h max O_3 concentrations less than **60 ppb**.
Respiratory Mortality	Aggregate population time-series studies specifically examining mortality from respiratory causes were limited in number and showed inconsistent associations between acute exposure to ambient O_3 exposure and respiratory mortality.	Recent multicity time-series studies and a multicontinent study consistently demonstrated associations between ambient O_3 and respiratory-related mortality visits across the U.S., Europe, and Canada with supporting evidence from single city studies. Generally, these studies had mean 8-h max O_3 concentrations less than **63 ppb**.
Cardiovascular effects	The limited evidence is highly suggestive that O_3 directly and/or indirectly contributes to cardiovascular-related morbidity, but much remains to be done to more fully substantiate the association.	Suggestive of a Causal Relationship
Central nervous system effects	Toxicological studies report that acute exposures to O_3 are associated with alterations in neurotransmitters, motor activity, short- and long-term memory, sleep patterns, and histological signs of neurodegeneration.	Suggestive of a Causal Relationship
Mortality	The evidence is highly suggestive that O_3 directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality.	Likely to be a Causal Relationship
Long-term Exposure to O_3		
Respiratory effects	The current evidence is suggestive but inconclusive for respiratory health effects from long-term O_3 exposure.	Likely to be a Causal Relationship
New onset asthma	No studies at this time.	Evidence for a relationship between different genetic variants (HMOX, GST, ARG) that, in combination with O_3 exposure, are related to new onset asthma. These results were observed when subjects living in areas where the mean annual 8-h max O_3 concentration was **55.2 ppb**, compared to those who lived where it was **38.4 ppb**.
Asthma hospital admissions	No studies at this time.	Chronic O_3 exposure was related to first childhood asthma hospital admissions in a positive concentration-response relationship. Generally, these studies had mean annual 8-h max O_3 concentrations less than **41 ppb**.
Pulmonary structure and function	Epidemiologic studies observed that reduced lung function growth in children was associated with seasonal exposure to O_3; however, cohort studies of annual or multiyear O_3 exposure observed little clear evidence for impacts of longer-term, relatively low-level O_3 exposure on lung function development in children. Animal toxicological studies reported chronic O_3-induced structural alterations in several regions of the respiratory tract including the centriacinar region. Morphologic evidence from studies using exposure regimens that mimic seasonal exposure patterns report increased lung injury compared to conventional chronic stable exposures.	Evidence for pulmonary function effects is inconclusive, with some new epidemiologic studies (mean annual 8-h max O_3 concentrations less than **65 ppb**). Information from toxicological studies indicates that long-term maternal exposure during gestation (**100 ppb**) or development (**500 ppb**) can result in irreversible morphological changes in the lung, which in turn can influence pulmonary function.
Pulmonary inflammation, injury and oxidative stress	Extensive human clinical and animal toxicological evidence, together with limited epidemiologic evidence available, suggests a causal role for O_3 in inflammatory responses in the airways.	Several epidemiologic studies (mean 8-h max O_3 concentrations less than **69 ppb**) and toxicology studies (as low as **500 ppb**) add to observations of O_3-induced inflammation and injury.

Health Outcome	Conclusions from 2006 O_3 AQCD	Conclusions from 2011 2nd Draft ISA
Lung host defenses	Toxicological studies provided evidence that chronic O_3 exposure as low as 100 ppb can cause increases in susceptibility to infectious diseases due to modulation of lung host defenses, but do not cause greater effects on infectivity than short exposures.	Consistent with decrements in host defenses observed in rodents exposed to **100 ppb** O_3, recent evidence demonstrates a decreased ability to respond to pathogenic signals in infant monkeys exposed to **500 ppb** O_3.
Allergic responses	Limited epidemiologic evidence supported an association between ambient O_3 and allergic symptoms. Little if any information was available from toxicological studies.	Evidence relates positive outcomes of allergic response and O_3 exposure but with variable strength for the effect estimates; exposure to O_3 may increase total IgE in adult asthmatics. Allergic indicators in monkeys were increased by exposure to O_3 concentrations of **500 ppb**.
Respiratory mortality	Studies of cardio-pulmonary mortality were insufficient to suggest a causal relationship between chronic O_3 exposure and increased risk for mortality in humans.	A single study demonstrated that exposure to O_3 (long-term mean O_3 less than **104 ppb**) elevated the risk of death from respiratory causes and this effect was robust to the inclusion of $PM_{2.5}$.
Cardiovascular Effects	No studies at this time.	Suggestive of a Causal Relationship
Reproductive and developmental effects	Limited evidence for a relationship between air pollution and birth-related health outcomes, including mortality, premature births, low birth weights, and birth defects, with little evidence being found for O_3 effects.	Suggestive of a Causal Relationship
Central nervous system effects	Toxicological studies reported that acute exposures to O_3 are associated with alterations in neurotransmitters, motor activity, short and long term memory, sleep patterns, and histological signs of neurodegeneration. Evidence regarding chronic exposure and neurobehavioral effects was not available.	Suggestive of a Causal Relationship
Cancer	Little evidence for a relationship between chronic O_3 exposure and increased risk of lung cancer.	Inadequate to infer a Causal Relationship
Mortality	There is little evidence to suggest a causal relationship between chronic O_3 exposure and increased risk for mortality in humans.	Suggestive of a Causal Relationship

2.6.1 Respiratory Effects

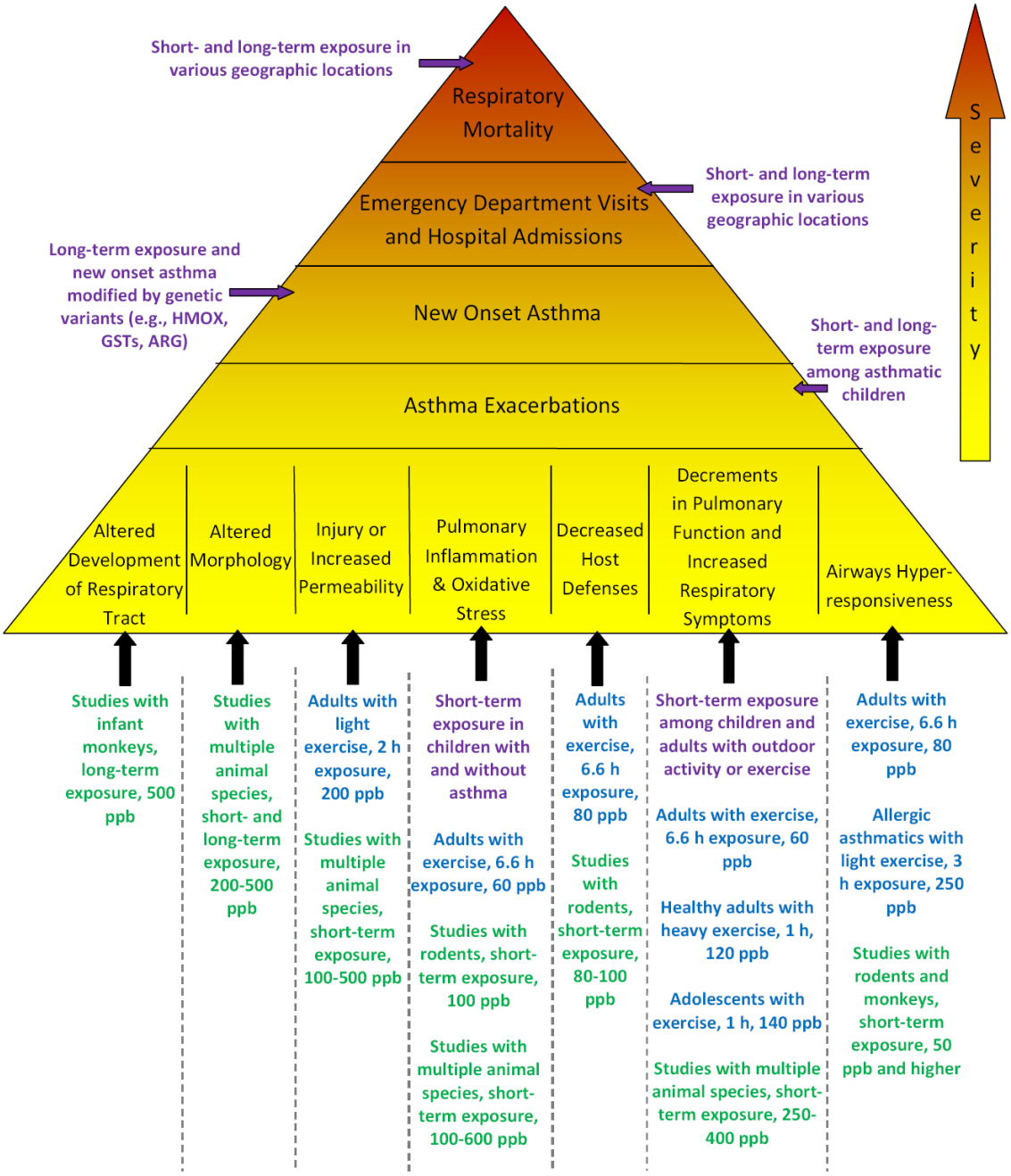
The clearest evidence for health effects associated with exposure to O_3 is provided by studies of respiratory effects. Collectively, there is a vast amount of evidence spanning several decades that supports a causal association between exposure to O_3 and a continuum of respiratory effects (Figure 2-3). The majority of this evidence is derived from studies investigating short-term exposure (i.e., hours to weeks) to O_3, although animal toxicological studies and recent epidemiologic evidence demonstrate that long-term exposure (i.e., months to years) may also be detrimental to the respiratory system.

The 2006 O_3 AQCD concluded that there was clear, consistent evidence of a causal relationship between short-term exposure to O_3 and respiratory health effects (U.S. EPA, 2006b). This causal association was substantiated by the coherence of effects observed across controlled human exposure, epidemiologic, and toxicological studies indicating associations of short-term O_3 exposures with a range of respiratory health endpoints from respiratory tract inflammation to respiratory emergency department (ED) visits and hospital admissions. Across disciplines, short-term O_3 exposures induced or were associated with statistically significant declines in lung function. An equally strong body

of evidence from controlled human exposure and toxicological studies demonstrated O_3-induced inflammatory responses, increased epithelial permeability, and airway hyperresponsiveness (both specific and nonspecific). Toxicological studies provided additional evidence for O_3-induced impairment of host defenses. Combined, these findings from experimental studies provided support for epidemiologic evidence, in which short-term O_3 exposure was consistently associated with increases in respiratory symptoms and asthma medication use in asthmatic children, respiratory-related hospital admissions, and asthma-related ED visits. Although O_3 was consistently associated with non-accidental and cardiopulmonary mortality, the contribution of respiratory causes to these findings was uncertain. The combined evidence across disciplines supports a causal relationship between short-term O_3 exposure and respiratory effects.

Mechanistic evidence for the effects of O_3 on the respiratory system was characterized in the 1996 O_3 AQCD, which identified O_3-induced changes in a variety of lung lipid species whose numerous biologically active metabolites, in turn, can affect host defenses, lung function, and the immune system. As summarized in Section 2.5 and fully characterized in Chapter 5, key events in the toxicity pathway of O_3 have been identified in humans and animal models. They include activation of neural reflexes, initiation of inflammation, alteration of epithelial barrier function, sensitization of bronchial smooth muscle, modification of innate/adaptive immunity, airway remodeling, and systemic inflammation and oxidative/nitrosative stress.

As demonstrated in Figure 2-3, O_3 is associated with a continuum of respiratory effects, including altered development of the respiratory tract. Recent toxicological studies of long-term exposure to O_3 occurring throughout various lifestages, beginning with prenatal and early life exposures, provide novel evidence for effects on the development of the respiratory system, including ultrastructural changes in bronchiole development, effects on the developing immune system, and increased offspring airway hyper-reactivity (Section 7.4.7. The strongest evidence for O_3-induced effects on the developing lung comes from a series of experiments using infant rhesus monkeys episodically exposed to 500 ppb O_3 for approximately 5 months, starting at one month of age. Functional changes in the conducting airways of infant rhesus monkeys exposed to either O_3 alone or O_3 + antigen were accompanied by a number of cellular and morphological changes. In addition to these functional and cellular changes, significant structural changes in the respiratory tract were observed. Importantly, the O_3-induced structural pathway changes persisted after recovery in filtered air for six months after cessation of the O_3 exposures. Exposure to O_3 has also been associated with similar types of alterations in pulmonary structure, including airway remodeling and pulmonary injury and increased permeability, in all adult laboratory animal species studied, from rats to monkeys (U.S. EPA, 1996a).



Green=Animal Toxicological Studies; Blue=Controlled Human Exposure Studies; Purple=Epidemiologic Studies; AM=Alveolar Macrophage.

Figure 2-3 Snapshot of evidence for the association of O_3 with the continuum of respiratory effects, including sub-clinical effects (bottom level of the pyramid) and clinical effects, increasing in severity moving up the pyramid.

In addition to effects on the development and structure of the respiratory tract, there is extensive evidence for the effects of short-term exposure to O_3 on pulmonary inflammation and oxidative stress. Previous evidence from controlled human exposure studies indicated that O_3 causes an inflammatory response in the lungs (U.S. EPA, 1996a). This inflammatory response to O_3 was detected after a single 1-h exposure with exercise to O_3 concentrations of 300 ppb; the increased levels of some inflammatory cells and mediators persisted for at least 18 hours. Toxicological studies provided additional evidence for increases in permeability and inflammation in rabbits at levels as low as 100 ppb O_3. Evidence summarized in the 2006 O_3 AQCD demonstrated that inflammatory responses were observed subsequent to 6.6 hours O_3 exposure to the lowest tested level of 80 ppb in healthy human adults, while toxicological studies provided extensive evidence that short-term (1-3 hours) O_3 exposure in the range of 100-500 ppb could cause lung inflammatory responses. The limited epidemiologic evidence reviewed in the 2006 O_3 AQCD demonstrated an association between short-term ambient O_3 exposure and airway inflammation in children (1-h max O_3 of approximately 100 ppb). Recent studies in animals and in vitro models described inflammatory and injury responses mediated by toll-like receptors (e.g., TLR4, TLR2), receptors for TNF or IL-1, multiple signaling pathways (e.g., p38, JNK, NFκB, MAPK/AP-1), and oxidative stress (Section 6.2.3.3). The most recent epidemiologic studies provide additional supporting evidence by demonstrating associations of ambient O_3 with mediators of airway inflammation and indicating that populations with diminished antioxidant capacity may have increased susceptibility to pulmonary inflammation and oxidative stress associated with O_3 exposure (Sections 6.2.4 and 8.1).

The normal inflammatory response in lung tissue is part of host defense that aids in removing microorganisms or particles that have reached the distal airways and alveolar surface. The 1996 O_3 AQCD concluded that short-term exposure to elevated concentrations of O_3 resulted in alterations in these host defense mechanisms in the respiratory system. Specifically, toxicological studies of short-term exposures as low as 100 ppb O_3 were shown to decrease the ability of alveolar macrophages to ingest particles, and short-term exposures as low as 80 ppb for 3 hours prevented mice from resisting infection with streptococcal bacteria and resulted in infection-related mortality. Similarly, alveolar macrophages removed from the lungs of human subjects after 6.6 hours of exposure to 80 and 100 ppb O_3 had decreased ability to ingest microorganisms, indicating some impairment of host defense capability. These altered host defense mechanisms can lead to susceptibility to respiratory infections, which are associated with increased risk of developing asthma when occurring in early life. Despite the strong toxicological evidence, in the limited body of epidemiologic evidence, O_3 exposure has not been consistently associated with hospital admissions or ED visits for respiratory infection, pneumonia, or influenza (Sections 6.2.7.2 and 6.2.7.3).

The most commonly observed and strongest evidence for respiratory effects associated with short-term exposure to O_3 is transient decrements in pulmonary function. Controlled human exposure studies characterized in previous NAAQS reviews demonstrated O_3-induced decrements in pulmonary function, characterized by alterations in lung volumes and flow and airway resistance and responsiveness for multihour exposures (up to 8 hours) to O_3 concentrations as low as 80 ppb (U.S. EPA, 1996a). A series of mobile laboratory studies of lung function and respiratory symptoms reported pulmonary function decrements at mean ambient O_3 concentrations of 140 ppb in exercising healthy adolescents and increased respiratory symptoms and pulmonary function decrements at 150 ppb in heavily exercising athletes and at 170 ppb in lightly exercising healthy and asthmatic subjects. Epidemiologic and animal toxicological evidence is coherent with the results of the controlled human exposure studies, both indicating decrements in lung function upon O_3 exposure. A combined statistical analysis of epidemiologic studies in children at summer camp demonstrated decrements in FEV_1 of 0.50 mL/ppb with previous hour O_3 concentration. For preadolescent children exposed to 120 ppb ambient O_3, this amounted to an average decrement of 2.4-3.0% in FEV_1. Key studies of lung function measurements (FEV_1) taken before and after well-defined outdoor exercise events in adults yielded exposure-response slopes of 0.40 and 1.35 mL/ppb ambient O_3 after exposure for up to 1 hour. Animal toxicological studies reported similar respiratory effects in rats at exposures as low as 200 ppb O_3 for 3 hours. The 2006 O_3 AQCD characterized the controlled human exposure and animal toxicological studies as providing clear evidence of causality for the associations observed between short-term ($\leq$ 24 hours) O_3 exposure and relatively small, but statistically significant declines in lung function observed in numerous recent epidemiologic studies. Declines in lung function were particularly noted in children, asthmatics, and adults who work or exercise outdoors.

Recent controlled human exposure studies examined lower concentration O_3 exposures (40-80 ppb) and demonstrated that FEV_1, respiratory symptoms, and inflammatory responses were affected by O_3 exposures of 6.6 hours and in the range of 60 to 80 ppb (Section 6.2.1.1 and 6.2.3.1). These studies demonstrated average decreases in FEV_1 in the range of 2.8 to 3.6% with O_3 exposures 6.6 hours in duration and as low as 60 ppb in concentration. However, considerable intersubject variability has been reported with some subjects experiencing considerably greater decrements than average. Recent epidemiologic studies provide greater insight into subject factors that may increase susceptibility for O_3-associated respiratory morbidity. It was in these potentially susceptible populations (e.g., individuals with asthma with concurrent respiratory infection, older adults with AHR or elevated body mass index, or groups with diminished antioxidant capacity) that O_3-associated decreases in lung function were consistently observed.

In addition to alterations in lung volumes and flow, changes in pulmonary function due to exposure to O_3 may manifest as respiratory symptoms (e.g., coughing, wheezing, shortness of breath). The 1996 O_3 AQCD identified an association between respiratory symptoms and increasing ambient O_3, particularly among asthmatic children. In the 2006 O_3 AQCD, symptoms of cough and pain on deep inspiration were well documented in young healthy adult subjects after exposure of ≥80 ppb O_3 for 6-8 hours during moderate exercise. Limited data suggested an increase in respiratory symptoms down to 60 ppb. More recently, these effects have been observed at 70 ppb in healthy adults. Controlled human exposure studies of healthy adults, have also reported an increased incidence of cough with O_3 exposures as low as 120 ppb and 1-3 hours in duration with very heavy exercise. The controlled human exposure studies also demonstrated lesser respiratory symptom responses in children and older adults relative to young healthy adults. Previous epidemiologic evidence showed significant associations between short-term exposure to ambient O_3 and increases in a wide variety of respiratory symptoms (e.g., cough, wheeze, production of phlegm, and shortness of breath) in asthmatic children (U.S. EPA, 2006b). Epidemiologic studies also indicated that short-term O_3 exposure is likely associated with increased asthma medication use in asthmatic children. Similar to what was observed for pulmonary function, recent epidemiologic studies provided insight into additional subject factors that may increase susceptibility for O_3-associated respiratory symptoms. It was in these potentially susceptible populations (e.g., asthmatics with diminished antioxidant capacity and infants with asthmatic mothers) where the recent evidence of O_3-associated increases in respiratory symptoms was the strongest. Additionally, recent epidemiologic studies provide evidence for an association between long-term exposure to O_3 and respiratory symptoms (Section 7.2.2).

Ozone exposure has been shown to result in both specific and non-specific airway hyperresponsiveness. Increased airway responsiveness is an important consequence of exposure to O_3 because its presence represents a change in airway smooth muscle reactivity and implies that the airways are predisposed to narrowing on inhalation of a variety of stimuli (e.g., specific allergens, SO_2, cold air). Specifically, short-term (2 or 3 hours) exposure to 250 or 400 ppb O_3 was found to cause increases in airway responsiveness in response to allergen challenges among allergic asthmatic subjects who characteristically already had somewhat increased airway responsiveness at baseline. Increased non-specific airway responsiveness has been demonstrated in healthy young adults down to 80 ppb O_3 following 6.6 hours of exposure during moderate exercise. While AHR has not been widely examined in epidemiologic studies, findings for O_3-induced increases in AHR in controlled human exposure (Section 6.2.2.1) and toxicological (Section 6.2.2.2) studies provide biological plausibility for associations observed between ambient O_3 exposure and increases in respiratory symptoms in subjects with asthma.

In addition to asthma exacerbations, recent epidemiologic evidence has revealed an association between long-term exposure to O_3 and new onset asthma (Section 7.2.1, Table 7-2). The new epidemiologic evidence base consists of studies using a variety of designs and analysis methods evaluating the relationship between long-term annual measures of exposure to ambient O_3 and measures of respiratory morbidity conducted by different research groups in different locations. Studies from two California cohorts have provided evidence for a relationship between different variants in genes related to oxidative or nitrosative stress (e.g., *HMOX, GSTs, ARG*) that, in combination with O_3 exposure, are related to new onset asthma. This is the first time that evidence has extended beyond the association of exposure to O_3 and asthma exacerbations to suggest that long-term exposure to O_3 may play a role in the development of the disease and contribute to incident cases of asthma.

When respiratory symptoms, asthma exacerbations, or other respiratory diseases become too serious to be cared for at home, they can result in ED visits or hospital admissions. The frequency of these types of ED visits and hospital admissions is associated with short-term changes in ambient O_3 concentrations. Summertime daily hospital admissions for respiratory causes in various locations of eastern North America were consistently associated with ambient levels of O_3 in studies reviewed in the 1996 O_3 AQCD. This association remained even when considering only concentrations below 120 ppb O_3. The 2006 O_3 AQCD concluded that aggregate population time-series studies demonstrate a positive and robust association between ambient O_3 concentrations and respiratory-related hospitalizations and asthma ED visits during the warm season. Recent epidemiologic time-series studies that include additional multicity studies and a multicontinent study further support that short-term exposures to ambient O_3 concentrations are consistently associated with increases in respiratory hospital admissions and ED visits specifically during the warm/summer months in multiple geographic locations and across a range of O_3 concentrations (Section 6.2.7). There is also recent evidence for an association between respiratory hospital admissions and long-term exposure to O_3 (Section 7.2.2).

Finally, O_3 exposure may contribute to death from respiratory causes. Recent evidence from several multicity studies and a multicontinent study demonstrate consistent positive associations between short-term exposure to ambient O_3 concentrations and increases in respiratory mortality (Section 6.6.2.5). Similarly, a study of long-term exposure to ambient O_3 concentrations also demonstrated an association between O_3 and increases in respiratory mortality (Section 7.7.1). Evidence from these recent mortality studies is consistent and coherent with the evidence from epidemiologic, controlled human exposure, and animal toxicological studies for the effects of short- and long-term exposure to O_3 on respiratory effects. Additionally, the evidence for respiratory morbidity

after short- and long-term exposure provides biological plausibility for mortality due to respiratory disease.

In summary, recent studies support or build upon the strong body of evidence presented in the 1996 and 2006 O_3 AQCDs that short-term O_3 exposure is causally associated with adverse respiratory health effects. Recent controlled human exposure studies demonstrate statistically significant group mean decreases in pulmonary function to exposures as low as 60-70 ppb O_3 in young, healthy adults. Equally strong evidence demonstrated associations of ambient O_3 with respiratory hospital admissions and ED visits across the U.S., Europe, and Canada. Most effect estimates ranged from a 1.6 to 5.4% increase in daily all respiratory-related ED visits or hospital admissions in all-year analyses for standardized increases in ambient O_3 concentrations. Several multicity studies and a multicontinent study reported associations between short-term exposure to ambient O_3 concentrations and increases in respiratory mortality. This evidence is supported by individual-level epidemiologic studies that provide new evidence for associations of ambient O_3 with mediators of airway inflammation and oxidative stress, and across endpoints, they indicate that groups with diminished antioxidant capacity or comorbidities such as atopy, AHR, or elevated body mass index may have increased susceptibility to respiratory morbidity associated with O_3 exposure. The potential susceptibility of these populations identified in recent epidemiologic studies are strongly supported by findings from experimental studies that demonstrated O_3-induced decreases in intracellular antioxidant levels, increases in airway responses with co-exposures to allergens, and increases in airway responses in animal models of obesity. By demonstrating O_3-induced airway hyperresponsiveness, decreased pulmonary function, allergic responses, lung injury, impaired host defense, and airway inflammation, toxicological studies have characterized O_3 modes of action and have provided biological plausibility for epidemiologic associations of ambient O_3 exposure with lung function and respiratory symptoms, hospital admissions, ED visits, and mortality. Together, the evidence integrated across controlled human exposure, epidemiologic, and toxicological studies and across the spectrum of respiratory health endpoints continues to demonstrate that **there is a causal relationship between short-term O_3 exposure and respiratory health effects.**

The strongest evidence for a relationship between long-term O_3 exposure and respiratory morbidity is contributed by recent studies from a single cohort demonstrating associations between long-term measures of O_3 exposure and new-onset asthma in children and increased respiratory symptom effects in asthmatics. While the evidence is limited, this U.S. multicommunity prospective cohort demonstrates that asthma risk is affected by interactions among genetic variability, environmental O_3 exposure, and behavior. Other recent studies provide coherent evidence for long-term O_3 exposure and

respiratory morbidity effects such as first asthma hospitalization and respiratory symptoms in asthmatics. Generally, the epidemiologic and toxicological evidence provides a compelling case that supports the hypothesis that a relationship exists between long-term exposure to ambient O_3 and measures of respiratory morbidity. The evidence for short-term exposure to O_3 and effects on respiratory endpoints provides coherence and biological plausibility for the effects of long-term exposure to O_3. Building upon that evidence, the more recent epidemiologic evidence, combined with toxicological studies in rodents and non-human primates, provides biologically plausible evidence that **there is likely to be a causal relationship between long-term exposure to O_3 and respiratory health effects.**

2.6.2 Mortality Effects

The 2006 O_3 AQCD concluded that the overall body of evidence was highly suggestive that short-term exposure to O_3 directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality, but additional research was needed to more fully establish underlying mechanisms by which such effects occur. The evaluation of new multicity studies that examined the association between short-term O_3 exposure and mortality found evidence which supports the conclusions of the 2006 O_3 AQCD. These new studies reported consistent positive associations between short-term O_3 exposure and total (nonaccidental) mortality, with associations being stronger during the warm season, as well as additional support for associations between O_3 exposure and cardiovascular mortality being similar or larger in magnitude compared to respiratory mortality. Additionally, these new studies examined previously identified areas of uncertainty in the O_3-mortality relationship. Taken together, the body of evidence indicates that **there is likely to be a causal relationship between short-term exposures to O_3 and all-cause mortality.**

The 2006 O_3 AQCD concluded that an insufficient amount of evidence existed "to suggest a causal relationship between chronic O_3 exposure and increased risk for mortality in humans" (U.S. EPA, 2006b). Several additional studies have been conducted since the last review, an ecologic study that finds no association between mortality and O_3, and a reanalysis of the ACS cohort that specifically points to a relationship between long-term O_3 exposure and an increased risk of respiratory mortality. The findings from the reanalysis of the ACS study are consistent and coherent with the evidence from epidemiologic, controlled human exposure, and animal toxicological studies for the effects of short- and long-term exposure to O_3 on respiratory effects. Additionally, the evidence for short- and long-term respiratory morbidity provides biological plausibility

for mortality due to respiratory disease. Collectively, the evidence **is suggestive of a causal relationship between long-term O_3 exposures and mortality.**

2.6.3 Cardiovascular Health Effects

In past O_3 AQCDs the effects of short- and long-term exposure to O_3 on the cardiovascular system could not be thoroughly evaluated due to the paucity of information available. However, studies investigating O_3-induced cardiovascular events have advanced in the last two decades. Overall, there is limited, inconsistent evidence for cardiovascular morbidity in epidemiologic studies examining both short- and long-term exposure to O_3. Positive associations between short-term O_3 exposure and cardiovascular mortality have been consistently reported in multiple epidemiologic studies. Animal toxicological studies provide more evidence for both short- and long-term O_3 exposure leading to cardiovascular morbidity. The toxicological studies demonstrate O_3-induced cardiovascular effects, specifically enhanced atherosclerosis and ischemia/reperfusion injury with or without the corresponding development of a systemic oxidative, pro-inflammatory environment, disrupted NO-induced vascular reactivity, decreased cardiac function, and increased HRV. Taking into consideration the positive toxicological studies and evidence for an association between O_3 exposure and cardiovascular mortality, the generally limited body of evidence **is suggestive of a causal relationship for both relevant short- and long-term exposures to O_3 and cardiovascular effects.**

2.6.4 Central Nervous System Effects

In rodents, O_3 exposure has been shown to cause physicochemical changes in the brain indicative of oxidative stress and inflammation. Recent toxicological studies add to earlier evidence that short- and long-term exposures to O_3 can produce a range of effects on the central nervous system and behavior. Previously observed effects, including neurodegeneration, alterations in neurotransmitters, short- and long-term memory, and sleep patterns, have been further supported by recent studies. In instances where pathology and behavior are both examined, animals exhibit decrements in behaviors tied to the brain regions or chemicals found to be affected or damaged. The single epidemiologic study conducted showed that long-term exposure to O_3 affects memory in humans as well. Notably, exposure to O_3 levels as low as 250 ppb has resulted in progressive neurodegeneration and deficits in both short- and long-term memory in rodents. Additionally, changes in the CNS, including biochemical, cellular, and behavioral effects, have been observed in animals whose sole exposure occurred *in utero*, at levels as a low as 300 ppb. Together the evidence from studies of short- and long-term

exposure to O_3 **is suggestive of a causal relationship between O_3 exposure and adverse CNS effects.**

2.6.5 Reproductive and Developmental Effects

There is limited though positive toxicological evidence for O_3-induced developmental effects, including effects on pulmonary structure and function and central nervous system effects after developmental exposure to O_3. Limited epidemiologic evidence exists for an association with O_3 concentration and decreased sperm concentration. A recent toxicological study provides limited evidence for a possible biological mechanism (histopathology showing impaired spermatogenesis and rescue with antioxidants) for such an association. Additionally, though the evidence for an association between O_3 concentrations and adverse birth outcomes is generally inconsistent, there are several influential studies that indicate an association with reduced birth weight and restricted fetal growth. Overall, the evidence **is suggestive of a causal relationship between long-term exposures to O_3 and reproductive and developmental effects.**

2.6.6 Cancer and Mutagenicity and Genotoxicity

The 2006 O_3 AQCD reported that evidence did not support ambient O_3 as a pulmonary carcinogen. Since the 2006 O_3 AQCD, very few epidemiologic and toxicological studies have been published that examine O_3 as a carcinogen, but collectively, study results indicate that O_3 may contribute to DNA damage. Overall, the evidence **is inadequate to determine if a causal relationship exists between ambient O_3 exposures and cancer.**

2.6.7 Policy Relevant Considerations

2.6.7.1 Populations at Increased Risk

Upon evaluating the association between short- and long-term exposure to O_3 and various health outcomes, studies also attempted to identify populations that are at increased risk for O_3-related health effects. These studies did so by conducting stratified epidemiologic analyses; by examining individuals with an underlying health condition, genetic polymorphism, or categorized by age, race, or sex in controlled human exposure studies; or by developing animal models that mimic the pathophysiological conditions associated with an adverse health effect. These studies identified a multitude of factors that could

potentially contribute to whether an individual is at increased risk for O_3-related health effects. The examination of at risk populations for O_3 exposure allows for the NAAQS to provide an adequate margin of safety for both the general population and for sensitive populations.

The populations identified in Chapter 8 that are most at risk for O_3-related health effects are individuals with influenza/infection, individuals with asthma, and younger and older age groups. There were a small number of studies on influenza/infection but both reported influenza/infection to modify the association between O_3 exposure and respiratory effects, with individuals having influenza or an infection being at increased risk. Asthma as a factor affecting risk was supported by controlled human exposure and toxicological studies, as well as some evidence from epidemiologic studies. Most studies comparing age groups reported greater effects of short-term O_3 exposure on mortality among older adults, although studies of other health outcomes had inconsistent findings regarding whether older adults were at increased risk. Generally, studies of age groups also reported positive associations for respiratory hospital admissions and ED visits among children. Biological plausibility for this increased risk is supported by toxicological and clinical research. Diet and obesity are also both likely factors that affect risk. Multiple epidemiologic, controlled human exposure, and toxicological studies reported that diets deficient in vitamins E and C are associated with risk of O_3 -related health effects. Similarly, studies of effect measure modification by body mass index (BMI) observed greater O_3 -related respiratory decrements for individuals who were obese.

Other potential factors [preexisting conditions (such as chronic obstructive pulmonary disease and cardiovascular disease), sex, and multiple genes (such as *GSTM1, GSTP1, HMOX-1, NQO1,* and *TNF-α)*] provided some evidence of susceptibility, but further investigation is warranted. In addition, examination of modification of the associations between O_3 exposure and health effects by SES and race were available in a limited number of studies, and demonstrated possible increased odds of health effects related to O_3 exposure among those with low SES and black race.

Individuals with increased ambient exposure were examined in a recent study of outdoor workers, in which no effect modification was observed, and in studies of air conditioning prevalence, which demonstrated inconsistent findings. However, previous evidence along with biological plausibility from toxicological and controlled human studies has shown individuals exposed to more outdoor air to be at increased risk of O_3-related health effects. Studies of physical conditioning and smoking were conducted but little evidence was available to determine whether increased risk of O_3-related health effects is present for these factors. The only studies examining effect measure modification by diabetes

examined O_3 exposure and cardiovascular outcomes and none reported increased risks for individuals with diabetes. Toxicological studies also identified hyperthyroidism to be a factor warranting further examination. Future research will provide additional insight into whether these factors affect risk of O_3-related health effects.

2.6.7.2 Lag Structure in Epidemiologic Studies

Epidemiologic studies have attempted to identify the time-frame in which exposure to O_3 can impart a health effect. Although O_3 exposure-response relationships have traditionally been examined using air quality data for a defined lag period (e.g., 1 day or average of 0-1 days), the relationship can potentially be influenced by a multitude of factors, such as the underlying susceptibility of an individual (e.g., age, pre-existing diseases), which could increase or decrease the lag times observed. Different lag times have been evaluated for specific health outcomes.

The epidemiologic evidence evaluated in the 2006 O_3 AQCD indicated that one of the remaining uncertainties in characterizing the O_3-mortality relationship was identifying the appropriate lag structure (e.g., single-day lags versus distributed lag model). An examination of lag times used in the epidemiologic studies evaluated in this assessment can provide further insight on the relationship between O_3 exposure and morbidity and mortality outcomes.

Collectively, recent epidemiologic studies of lung function, respiratory symptoms, and biological markers of airway inflammation and oxidative stress examined associations with single-day ambient O_3 exposures (using various averaging times) lagged from 0 to 7 days as well as concentrations averaged over 2 to 19 days. Lags of 0 and 1 day ambient O_3 exposures were associated with decreases in lung function and increases in respiratory symptoms, airway inflammation, and oxidative stress. Additionally, several studies found that multiday averages of O_3 exposure were associated with these endpoints, indicating that not only single day, but exposures accumulated over several days led to a respiratory health effect. In studies of respiratory hospital admissions and ED visits, investigators either examined the lag structure of associations by including both single-day and the average of multiday lags, or selecting lags a priori. Of the studies evaluated, the collective evidence indicates a rather immediate response within the first few days of O_3 exposure (i.e., for lags days averaged at 0-1, 0-2, and 0-3 days) for hospital admissions and ED visits for all respiratory outcomes, asthma, and chronic obstructive pulmonary disease in all-year and seasonal analyses.

The majority of epidemiologic studies that focused on the association between short-term O_3 exposure and mortality (i.e., all-cause, respiratory and cardiovascular) examined the

average of multiday lags with some studies examining single-day lags. Across a range of multiday lags (i.e., average of 0-1 to 0-6 days), the studies evaluated consistently demonstrate that the O_3 effects on mortality occur within a few days of exposure (Figure 6-28). Additionally, several recent studies have conducted more extensive analysis of lag structure to investigate "mortality displacement" (i.e., deaths are occurring in frail individuals and exposure is only moving the day of death to a day slightly earlier), which also inform upon the lag structure of associations (Section 6.6.2.4). Collectively, these studies suggest that the positive associations between O_3 and mortality are observed mainly in the first few days after exposure.

2.6.7.3 Ozone Concentration-Response Relationship

An important consideration in characterizing the O_3-morbidity and mortality association is whether the C-R relationship is linear across the full concentration range that is encountered or if there are concentration ranges where there are departures from linearity (i.e., nonlinearity). In this ISA studies have been identified that attempt to characterize the shape of the O_3 C-R curve along with possible O_3 "thresholds" (i.e., O_3 levels which must be exceeded in order to elicit a health response). The controlled human exposure and epidemiologic studies that examined the shape of the C-R curve and the potential presence of a threshold have indicated a generally linear C-R function with no indication of a threshold for O_3 concentrations greater than 30 or 40 ppb, which corresponds with PRB and the lower bound of O_3 concentrations included in the C-R functions.

Controlled human exposure studies have provided strong and quantifiable C-R data on the human health effects of O_3. The magnitude of respiratory effects in these studies is generally a function of O_3 exposure, i.e., the product of concentration (C), minute ventilation (V_E), and exposure duration. Recent studies provide evidence for a smooth C-R curve without indication of a threshold in young healthy adults, exposed during moderate exercise for 6.6 hours to O_3 concentrations between 40 and 120 ppb (Figure 6-1).

Although relatively few epidemiologic studies have examined the O_3-health effects C-R relationship, the C-R relationship has been examined across multiple health endpoints and exposure durations. Some studies of populations engaged in outdoor activity found that associations between O_3 and lung function decrements persisted at lower O_3 concentrations (Table 6-5). For example, a study found ambient O_3 exposure (10-min to 1-h) during outdoor exercise to be associated with decreases in lung function in analyses restricted to concentrations less than 51 ppb, though effect estimates were near zero with O_3 concentrations less than 41 ppb. In contrast, a subsequent study found associations

persisted with 1-h max O_3 concentrations less than 40 ppb. A study examining the C-R relationship between short-term O_3 exposure and pediatric asthma ED visits found no evidence of a threshold. In both quintile and loess dose-response analyses this study found evidence that suggests that there are elevated associations for pediatric asthma ED visits with O_3 concentrations as low as 30 ppb (Figure 6-11). In an additional study, authors used a smooth function while also accounting for the potential confounding effects of $PM_{2.5}$, to examine whether the shape of the C-R curve for short-term exposure to O_3 and asthma hospital admissions (i.e., both general and ICU for all ages) is linear. When comparing the curve to a linear fit, the authors found that the linear fit is a reasonable approximation of the C-R relationship between O_3 and asthma hospital admissions around and below the current NAAQS (Figure 6-9). Although the C-R relationship between short-term O_3 exposure and respiratory-related hospital admissions and ED visits has not been extensively examined, these preliminary examinations indicate a linear, no threshold relationship between short-term O_3 exposure and pediatric asthma ED visits and asthma hospitalizations.

The O_3-health effects C-R relationship was further examined in studies of short-term O_3 exposure and mortality. Evaluation of the C-R relationship for short-term exposure to O_3 and mortality is difficult due to the evidence from multicity studies indicating highly heterogeneous O_3-mortality associations across regions of the U.S. In addition, there are numerous issues that may influence the shape of the O_3-mortality C-R relationship that need to be taken into consideration including: multiday effects (distributed lags), potential adaptation and mortality displacement (i.e., hastening of death by a short period). Several recent studies applied a variety of statistical approaches to examine the shape of the O_3-mortality C-R relationship and whether a threshold exists. These studies did not find any evidence that supports a threshold for the association between short-term exposure to O_3 and mortality within a range of O_3 concentrations observed in the U.S. Recent evidence also suggests that the shape of the O_3-mortality C-R curve remains linear across the full range of the O_3 concentrations. However, studies have also demonstrated heterogeneity in the O_3-mortality relationship across cities (or regions), which complicates the interpretation of a combined C-R curve and threshold analysis. Additionally, given the effect modifiers identified in mortality analyses that are also expected to vary regionally (e.g., temperature, air conditioning prevalence), a national or combined analysis may not be appropriate to identify whether a threshold exists in the O_3-mortality C-R relationship.

An evaluation of long-term exposure studies identified studies of long-term exposure to O_3 and birth outcomes that have characterized the C-R relationship. Evidence from the southern California Children's Health Study identified a C-R relationship of birth weight with 24-h avg O_3 concentrations averaged over the entire pregnancy that was clearest

above the 30 ppb level (Figure 7-4). Relative to the lowest decile of 24-h avg O_3, estimates for the next 5 lowest deciles were approximately -40 g to -50 g, with no clear trend and with 95% confidence bounds that included zero. The highest four deciles of O_3 exposure showed an approximately linear decrease in birth weight, and all four 95% CIs excluded zero, and ranged from mean decreases of 74 grams to decreases of 148 grams. Another study conducted in southern California reported increased risks for cardiac birth defects in a dose-response manner with second-month O_3 exposure.

Collectively, both short- and long-term exposure studies that examined the O_3-health effects C-R relationship have provided no evidence of a threshold. Additionally, these studies indicate a linear C-R relationship across the full range of O_3 concentrations observed in the U.S.

2.7 Integration of Effects on Vegetation and Ecosystems

Chapter 9 presents the most policy-relevant information related to this review of the NAAQS for the effects of O_3 on vegetation and ecosystems. This section integrates the key findings from the disciplines evaluated in this assessment of the O_3 scientific literature, which includes plant physiology, whole plant biology, ecosystems, and exposure-response.

Ozone effects at small spatial scales, such as the leaf of an individual plant, can result in effects at a continuum of larger spatial scales. Figure 2-4 is a simplified illustrative diagram of the major pathway through which O_3 enters leaves and the major endpoints O_3 may affect in vegetation and ecosystems. The sections of Chapter 9 are organized according to increasing spatial scales, starting with the cellular and subcellular level, then the whole plant and finally, ecosystem-level processes. Ozone enters leaves through stomata, and can alter stomatal conductance and disrupt CO_2 fixation (Section 9.3). These effects can change rates of leaf gas exchange, growth and reproduction at the individual plant level and result in changes in ecosystems, such as productivity, C storage, water cycling, nutrient cycling, and community composition (Section 9.4). The framework for causal determinations has been applied to the body of scientific evidence to collectively examine effects attributed to O_3 exposure (Table 2-2). The summary below provides brief integrated summaries of the evidence that supports the causal determinations. The detailed discussion of the underlying evidence used to formulate each causal determination can be found in Chapters 9. This summary ends with a short discussion of policy relevant considerations.

2.7.1 Visible Foliar Injury

Visible foliar injury resulting from exposure to O_3 has been well characterized and documented over several decades of research on many tree, shrub, herbaceous, and crop species (U.S. EPA, 2006b, 1996b, 1984, 1978a) (Section 9.4.2). Ozone-induced visible foliar injury symptoms on certain bioindicator plant species are considered diagnostic as they have been verified experimentally in exposure-response studies, using exposure methodologies such as continuous stirred tank reactors (CSTRs), open-top chambers (OTCs), and free-air fumigation. Experimental evidence has clearly established a consistent association of visible injury with O_3 exposure, with greater exposure often resulting in greater and more prevalent injury. Since the 2006 O_3 AQCD, several multiple-year field surveys of O_3-induced visible foliar injury have been conducted at National Wildlife Refuges in Maine, Michigan, New Jersey, and South Carolina. New sensitive species showing visible foliar injury continue to be identified from field surveys and verified in controlled exposure studies.

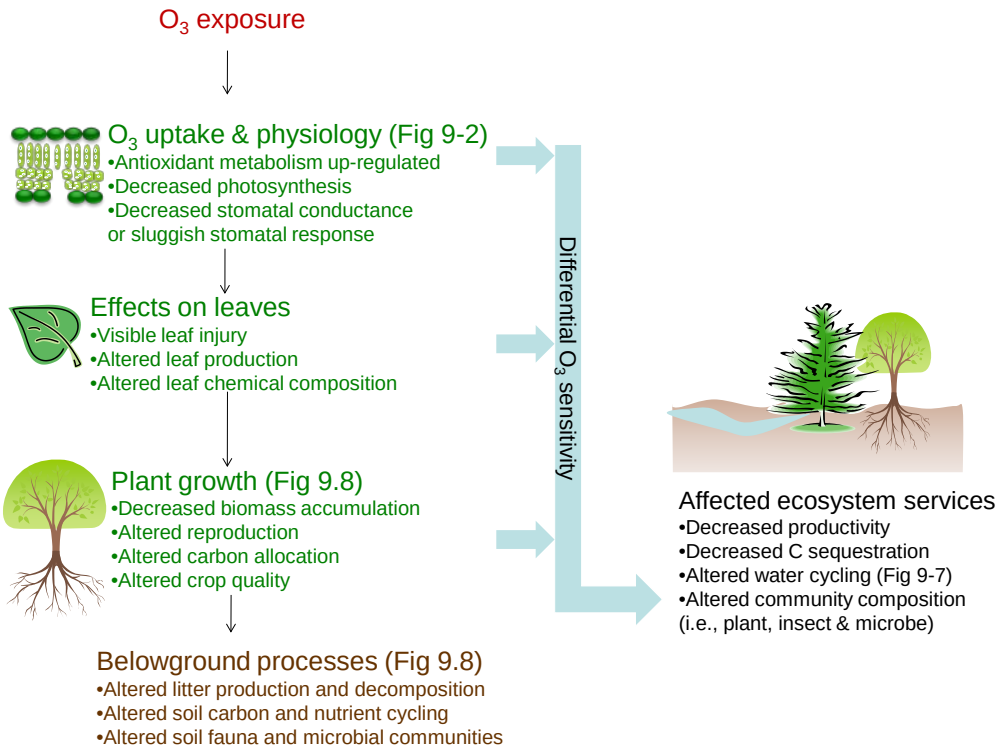


Figure 2-4 An illustrative diagram of the major pathway through which O_3 enters leaves and the major endpoints that O_3 may affect in plants and ecosystems.

Table 2-2 Summary of ozone causal determinations for vegetation and ecosystem effects

Vegetation and Ecosystem Effects	Conclusions from 2006 O_3 AQCD	Conclusions from 2011 2nd Draft ISA
Visible Foliar Injury Effects on Vegetation	Data published since the 1996 O_3 AQCD strengthen previous conclusions that there is strong evidence that current ambient O_3 concentrations cause impaired aesthetic quality of many native plants and trees by increasing foliar injury.	Causal Relationship
Reduced Vegetation Growth	Data published since the 1996 O_3 AQCD strengthen previous conclusions that there is strong evidence that current ambient O_3 concentrations cause decreased growth and biomass accumulation in annual, perennial and woody plants, including agronomic crops, annuals, shrubs, grasses, and trees.	Causal Relationship
Reduced Productivity in Terrestrial Ecosystems	There is evidence that O_3 is an important stressor of ecosystems and that the effects of O_3 on individual plants and processes are scaled up through the ecosystem, affecting net primary productivity.	Causal Relationship
Reduced Carbon (C) Sequestration in Terrestrial Ecosystems	Limited studies from previous review	Likely to be a Causal Relationship
Reduced Yield and Quality of Agricultural Crops	Data published since the 1996 O_3 AQCD strengthen previous conclusions that there is strong evidence that current ambient O_3 concentrations cause decreased yield and/or nutritive quality in a large number of agronomic and forage crops.	Causal Relationship
Alteration of Terrestrial Ecosystem Water Cycling	Ecosystem water quantity may be affected by O_3 exposure at the landscape level.	Likely to be a Causal Relationship
Alteration of Below-ground Biogeochemical Cycles	Ozone-sensitive species have well known responses to O_3 exposure, including altered C allocation to below-ground tissues, and altered rates of leaf and root production, turnover, and decomposition. These shifts can affect overall C and N loss from the ecosystem in terms of respired C, and leached aqueous dissolved organic and inorganic C and N.	Causal Relationship
Alteration of Terrestrial Community Composition	Ozone may be affecting above- and below -ground community composition through impacts on both growth and reproduction. Significant changes in plant community composition resulting directly from O_3 exposure have been demonstrated.	Likely to be a Causal Relationship

The use of biological indicators in field surveys to detect phytotoxic levels of O_3 is a longstanding and effective methodology. The USDA Forest Service through the Forest Health Monitoring (FHM) Program (1990-2001) and currently the Forest Inventory and Analysis (FIA) Program has been collecting data regarding the incidence and severity of visible foliar injury on a variety of O_3 sensitive plant species throughout the U.S. The network has provided evidence that O_3 concentrations were high enough to induce visible symptoms on sensitive vegetation. From repeated observations and measurements made over a number of years, specific geographical patterns of visible O_3 injury symptoms can be identified. In addition, a study assessed the risk of O_3-induced visible foliar injury on bioindicator plants in 244 national parks in support of the National Park Service's Vital Signs Monitoring Network. The results of the study demonstrated that the risk of visible foliar injury was high in 65 parks (27%), moderate in 46 parks (19%), and low in 131 parks (54%). Some of the well-known parks with a high risk of O_3-induced visible foliar injury include Gettysburg, Valley Forge, Delaware Water Gap, Cape Cod, Fire Island, Antietam, Harpers Ferry, Manassas, Wolf Trap Farm Park, Mammoth Cave, Shiloh,

Sleeping Bear Dunes, Great Smoky Mountains, Joshua Tree, Sequoia and Kings Canyon, and Yosemite. **Overall, evidence is sufficient to conclude that there is a causal relationship between ambient O_3 exposure and the occurrence of O_3-induced visible foliar injury on sensitive vegetation across the U.S.**

2.7.2 Growth, Productivity, Carbon Storage and Agriculture

Ambient O_3 concentrations have long been known to cause decreases in photosynthetic rates and plant growth. The O_3-induced damages at the plant scale may translate to the ecosystem scale, and cause changes in productivity and C storage. The effects of O_3 exposure on photosynthesis, growth, biomass allocation, ecosystem production and ecosystem C sequestration were reviewed for the natural ecosystems, and crop productivity and crop quality were reviewed for the agricultural ecosystems.

2.7.2.1 Natural Ecosystems

The previous O_3 AQCDs concluded that there is strong and consistent evidence that ambient concentrations of O_3 decrease plant photosynthesis and growth in numerous plant species across the U.S. Studies published since the last review continue to support that conclusion (Section 9.4.3.1). New studies, based on the Aspen free-air carbon-dioxide/ozone enrichment (FACE) experiment, found that O_3 caused reductions in total biomass relative to the control in aspen, paper birch, and sugar maple communities during the first seven years of stand development. Overall, the studies at the Aspen FACE experiment were consistent with the open-top chamber (OTC) studies that were the foundation of previous O_3 NAAQS reviews. These results strengthen our understanding of O_3 effects on forests and demonstrate the relevance of the knowledge gained from trees grown in open-top chamber studies.

A set of meta-analyses assessed the effects of O_3 on plant photosynthesis and growth across different species and fumigation methods (such as OTC and FACE). Those studies reported that current O_3 concentrations in the northern hemisphere are decreasing photosynthesis (~11%) across tree species, and the decreases in photosynthesis are consistent with cumulative uptake of O_3 into the leaf. The current ambient O_3 concentrations (~40 ppb) significantly decreased annual total biomass growth of forest species by an average of 7%, with potentially greater decreases (11-17%) in areas that have higher O_3 concentrations (Section 9.4.3.1). The meta-analyses further confirmed that reduction of plant photosynthesis and growth under O_3 exposure are coherent across numerous species and various experimental techniques.

Studies during recent decades have also demonstrated O_3 alters biomass allocation and plant reproduction (Section 9.4.3). Recent meta-analyses have generally indicated that O_3 reduced C allocated to roots, although the findings of individual studies were mixed. Several recent studies published since the 2006 O_3 AQCD further demonstrate that O_3 altered reproductive processes, such as timing of flowering, number of flowers, fruits and seeds, in herbaceous and woody plant species. However, a knowledge gap still exists pertaining to the exact mechanism of the responses of reproductive processes to O_3 exposure (Section 9.4.3.3).

Studies at the leaf and plant scales showed that O_3 reduced photosynthesis and plant growth, providing coherence and biological plausibility for the reported decreases in ecosystem productivity. During the previous NAAQS reviews, there were very few studies that investigated the effect of O_3 exposure on ecosystem productivity and C sequestration. Recent studies from long-term FACE experiments and ecosystem models provided evidence of the association of O_3 exposure and reduced productivity at the ecosystem scale. Elevated O_3 reduced stand biomass at Aspen FACE after 7 years of O_3 exposure, and annual volume growth at the Kranzberg Forest in Germany. Results across different ecosystem models were consistent with the FACE experimental evidence, which showed that O_3 reduced ecosystem productivity (Section 9.4.3.4). In addition to primary productivity, other indicators such as net ecosystem CO_2 exchange (NEE) and C sequestration were often assessed by model studies. Model simulations consistently found that O_3 exposure caused negative impacts on those indicators (Section 9.4.3.4, Table 9-3), but the severity of these impacts was influenced by multiple interactions of biological and environmental factors. The suppression of ecosystem C sinks results in more CO_2 accumulation in the atmosphere. A recent study suggested that the indirect radiative forcing caused by O_3 exposure through lowering ecosystem C sink could have an even greater impact on global warming than the direct radiative forcing of O_3.

Although O_3 generally causes negative effects on ecosystem productivity, the magnitude of the response varies among plant communities (Section 9.4.3.4). For example, O_3 had little impact on white fir, but greatly reduced growth of ponderosa pine in southern California. Ozone decreased net primary production (NPP) of most forest types in Mid-Atlantic region, but had small impacts on spruce-fir forest. Ozone could also affect regional C budgets through interacting with multiple factors, such as N deposition, elevated CO_2 and land use history. Model simulations suggested that O_3 partially offset the growth stimulation caused by elevated CO_2 and N deposition in both Northeast- and Mid-Atlantic-region forest ecosystems of the U.S.

Overall, evidence is sufficient to conclude that there is a causal relationship between O_3 exposure and reduced plant growth and productivity, and a likely

causal relationship between O_3 exposure and reduced carbon sequestration in terrestrial ecosystems.

2.7.2.2 Agricultural Crops

The detrimental effect of O_3 on crop production has been recognized since the 1960's and a large body of research has subsequently stemmed from those initial findings. Previous O_3 AQCDs have extensively reviewed this body of literature. Current O_3 concentrations across the U.S. are high enough to cause yield loss for a variety of agricultural crops including, but not limited to, soybean, wheat, potato, watermelon, beans, turnip, onion, lettuce, and tomato (Section 9.4.4.1). Continued increases in O_3 concentration may further decrease yield in these sensitive crops. Despite the well-documented yield losses due to increasing O_3 concentration, there is still a knowledge gap pertaining to the exact mechanism of O_3-induced yield loss. Research has linked increasing O_3 concentration to decreased photosynthetic rates and accelerated senescence, which are related to yield.

In addition, new research has highlighted the effects of O_3 on crop quality. Increasing O_3 concentration decreases nutritive quality of grasses, decreases macro- and micro-nutrient concentrations in fruits and vegetable crops, and decreases cotton fiber quality. These areas of research require further investigation to determine the mechanism and dose-responses (Section 9.4.4.2).

During the previous NAAQS reviews, there were very few studies that estimate O_3 impacts on crop yields at large spatial scales. Recent modeling studies found that O_3 generally reduced crop yield, but the impacts varied across regions and crop species (Section 9.4.4.1). For example, the largest O_3-induced crop yield losses occurred in high-production areas exposed to high O_3 concentrations, such as the Midwest and the Mississippi Valley regions of the U.S. Among crop species, the estimated yield loss for wheat and soybean were higher than rice and maize. Satellite and ground-based O_3 measurements have been used to assess yield loss caused by O_3 over the continuous tri-state area of Illinois, Iowa and Wisconsin. The results showed that O_3 concentrations significantly reduced soybean yield, which correlates well with the previous results from FACE-type experiments and OTC experiments (Section 9.4.4.1).

Evidence is sufficient to conclude that there is a causal relationship between O_3 exposure and reduced yield and quality of agricultural crops.

2.7.3 Water Cycling

Ozone can affect water use in plants and ecosystems through several mechanisms including damage to stomatal functioning and loss of leaf area. Section 9.3.6 reviewed possible mechanisms for O_3 exposure effects on stomatal functioning including the build-up of CO_2 in substomatal cavity, impacts on signal transduction pathways and direct O_3 impact on guard cells. Regardless of the mechanism, O_3 exposure has been shown to alter stomatal performance, which may affect plant and stand transpiration and therefore possibly affecting hydrological cycling.

Although the evidence was from a limited number of field and modeling studies, these findings showed an association of O_3 exposure and the alteration of water use and cycling in vegetation and ecosystem level (Section 9.4.5). There is not a clear consensus on the nature of leaf-level stomatal conductance response to O_3 exposure. When measured at steady-state high light conditions, leaf-level stomatal conductance is often found to be reduced when exposed to O_3. However, measurements of stomatal conductance under dynamic light and vapor pressure deficit conditions indicate sluggish responses under elevated O_3 exposure which could potentially lead to increased water loss from vegetation. Field studies suggested that peak hourly O_3 exposure increased the rate of water loss from several tree species, and led to a reduction in the late-season modeled stream flow in three forested watersheds in eastern Tennessee. Sluggish stomatal responses during O_3 exposure was suggested as a possible mechanism for increased water loss during peak O_3 exposure. Currently, the O_3-induced reduction in stomatal aperture is the biological assumption for most process-based models. Therefore, results of those models normally found that O_3 reduced water loss. For example, one study found that O_3 damage and N limitation together reduced evapotranspiration and increase runoff.

Although the direction of the response differed among studies, **the evidence is sufficient to conclude that there is likely to be a causal relationship between O_3 exposure and the alteration of ecosystem water cycling.**

2.7.4 Below-Ground Processes

Below-ground processes are tightly linked with aboveground processes. The responses of aboveground process to O_3 exposure, such as reduced photosynthetic rates, increased metabolic cost, and reduced root C allocation, have provided biologically plausible mechanisms for the alteration of below-ground processes. Since the 2006 O_3 AQCD, more evidence has shown that although the responses are often species specific, O_3 altered the quality and quantity of C input to soil, microbial community composition, and C and nutrient cycling.

Results from Aspen FACE and other experimental studies consistently found that O_3 reduced litter production and altered C chemistry, such as soluble sugars, soluble phenolics, condensed tannins, lignin, and macro/micro nutrient concentration in litter (Section 9.4.6.1). The changes in substrate quality and quantity could alter microbial metabolism under elevated O_3, and therefore soil C and nutrient cycling. Several studies indicated that O_3 generally suppressed soil enzyme activities (Section 9.4.6.2). However, the impact of O_3 on litter decomposition was inconsistent and varied among species, sites and exposure length. Similarly, O_3 had inconsistent impacts on dynamics of micro and macro nutrients (Section 9.4.6.4).

Studies from the Aspen FACE experiment suggested that the response of below-ground C cycle to O_3 exposure, such as litter decomposition, soil respiration and soil C content, changed over time. For example, in the early part of the experiment (1998-2003), O_3 had no impact on soil respiration but reduced the formation rates of total soil C under elevated CO_2. However, after 10 to 11 years of exposure, O_3 was found to increase soil respiration but have no significant impact on soil C formation under elevated CO_2 (Section 9.4.6.3).

The evidence is sufficient to infer that there is a causal relationship between O_3 exposure and the alteration of below-ground biogeochemical cycles.

2.7.5 Community Composition

In the 2006 O_3 AQCD, the impact of O_3 exposure on species competition and community composition was assessed. Ozone was found to be one of the dominant factors causing a significant decline in ponderosa and Jeffrey pine in the San Bernardino Mountains in southern California. Ozone exposure also tended to shift the grass-legume mixtures in favor of grass species. Since the 2006 O_3 AQCD, more evidence has shown that O_3 exposure changed the competitive interactions and led to loss of O_3 sensitive species or genotypes. Studies found that the severity of O_3 damage on growth, reproduction and foliar injury varied among species (Section 9.4.3), which provided the biological plausibility for the alteration of community composition. Additionally, research since the last review has shown that O_3 can alter community composition and diversity of soil microbial communities.

The decline of conifer forests under O_3 exposure was continually observed in several regions. Ozone damage was believed to be an important causal factor in the dramatic decline of sacred fir in the valley of Mexico, as well as cembran pine in southern France and Carpathian Mountains, although several factors, such as drought, insect outbreak and forest management, may also contribute to or even be the dominant factors causing the

mortality of the conifer trees. Results from the Aspen FACE site indicated that O_3 could alter community composition of broadleaf forests as well. At the Aspen FACE site, O_3 reduced growth and increased mortality of a sensitive aspen clone, while the O_3 tolerant clone emerged as the dominant clone in the pure aspen community. In the mixed aspen-birch and aspen-maple communities, O_3 reduced the competitive capacity of aspen compared to birch and maple (Section 9.4.7.1).

The tendency for O_3-exposure to shift the biomass of grass-legume mixtures in favor of grass species was reported in the 2006 O_3 AQCD and has been generally confirmed by recent studies. However, in a high elevation mature/species-rich grass-legume pasture, O_3 fumigation showed no significant impact on community composition (Section 9.4.7.2).

Ozone exposure not only altered community composition of plant species, but also microorganisms. The shift in community composition of bacteria and fungi has been observed in both natural and agricultural ecosystems, although no general patterns could be identified (Section 9.4.7.3).

The evidence is sufficient to conclude that there is likely a causal relationship between O_3 exposure and the alteration of community composition.

2.7.6 Policy Relevant Considerations

2.7.6.1 Air Quality Indices

Exposure indices are metrics that quantify exposure as it relates to measured plant damage (e.g., reduced growth). They are summary measures of monitored ambient O_3 concentrations over time intended to provide a consistent metric for reviewing and comparing exposure-response effects obtained from various studies. No new information is available since 2006 that alters the basic conclusions put forth in the 2006 and 1996 O_3 AQCDs. These AQCDs focused on the research used to develop various exposure indices to help quantify effects on growth and yield in crops, perennials, and trees (primarily seedlings). The performance of indices was compared through regression analyses of earlier studies designed to support the estimation of predictive O_3 exposure-response models for growth and/or yield of crops and tree (seedling) species.

Another approach for improving risk assessment of vegetation response to ambient O_3 is based on determining the O_3 concentration from the atmosphere that enters the leaf (i.e., flux or deposition). Interest has been increasing in recent years, particularly in Europe, in using mathematically tractable flux models for O_3 assessments at the regional, national, and European scale. While some efforts have been made in the U.S. to calculate O_3 flux

into leaves and canopies, little information has been published relating these fluxes to effects on vegetation. There is also concern that not all O_3 stomatal uptake results in a yield reduction, which depends to some degree on the amount of internal detoxification occurring with each particular species. Species having high detoxification capacity may show little relationship between O_3 stomatal uptake and plant response. The lack of data in the U.S. and the lack of understanding of detoxification processes have made this technique less viable for vulnerability and risk assessments in the U.S.

The main conclusions from the 1996 and 2006 O_3 AQCDs regarding indices based on ambient exposure remain valid. These key conclusions can be restated as follows:

- O_3 effects in plants are cumulative;
- higher O_3 concentrations appear to be more important than lower concentrations in eliciting a response;
- plant sensitivity to O_3 varies with time of day and plant development stage; and
- exposure indices that cumulate hourly O_3 concentrations and preferentially weight the higher concentrations have better statistical fits to growth/yield response data than do the mean and peak indices.

Various weighting functions have been used, including threshold-weighted (e.g., SUM06) and continuous sigmoid-weighted (e.g., W126) functions. Based on statistical goodness-of-fit tests, these cumulative, concentration-weighted indices could not be differentiated from one another using data from previous exposure studies. Additional statistical forms for O_3 exposure indices are summarized in Section 9.5 of this ISA. The majority of studies published since the 2006 O_3 AQCD do not change earlier conclusions, including the importance of peak concentrations, and the duration and occurrence of O_3 exposures in altering plant growth and yield.

Given the current state of knowledge and the best available data, exposure indices that cumulate and differentially weight the higher hourly average concentrations and also include the mid-level values continue to offer the most defensible approach for use in developing response functions and comparing studies, as well as for defining future indices for vegetation protection.

2.7.6.2 Exposure-Response

None of the information on effects of O_3 on vegetation published since the 2006 O_3 AQCD has modified the assessment of quantitative exposure-response relationships that was presented in that document (U.S. EPA, 2006b). This assessment updates the 2006

exposure-response models by computing them using the W126 metric, cumulated over 90 days. Almost all of the experimental research on the effects of O_3 on growth or yield of plants published since 2006 used only two levels of exposure. In addition, hourly O_3 concentration data that would allow calculations of exposure using the W126 metric are generally unavailable. However, two long-term experiments, one with a crop species (soybean), one with a tree species (aspen), have produced data that are used in Section 9.6 to validate the exposure-response models presented in the 2006 O_3 AQCD, and the methodology used to derive them. EPA compared predictions from the models presented in the 2006 O_3 AQCD, updated to use the 90 day 12hr W126 metric, with more recent observations for yield of soybean and biomass growth of trembling aspen. The models were parameterized using data from the NCLAN and NHEERL-WED projects, which were conducted in OTCs. The more recent observations were from experiments using FACE technology, which is intended to provide conditions closer to natural environments than OTC. Observations from these new experiments were exceptionally close to predictions from the models. The accuracy of model predictions for two widely different plant species, grown under very different conditions, provides support for the validity of the models for crops and trees developed using the same methodology and data for other species. However, variability observed among species in the NCLAN and NHEERL-WED projects indicates that the range of sensitivity between and among species is likely quite wide.

Results from several meta-analyses have provided approximate values for responses of yield of soybean, wheat, rice and other crops under broad categories of exposure, relative to charcoal-filtered air. Additional reports have summarized yield data for six crop species under various broad comparative exposure categories, and reviewed 263 studies that reported effects on tree biomass. However, these analyses have proved difficult to compare with exposure-response models, especially given that exposure was not expressed on the same W126 scale.

2.8 The Role of Tropospheric Ozone in Climate Change and UV-B Effects

Atmospheric O_3 plays an important role in the Earth's energy budget by interacting with incoming solar radiation and outgoing infrared radiation. Tropospheric O_3 makes up only a small portion of the total column of O_3, but it has important incremental effects on the overall radiation budget. Chapter 10 assesses the specific role of tropospheric O_3 in the earth's radiation budget and how perturbations in tropospheric O_3 might affect (1) climate through its role as a greenhouse gas, and (2) health, ecology and welfare through its role in shielding the earth's surface from solar ultraviolet (UV) radiation.

2.8.1 Tropospheric Ozone as a Greenhouse Gas

Ozone is an important greenhouse gas, and increases in its abundance in the troposphere may contribute to climate change according to the 2007 climate assessment by the Intergovernmental Panel on Climate Change (IPCC). Models calculate that the global burden of tropospheric O_3 has doubled since the preindustrial era, while observations indicate that in some regions O_3 may have increased by factors as great as 4 or 5. These increases are tied to the rise in emissions of O_3 precursors from human activity, mainly fossil fuel consumption and agricultural processes.

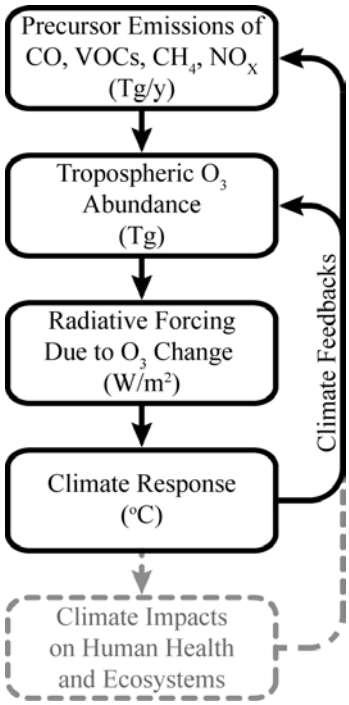
Units shown are those typical for each quantity illustrated. Feedbacks from both the climate response and climate impacts can, in turn, affect the abundance of tropospheric O3 and O3 precursors through multiple feedback mechanisms. Climate impacts are deemphasized in the figure since these downstream effects are extremely complex and outside the scope of this assessment.

Figure 2-5 shows the main steps involved in the influence of tropospheric O_3 on climate. Emissions of O_3 precursors including CO, VOCs, CH_4, and NO_X lead to production of tropospheric O_3. A change in the abundance of tropospheric O_3 perturbs the radiative balance of the atmosphere, an effect quantified by the radiative forcing (RF) metric. The earth-atmosphere-ocean system responds to the forcing with a climate response, typically expressed as a change in surface temperature. Finally, the climate response causes downstream climate-related health and ecosystem impacts, such as redistribution of diseases or ecosystem characteristics due to temperature changes. Feedbacks from both the climate response and downstream impacts can, in turn, affect the abundance of tropospheric O_3 and O_3 precursors through multiple feedback mechanisms as indicated in Figure 2-5. Direct feedbacks are discussed in Section 10.2.3.4 while downstream climate impacts and their feedbacks are extremely complex and outside the scope of this assessment.

The impact of the tropospheric O_3 change since preindustrial times on climate has been estimated to be about 25-40% of anthropogenic CO_2 impact and about 75% of anthropogenic CH_4 impact according to the IPCC, ranking it third in importance among the greenhouse gases. There are large uncertainties in the RF estimate attributed to tropospheric O_3, however, making the impact of tropospheric O_3 on climate more uncertain than the impact of the long-lived greenhouse gases. Despite these uncertainties, the evidence supports **a causal relationship between changes in tropospheric O_3 concentrations and radiative forcing.**

RF does not take into account the climate feedbacks that could amplify or dampen the actual surface temperature response. Quantifying the change in surface temperature

requires a complex climate simulation in which all important feedbacks and interactions are accounted for. As these processes are not well understood or easily modeled, the surface temperature response to a given RF is highly uncertain and can vary greatly among models and from region to region within the same model. In light of these uncertainties, the evidence supports **a likely to be a causal relationship between changes in tropospheric O_3 concentrations and climate change.**



Units shown are those typical for each quantity illustrated. Feedbacks from both the climate response and climate impacts can, in turn, affect the abundance of tropospheric O_3 and O_3 precursors through multiple feedback mechanisms. Climate impacts are deemphasized in the figure since these downstream effects are extremely complex and outside the scope of this assessment.

Figure 2-5 Schematic illustrating the effects of tropospheric O_3 on climate including the relationship between precursor emissions, tropospheric O_3 abundance, radiative forcing, climate response, and climate impacts. Tropospheric Ozone and UV-B related effects

UV radiation emitted from the Sun contains sufficient energy when it reaches the Earth to break (photolyze) chemical bonds in molecules, thereby leading to damaging effects on living organisms and materials. Atmospheric O_3 plays a crucial role in reducing exposure to solar UV radiation at the Earth's surface. Ozone in the stratosphere is responsible for the majority of this shielding effect, as approximately 90% of total atmospheric O_3 is located there over mid-latitudes. Ozone in the troposphere provides supplemental shielding of radiation in the wavelength band from 280-315 nm, referred to as UV-B

radiation. UV-B radiation has important effects on human health and ecosystems, and is associated with materials damage.

Adverse human health effects associated with solar UV-B radiation exposure include erythema, skin cancer, ocular damage, and immune system suppression. A potential human health benefit of increased UV-B exposure involves the UV-induced production of vitamin D which may help reduce the risk of metabolic bone disease, type I diabetes, mellitus, and rheumatoid arthritis, and may provide beneficial immunomodulatory effects on multiple sclerosis, insulin-dependent diabetes mellitus, and rheumatoid arthritis.

Adverse ecosystem and materials damage effects associated with solar UV-B radiation exposure include terrestrial and aquatic ecosystem impacts, alteration of biogeochemical cycles, and degradation of man-made materials. Terrestrial ecosystem effects from increased UV-B radiation include reduced plant productivity and plant cover, changes in biodiversity, susceptibility to infection, and increases in natural UV protective responses. In general, however, these effects are small for moderate UV-B increases at mid-latitudes. Aquatic ecosystem effects from increased UV-B radiation include sensitivity in growth, immune response, and behavioral patterns of aquatic organisms and the potential for increased catalysis and mobility of trace metals. Biogeochemical cycles, particularly the carbon cycle, can also be influenced by increased UV-B radiation with effects ranging from UV-induced increases in CO_2 uptake through soil respiration to UV-induced release of CO_2 through photodegradation of above-ground plant litter. Changes in solar UV radiation may also have effects on carbon cycling and CO_2 uptake in the oceans as well as release of dissolved organic matter from sediment and algae. Finally, materials damage from increased UV-B radiation includes UV-induced photodegradation of wood and plastics.

There is a lack of published studies that critically examine the incremental health or welfare effects (adverse or beneficial) attributable specifically to changes in UV-B exposure resulting from perturbations in tropospheric O_3 concentrations. The effects are expected to be small and they cannot yet be critically assessed within reasonable uncertainty. Overall, the evidence is **inadequate to determine if a causal relationship exists between tropospheric O_3 and UV-B related health and welfare effects.**

2.9 Summary of Causal Determinations for Health Effects and Welfare Effects

This chapter has provided an overview of the underlying evidence used in making the causal determinations for the health and welfare effects of O_3. This review builds upon the conclusions of the previous AQCDs for O_3.

The evaluation of the epidemiologic, toxicological, and controlled human exposure studies published since the completion of the 2006 O_3 AQCD have provided additional evidence for O_3-related health outcomes. Table 2-3 provides an overview of the causal determinations for all of the health outcomes evaluated. Causal determinations for O_3 and welfare effects are included in Table 2-4, while causal determinations for climate change and UV-B effects are in Table 2-5. Detailed discussions of the scientific evidence and rationale for these causal determinations are provided in subsequent chapters of this ISA.

Table 2-3 Summary of ozone causal determinations by exposure duration and health outcome

Health Outcome	Conclusions from 2006 O_3 AQCD	Conclusions from 2011 1st Draft ISA
Short-Term Exposure to O_3		
Respiratory effects	The overall evidence supports a causal relationship between acute ambient O_3 exposures and increased respiratory morbidity outcomes.	Causal Relationship
Cardiovascular effects	The limited evidence is highly suggestive that O_3 directly and/or indirectly contributes to cardiovascular-related morbidity, but much remains to be done to more fully substantiate the association.	Suggestive of a Causal Relationship
Central nervous system effects	Toxicological studies report that acute exposures to O_3 are associated with alterations in neurotransmitters, motor activity, short and long term memory, sleep patterns, and histological signs of neurodegeneration.	Suggestive of a Causal Relationship
Mortality	The evidence is highly suggestive that O_3 directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality.	Likely to be a Causal Relationship
Long-term Exposure to O_3		
Respiratory effects	The current evidence is suggestive but inconclusive for respiratory health effects from long-term O_3 exposure.	Likely to be a Causal Relationship
Cardiovascular Effects	No studies from previous review	Suggestive of a Causal Relationship
Reproductive and developmental effects	Limited evidence for a relationship between air pollution and birth-related health outcomes, including mortality, premature births, low birth weights, and birth defects, with little evidence being found for O_3 effects.	Suggestive of a Causal Relationship
Central nervous system effects	Evidence regarding chronic exposure and neurobehavioral effects was not available.	Suggestive of a Causal Relationship
Cancer	Little evidence for a relationship between chronic O_3 exposure and increased risk of lung cancer.	Inadequate to infer a Causal Relationship
Mortality	There is little evidence to suggest a causal relationship between chronic O_3 exposure and increased risk for mortality in humans.	Suggestive of a Causal Relationship

Table 2-4 Summary of ozone causal determination for welfare effects

Vegetation and Ecosystem Effects	Conclusions from 2006 O_3 AQCD	Conclusions from 2011 2nd Draft ISA
Visible Foliar Injury Effects on Vegetation	Data published since the 1996 O_3 AQCD strengthen previous conclusions that there is strong evidence that current ambient O_3 concentrations cause impaired aesthetic quality of many native plants and trees by increasing foliar injury.	Causal Relationship
Reduced Vegetation Growth	Data published since the 1996 O_3 AQCD strengthen previous conclusions that there is strong evidence that current ambient O_3 concentrations cause decreased growth and biomass accumulation in annual, perennial and woody plants, including agronomic crops, annuals, shrubs, grasses, and trees.	Causal Relationship
Reduced Productivity in Terrestrial Ecosystems	There is evidence that O_3 is an important stressor of ecosystems and that the effects of O_3 on individual plants and processes are scaled up through the ecosystem, affecting net primary productivity.	Causal Relationship
Reduced Carbon (C) Sequestration in Terrestrial Ecosystems	Limited studies from previous review	Likely to be a Causal Relationship
Reduced Yield and Quality of Agricultural Crops	Data published since the 1996 O_3 AQCD strengthen previous conclusions that there is strong evidence that current ambient O_3 concentrations cause decreased yield and/or nutritive quality in a large number of agronomic and forage crops.	Causal Relationship
Alteration of Terrestrial Ecosystem Water Cycling	Ecosystem water quantity may be affected by O_3 exposure at the landscape level.	Likely to be a Causal Relationship
Alteration of Below-ground Biogeochemical Cycles	Ozone-sensitive species have well known responses to O_3 exposure, including altered C allocation to below-ground tissues, and altered rates of leaf and root production, turnover, and decomposition. These shifts can affect overall C and N loss from the ecosystem in terms of respired C, and leached aqueous dissolved organic and inorganic C and N.	Causal Relationship
Alteration of Terrestrial Community Composition	Ozone may be affecting above- and below -ground community composition through impacts on both growth and reproduction. Significant changes in plant community composition resulting directly from O_3 exposure have been demonstrated.	Likely to be a Causal Relationship

Table 2-5 Summary of ozone causal determination for climate change and UV-B effects

Effects	Conclusions from 2006 O_3 AQCD	Conclusions from 2011 1st Draft ISA
Radiative Forcing	Climate forcing by O_3 at the regional scale may be its most important impact on climate.	Causal Relationship
Climate Change	While more certain estimates of the overall importance of global-scale forcing due to tropospheric O_3 await further advances in monitoring and chemical transport modeling, the overall body of scientific evidence suggests that high concentrations of O_3 on the regional scale could have a discernable influence on climate, leading to surface temperature and hydrological cycle changes.	Likely to be a Causal Relationship
UV-B Related Health and Welfare Effects	UV-B has not been studied in sufficient detail to allow for a credible health benefits assessment. In conclusion, the effect of changes in surface-level O_3 concentrations on UV-induced health outcomes cannot yet be critically assessed within reasonable uncertainty.	Inadequate to Determine if a Causal Relationship Exists

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2.10 References

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3 ATMOSPHERIC CHEMISTRY AND AMBIENT CONCENTRATIONS

3.1 Introduction

In the stratosphere, O_3 serves the beneficial role of blocking the Sun's harmful ultraviolet radiation and preventing the majority of this radiation from reaching the Earth's surface. In the troposphere, however, O_3 and other photochemical oxidants are air pollutants with potentially harmful effects on living organisms. This chapter discusses the atmospheric chemistry associated with tropospheric O_3 and other related photochemical oxidants and provides a detailed description of their surface-level concentrations. The focus of this chapter is on O_3 since it is the NAAQS indicator for all photochemical oxidants. To the extent possible, other photochemical oxidants are discussed, but limited information is currently available. Although O_3 is involved in reactions in indoor air, the focus in this chapter will be on chemistry occurring in outdoor, ambient air.

The material in this chapter is organized as follows. Section 3.2 outlines the physical and chemical processes involved in O_3 formation and removal. Section 3.3 describes the latest methods used to model global O_3 concentrations, and Section 3.4 describes the application of these methods for estimating background concentrations of O_3 that are useful for risk and policy assessments informing decisions about the NAAQS. Section 3.1 includes a comprehensive description of available O_3 monitoring techniques and monitoring networks, while Section 3.6 presents information on the spatial and temporal variability of O_3 concentrations across the U.S. and their associations with other pollutants using available monitoring data. Section 3.7 summarizes the main conclusions of Chapter 3. Section 3.8 provides supplemental material for atmospheric model predictions of background O_3 concentrations described in Section 3.4; Section 3.9 contains supplemental material for model predictions of background O_3 concentrations using a more recent version of the atmospheric model described in Section 3.4; and Section 3.10 contains supplemental figures of observed ambient O_3 concentrations.

3.2 Physical and Chemical Processes

O_3 in the troposphere is a secondary pollutant formed by photochemical reactions of precursor gases and is not directly emitted from specific sources. Ozone and other oxidants, such as PAN and H_2O_2 form in polluted areas by atmospheric reactions

involving two main classes of precursor pollutants: VOCs and NO_X.[1] Carbon monoxide (CO) is also important for O_3 formation in polluted areas and in the remote troposphere. The formation of O_3, other oxidants and oxidation products from these precursors is a complex, nonlinear function of many factors including (1) the intensity and spectral distribution of sunlight; (2) atmospheric mixing; (3) concentrations of precursors in the ambient air and the rates of chemical reactions of these precursors; and (4) processing on cloud and aerosol particles.

Ozone is present not only in polluted urban atmospheres, but throughout the troposphere, even in remote areas of the globe. The same basic processes involving sunlight-driven reactions of NO_X, VOCs and CO contribute to O_3 formation throughout the troposphere. These processes also lead to the formation of other photochemical products, such as PAN, HNO_3, and H_2SO_4, and to other compounds, such as HCHO and other carbonyl compounds, and to secondary components of particulate matter.

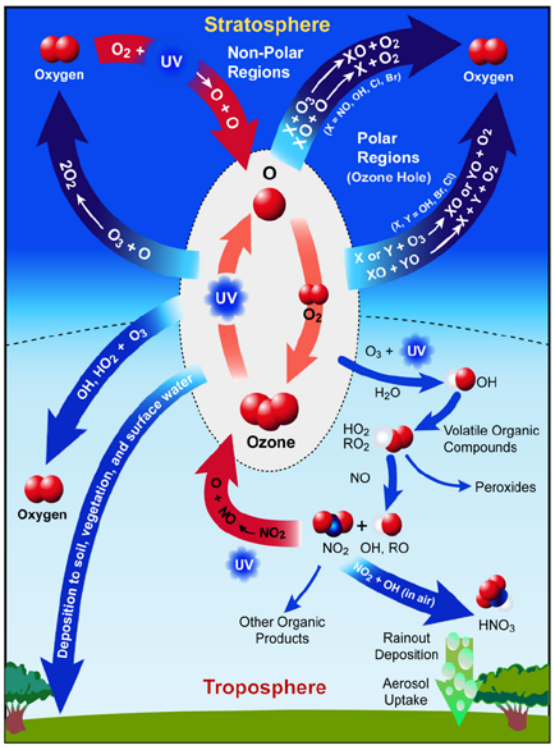


Figure 3-1 Schematic overview of photochemical processes influencing stratospheric and tropospheric ozone.

[1] The term VOCs refers to all organic gas-phase compounds in the atmosphere, both biogenic and anthropogenic in origin. This definition excludes CO and CO_2. NO_x, also referred to as nitrogen oxides, is equal to the sum of NO and NO_2.

The processes responsible for producing summertime O_3 episodes are fairly well understood, and were covered in detail in the previous O_3 AQCD. This section focuses on topics that form the basis for discussions in later chapters and for which there is substantial new information since the previous O_3 AQCD. A schematic overview of the major photochemical cycles influencing O_3 in the troposphere and the stratosphere is given in Figure 3-1.

Major episodes of high O_3 concentrations in the eastern U.S. 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 skies, with light winds. The sinking of air results in the development of stable conditions near the surface which inhibit or reduce the vertical mixing of O_3 precursors. The combination of inhibited vertical mixing and light winds minimizes the dispersal of 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 during the warmer seasons. In the eastern U.S., concentrations of O_3 and other secondary pollutants are determined by meteorological and chemical processes extending typically over areas of several hundred thousand square kilometers (Civerolo et al., 2003; Rao et al., 2003). Ozone episodes are thus best regarded as regional in nature. The conditions conducive to formation of high O_3 can persist for several days. These conditions have been described in greater detail in the 1996 and 2006 O_3 AQCDs (U.S. EPA, 2006b, 1996a). The transport of pollutants downwind of major urban centers is characterized by the development of urban plumes. Mountain barriers limit mixing (as in Los Angeles and Mexico City) and result in a higher frequency and duration of days with high O_3 concentrations. However, orographic lifting over the San Gabriel Mountains results in O_3 transport from Los Angeles to areas hundreds of kilometers downwind (e.g., in Colorado and Utah) (Langford et al., 2009). Ozone concentrations in southern urban areas (such as Houston, TX and Atlanta, GA) tend to decrease with increasing wind speed. In northern U.S. cities (such as Chicago, IL; New York, NY; Boston, MA; and Portland, ME), the average O_3 concentrations over the metropolitan areas increase with wind speed, indicating that transport of O_3 and its precursors from upwind areas is important (Schichtel and Husar, 2001; Husar and Renard, 1998).

Aircraft observations indicate that there can be substantial differences in mixing ratios of key species between the surface and the overlying atmosphere (Berkowitz and Shaw, 1997; Fehsenfeld et al., 1996). In particular, mixing ratios of O_3 can be higher in the lower free troposphere (aloft) than in the planetary boundary layer (PBL) during multiday O_3 episodes (Taubman et al., 2006; Taubman et al., 2004). Convective processes and turbulence transport O_3 and other pollutants both upward and downward throughout the

planetary boundary layer and the free troposphere. During the day, convection driven by heating of the earth's surface results in a deeper PBL with vertically well mixed O_3 and precursors. As solar heating of the surface decreases going into night, the daytime boundary layer collapses leaving behind O_3 and its precursors in a residual layer above a shallow nighttime boundary layer. Pollutants in the residual layer have now become essentially part of the free troposphere, as described in Section AX2.3.2 of the 2006 O_3 AQCD. Winds in the free troposphere tend to be stronger than those closer to the surface and so are capable of transporting pollutants over long distances. Thus, O_3 and its precursors can 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 O_3 concentrations showing large diurnal variations at the surface in southern New England were associated with the presence of such layers (Berkowitz et al., 1998). 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 O_3 in the eastern U.S. (Blumenthal et al., 1997). These considerations suggest that in many areas of the U.S., O_3 and its precursors can be transported over hundreds if not thousands of kilometers.

Nocturnal low level jets (LLJs) are an efficient means for transporting pollutants over hundreds of kilometers that have been entrained into the residual boundary layer. LLJs are most prevalent in the central U.S. extending northward from eastern Texas, and along the Atlantic states extending southwest to northeast. LLJs have also been observed off the coast of California. Turbulence induced by wind shear associated with LLJs brings pollutants to the surface and results in secondary O_3 maxima during the night and early morning in many locations (Corsmeier et al., 1997). Comparison of observations at low-elevation surface sites with those at nearby high-elevation sites at night can be used to discern the effects of LLJs. For example, Fischer et al. (2004) found occasions when O_3 at the base of Mt. Washington during the night was much higher than typically observed, and closer to those observed at the summit of Mt. Washington. They suggested that mechanically driven turbulence due to wind shear caused O_3 from aloft to penetrate the stable nocturnal inversion thus causing O_3 to increase near the base of Mt. Washington. The high wind speeds causing this mechanically driven turbulence could have resulted from the development of an LLJ. Stratospheric intrusions and intercontinental transport of O_3 are also important and are covered in Section 3.4 in relation to policy relevant background concentrations.

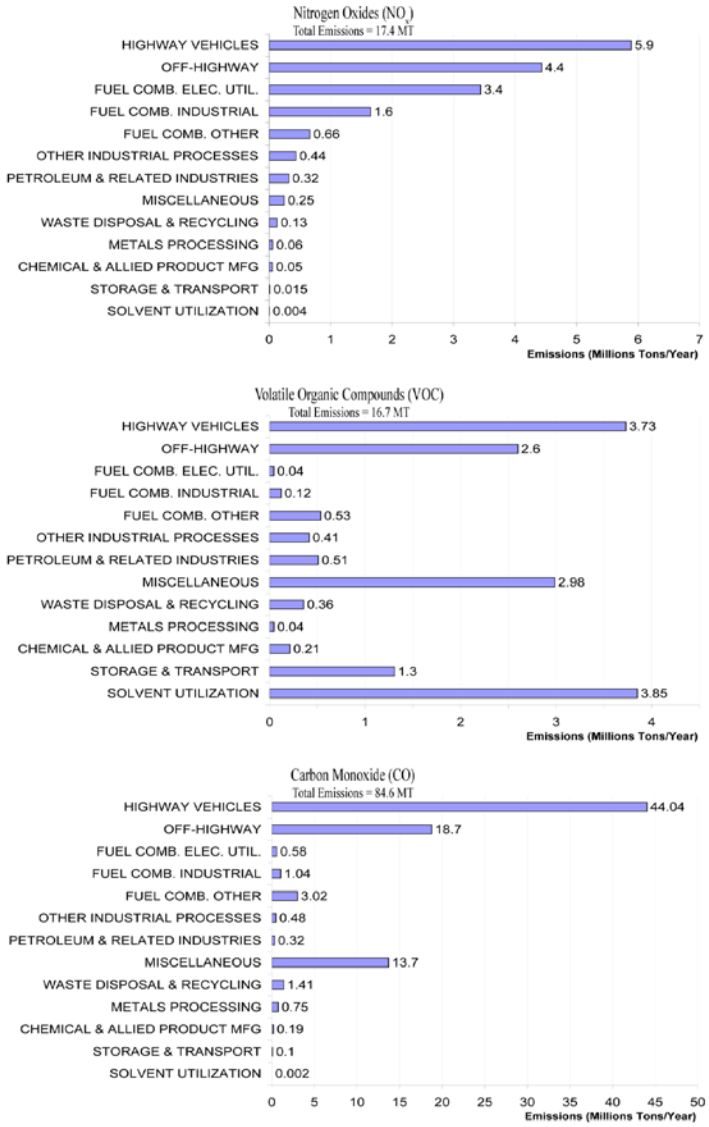
3.2.1 Sources of Precursors Involved in Ozone Formation

Emissions of O_3 precursor compounds (NO_X, VOCs, and CO) can be divided into natural and anthropogenic source categories. Natural sources can be further divided into biogenic from vegetation, microbes, and animals, and abiotic from biomass burning, lightning, and geogenic sources. However, the distinction between natural and anthropogenic sources is often difficult to make in practice, as human activities directly or indirectly affect emissions from what would have been considered natural sources during the preindustrial era. Thus, emissions from plants and animals used in agriculture have been referred to as anthropogenic or biogenic in different applications. Wildfire emissions can be considered natural, except that forest management practices can lead to buildup of fuels on the forest floor, thereby altering the frequency and severity of forest fires.

Estimates of emissions for NO_X, VOCs, and CO (U.S. EPA, 2008a) are shown in Figure 3-2 to provide a general indication of the relative importance of the different sources in the U.S. as a whole. The magnitudes of the sources are strongly location and time dependent and so should not be used to apportion sources of exposure. Shown in Figure 3-2 are Tier 1 categories. The miscellaneous category can be quite large compared to total emissions, especially for CO and VOCs. The miscellaneous category includes agriculture and forestry, wildfires, prescribed burns, and a much more modest contribution from structural fires.

Anthropogenic NO_X emissions are associated with combustion processes. Most emissions are in the form of NO, which is formed at high combustion temperatures from atmospheric nitrogen (N_2) and oxygen (O_2) and from fuel nitrogen (N). According to the 2005 National Emissions Inventory (U.S. EPA, 2008a), the largest sources of NO_X are on- and off-road mobile sources and electric power generation plants. Emissions of NO_X therefore are highest in areas having a high density of power plants and in urban regions having high traffic density. Dallman and Harley (2010) compared NO_X emissions estimates from the National Emissions Inventory, mobile sector data (U.S. EPA, 2008a) with an alternative method based on fuel consumption and found reasonable agreement in total U.S. anthropogenic emissions between the two techniques (to within about 5%). However, emissions from on-road diesel engines in the fuel based inventory constituted 46% of total mobile source NO_X compared to 35% in the EPA inventory. As a result, emissions from on-road diesel engines in the fuel based approach are even larger than electric power generation as estimated in the 2005 NEI, and on-road diesel engines might represent the largest single NO_X source category. Differences between the two techniques are largely accounted for by differences in emissions from on-road gasoline engines. Uncertainties in the fuel consumption inventory ranged from 3% for on-road gasoline engines to 20% for marine sources, and in the EPA inventory uncertainties ranged from

16% for locomotives to 30% for off-road diesel engines. It should be noted that the on-road diesel engine emissions estimate by Dallman and Harley (2010) is still within the uncertainty of the EPA estimate (22%).



Source: U.S. EPA (2008a)
NO_X (top), VOCs (middle), and CO (bottom) in the U.S. in million metric tons (MT) per year.

Figure 3-2 Estimated anthropogenic emissions of ozone precursors for 2005.

Major natural sources of NO_X in the U.S. include lightning, soils, and wildfires. Uncertainties in natural NO_X emissions are much larger than for anthropogenic NO_X

emissions. Fang et al. (2010) estimated lightning generated NO_X of ~0.6 MT for July 2004. This value is ~40% of the anthropogenic emissions for the same period, but Fang et al. estimated that ~98% is formed in the free troposphere and so contributions to the surface NO_X burden are low because most of this NO_X is oxidized to nitrate containing species during downward transport into the planetary boundary layer. The remaining 2% is formed within the planetary boundary layer. Both nitrifying and denitrifying organisms in the soil can produce NO_X, mainly in the form of NO. Emission rates depend mainly on fertilization amount and soil temperature and moisture. Nationwide, about 60% of the total NO_X emitted by soils is estimated to occur in the central corn belt of the U.S. Spatial and temporal variability in soil NO_X emissions leads to considerable uncertainty in emissions estimates. However, these emissions are relatively low, only ~0.97 MT/year, or about 6% of anthropogenic NO_X emissions. However, these emissions occur mainly during summer when O_3 is of most concern.

Hundreds of VOCs, containing mainly 2 to ~12 carbon (C) atoms, are emitted by evaporation and combustion processes from a large number of anthropogenic sources. The two largest anthropogenic source categories in the U.S. EPA's emissions inventories are industrial processes and transportation. Emissions of VOCs from highway vehicles account for roughly two-thirds of the transportation-related emissions. The accuracy of VOC emission estimates is difficult to determine, both for stationary and mobile sources. Evaporative emissions, which depend on temperature and other environmental factors, compound the difficulties of assigning accurate emission factors. In assigning VOC emission estimates to the mobile source category, models are used that incorporate numerous input parameters (e.g., type of fuel used, type of emission controls, and age of vehicle), each of which has some degree of uncertainty.

On the U.S. and global scales, emissions of VOCs from vegetation are much larger than those from anthropogenic sources. Emissions of VOCs from anthropogenic sources in the 2005 NEI were ~17 MT/year (wildfires constitute ~1/6 of that total and were included in the 2005 NEI under the anthropogenic category, but see Section 3.4 for how wildfires are treated for background.), but were 29 MT/year from biogenic sources. Uncertainties in both biogenic and anthropogenic VOC emission inventories prevent determination of the relative contributions of these two categories, at least in many areas. Vegetation emits significant quantities of VOCs, such as terpenoid compounds (isoprene, 2-methyl-3-buten-2-ol, monoterpenes), compounds in the hexanal family, alkenes, aldehydes, organic acids, alcohols, ketones, and alkanes. The major chemicals emitted by plants are isoprene (40%), other terpenoid and sesqui-terpenoid compounds (25%) and the remainder consists of assorted oxygenated compounds and hydrocarbons according to the 2005 NEI. Coniferous forests represent the largest source on a nationwide basis because of their extensive land coverage. Most 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 and because of species variations. The uncertainty in natural emissions is about 50% for isoprene under midday summer conditions and could be as much as a factor of ten higher for some compounds (Guenther et al., 2000). In EPA's regional modeling efforts, biogenic emissions of VOCs are estimated using the BEIS model (U.S. EPA, 2010b) with data from the Biogenic Emissions Landcover Database (BELD) and annual meteorological data. However, other emissions models are used such as MEGAN (Model of Emissions of Gases and Aerosols from Nature) (Guenther et al., 2006), especially in global modeling efforts.

Anthropogenic CO is emitted primarily by incomplete combustion of carbon-containing fuels. In general, any increase in fuel O_2 content, burn temperature, or mixing time in the combustion zone will tend to decrease production of CO relative to CO_2. However, it should be noted that controls mute the response of CO formation to fuel-oxygen. CO emissions from large fossil-fueled power plants are typically very low since the boilers at these plants are tuned for highly efficient combustion with the lowest possible fuel consumption. Additionally, the CO-to-CO_2 ratio in these emissions is shifted toward CO_2 by allowing time for the furnace flue gases to mix with air and be oxidized by OH to CO_2 in the hot gas stream before the OH concentrations drop as the flue gases cool,. Nationally, on-road mobile sources constituted about half of total CO emissions in the 2005 NEI. When emissions from non-road vehicles are included, it can be seen from Figure 3-2 that all mobile sources accounted for about three-quarters of total anthropogenic CO emissions in the U.S.

Analyses by Harley et al. (2005) and Parrish (2006) are consistent with the suggestion in Pollack et al. (2004) that the EPA MOBILE6 vehicle emissions model (U.S. EPA, 2010d) overestimates vehicle CO emissions by a factor of ~2. Field measurements by Bishop and Stedman (2008) were in accord with Parrish's (2006) findings that the measured trends of CO and NO_X concentrations from mobile sources in the U.S. indicated that modeled CO emission estimates were substantially too high. Hudman et al. (2008) found that the NEI overestimated anthropogenic CO emissions by 60% for the eastern U.S. during the period July 1-August 15, 2004 based on comparison of aircraft observations of CO from the International Consortium for Atmospheric Research on Transport and Transformation (ICARTT) campaign (Fehsenfeld et al., 2006) and results from a tropospheric chemistry model (GEOS-Chem). Improvements in emissions technologies not correctly represented in MOBILE emission models have been suggested as one cause for this discrepancy. For example, Pokharel et al. (2003, 2002) demonstrated substantial decrements in the CO fraction of tailpipe exhaust in several U.S. cities and Burgard et al. (2006) documented improvements in emission from heavy-duty on-road diesel engines. Some of the largest

errors in the MOBILE models are addressed in the successor model, MOVES (U.S. EPA, 2011e).

Estimates of biogenic CO emissions in the 2005 NEI are made in a manner similar to that for VOCs. National biogenic emissions, excluding fires, were estimated to contribute ~7% and wildfires added another ~16% to the national CO emissions total. Photodecomposition of organic matter in oceans, rivers, lakes, and other surface waters, and from soil surfaces also releases CO (Goldstein and Galbally, 2007). However, soils can act as a CO source or a sink depending on soil moisture, UV flux reaching the soil surface, and soil temperature (Conrad and Seiler, 1985). Soil uptake of CO is driven by anaerobic bacteria (Inman et al., 1971). Emissions of CO from soils appear to occur by abiotic processes, such as thermo- or photodecomposition of organic matter. In general, warm and moist conditions found in most soils favor CO uptake, whereas hot and dry conditions found in deserts and some savannas favor the release of CO (King, 1999).

3.2.2 Gas Phase Reactions Leading to Ozone Formation

Photochemical processes involved in O_3 formation have been extensively reviewed in a number of books (Jacobson, 2002; Jacob, 1999; Seinfeld and Pandis, 1998; Finlayson-Pitts and Pitts, 1986) and in the previous O_3 AQCDs. The photochemical formation of O_3 in the troposphere proceeds through the oxidation of NO to nitrogen dioxide (NO_2) by organic (RO_2) or hydro-peroxy (HO_2) radicals. The photolysis of NO_2 yields NO and a ground-state oxygen atom, $O(^3P)$, which then reacts with molecular oxygen to form O_3. Free radicals oxidizing NO to NO_2 are formed during the oxidation of VOCs (Annex AX2.2.2 in the 2006 O_3 AQCD) (U.S. EPA, 2006b).

VOCs important for the photochemical formation of O_3 include alkanes, alkenes, aromatic hydrocarbons, carbonyl compounds (e.g., aldehydes and ketones), alcohols, organic peroxides, and halogenated organic compounds (e.g., alkyl halides). This array of compounds encompasses a wide range of chemical properties and lifetimes: isoprene has an atmospheric lifetime of approximately an hour, whereas methane has an atmospheric lifetime of about a decade.

In urban areas, compounds representing all classes of VOCs and CO are important for O_3 formation. In nonurban vegetated areas, biogenic VOCs emitted from vegetation tend to be the most important. In the remote troposphere, methane (CH_4) and CO are the main carbon-containing precursors to O_3 formation. The oxidation of VOCs is initiated mainly by reaction with hydroxyl (OH) radicals. The primary source of OH radicals in the atmosphere is the reaction of electronically excited O atoms, $O(^1D)$, with water vapor. $O(^1D)$ is produced by the photolysis of O_3 in the Hartley bands. In polluted areas, the

photolysis of aldehydes (e.g., HCHO), HONO and H_2O_2 can also be significant sources of OH, or HO_2 radicals that can rapidly be converted to OH (Eisele et al., 1997). O_3 can oxidize alkenes, as can NO_3 radicals. NO_3 radicals are most effective at night when they are most abundant. In coastal environments and other selected environments, atomic Cl and Br radicals can also initiate the oxidation of VOCs (Annex AX2.2.3 in the 2006 O_3 AQCD) (U.S. EPA, 2006b). It should also be emphasized that the reactions of oxygenated VOCs are important components of O_3 formation (Annex AX2.2.9 in the 2006 O_3 AQCD) (U.S. EPA, 2006b). They may be present in ambient air not only as the result of the atmospheric oxidation of hydrocarbons but also by direct emissions. For example, motor vehicles and some industrial processes emit formaldehyde (Rappenglück et al., 2009) and vegetation emits methanol.

There are a large number of oxidized N-containing compounds in the atmosphere including NO, NO_2, NO_3, HNO_2, HNO_3, N_2O_5, HNO_4, PAN and its homologues, other organic nitrates, such as alkyl nitrates, isoprene nitrates and particulate nitrate. Collectively these species are referred to as NO_Y. Oxidized nitrogen compounds are emitted to the atmosphere mainly as NO which rapidly interconverts with NO_2 and so NO and NO_2 are often "lumped" together into their own group or family, which is referred to as NO_X. All the other species mentioned above in the definition of NO_Y are products of NO_X reactions are referred to as NO_Z, such that $NO_Y = NO_X + NO_Z$. The major reactions involving interconversions of oxidized N species were covered in the 2006 O_3 AQCD (Annex AX2.2.4). Mollner et al. (2010) identified pernitrous acid (HOONO), an unstable isomer of nitric acid, as a product of the major gas phase reaction forming HNO_3. However, since pernitrous acid is unstable, it is not a significant reservoir for NO_X. This finding stresses the importance of identifying products in addition to measuring the rate of disappearance of reactants in kinetic studies.

The photochemical cycles by which the oxidation of hydrocarbons leads 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 for 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). In the polluted atmosphere, the underlying chemical principles are the same, as discussed in the 2006 O_3 AQCD (U.S. EPA, 2006b) (Annex AX2.2.5). The conversion of NO to NO_2 occurring with the oxidation of VOCs is accompanied by the production of O_3 and the efficient regeneration of the OH radical, which in turn can react with other VOCs as shown in Figure 3-1.

The oxidation of alkanes and alkenes in the atmosphere has been treated in depth in the 1996 O_3 AQCD and was updated in the 2006 O_3 AQCD (Annexes AX2.2.6 and

AX2.2.7). In contrast to simple hydrocarbons containing one or two C atoms, detailed kinetic information about the gas phase oxidation pathways of many anthropogenic hydrocarbons (e.g., aromatic compounds such as benzene and toluene), biogenic hydrocarbons (e.g., isoprene, the monoterpenes), and their intermediate oxidation products (e.g., epoxides, nitrates, and carbonyl compounds) is lacking. Reaction with OH radicals represents the major loss process for alkanes. Reaction with chlorine (Cl) atoms is an additional sink for alkanes. Stable products of alkane photooxidation are known to include carbonyl compounds, alkyl nitrates, and d-hydroxycarbonyls. Major uncertainties in the atmospheric chemistry of the alkanes concern the chemistry of alkyl nitrate formation; these uncertainties affect the amount of NO-to-NO_2 conversion occurring and, hence, the amounts of O_3 formed during photochemical degradation of the alkanes.

The reaction of OH radicals with aldehydes produced during the oxidation of alkanes forms acyl (R′CO) radicals, and acyl peroxy radicals (R´C(O)−O_2) are formed by the further addition of O_2. As an example, the oxidation of ethane (C_2H_5−H) yields acetaldehyde (CH_3−CHO). The reaction of CH_3−CHO with OH radicals yields acetyl radicals (CH_3−CO). The acetyl radicals will then participate with O_2 in a termolecular recombination reaction to form acetyl peroxy radicals, which can then react with NO to form CH_3 + CO_2 or they can react with NO_2 to form PAN. PAN acts as a temporary reservoir for NO_2. Upon the thermal decomposition of PAN, either locally or elsewhere, NO_2 is released to participate in the O_3 formation process again.

Alkenes react in ambient air with OH, NO_3, and Cl radicals and with O_3. All of these reactions are important atmospheric transformation processes, and all proceed by initial addition to the carbon double bonds. Major products of alkene photooxidation include carbonyl compounds. Hydroxynitrates and nitratocarbonyls, and decomposition products from the energy-rich biradicals formed in alkene-O_3 reactions are also produced. Major uncertainties in the atmospheric chemistry of the alkenes concern the products and mechanisms of their reactions with O_3, especially the yields of free radicals that participate in O_3 formation. Examples of oxidation mechanisms of complex alkanes and alkenes can be found in comprehensive texts such as Seinfeld and Pandis (1998). Apart from the effects of the oxidation of isoprene on production of free radicals and O_3 formation, isoprene nitrates appear to play an important role as NO_X reservoirs over the eastern U.S. (e.g., Perring et al., 2009). Their decomposition leads to the recycling of NO_X, which can participate in the O_3 formation process again as was the case with decomposition of PAN and the even more unstable pernitrous acid. Although the photochemistry of isoprene is crucial for understanding ozone formation, major uncertainties in its oxidation pathways still exist. Issues concern the lack of regeneration of OH + HO_2 radicals especially in low NO_X (<~ 1 ppb) environments. The isomerization of the isoprene hydroxy-peroxy radicals that are formed after initial OH

attack and subsequent reactions could resolve this problem (Peeters and Müller, 2010; Peeters et al., 2009) and result in increases in OH concentrations from 20 to 40% over the southeastern U.S. (Archibald et al., 2011). Hofzumahaus et al. (2009) also found under predictions of OH in the Pearl River Delta. They also note that the sequence of reactions beginning with OH attack on VOCs introduces enormous complexity which is far from being explored.

The oxidation of aromatic hydrocarbons constitutes an important component of the chemistry of O_3 formation in urban atmospheres (Annex AX2.2.8 in the 2006 O_3 AQCD) (U.S. EPA, 2006b). Virtually all of the important aromatic hydrocarbon precursors emitted in urban atmospheres are lost through reaction with the hydroxyl radical. Loss rates for these compounds vary from slow (e.g., benzene) to moderate (e.g., toluene), to very rapid (e.g., xylene and trimethylbenzene isomers). However, the mechanism for the oxidation of aromatic hydrocarbons following reaction with OH is poorly understood, as is evident from the poor mass balance of the reaction products. The mechanism for the oxidation of toluene has been studied most thoroughly, and there is general agreement on the initial steps in the mechanism. However, at present there is no promising approach for resolving the remaining issues concerning the later steps. The oxidation of aromatic hydrocarbons also leads to particle formation that could remove gas-phase constituents that participate in O_3 formation.

Adequate analytical techniques needed to identify and quantify key intermediate species are not available for many compounds. In addition, methods to synthesize many of the suspected intermediate compounds are not available so that laboratory studies of their reaction kinetics cannot be performed. Similar considerations apply to the oxidation of biogenic hydrocarbons besides isoprene. These considerations are important because oxidants, other than O_3, that are formed from the chemistry described above could exert effects on human health and perhaps also on vegetation (Doyle et al., 2007; Doyle et al., 2004; Sexton et al., 2004). Gas phase oxidants include PAN, H_2O_2, CH_3OOH and other organic hydroperoxides.

Ozone is lost through a number of gas phase reactions and deposition to surfaces. The reaction of O_3 with NO to produce NO_2, e.g., in urban centers near roads, mainly results in the recycling of O_3 downwind via the recombination of $O(^3P)$ with O_2 to re-form O_3. By itself, this reaction does not lead to a net loss of O_3 unless the NO_2 is converted to stable end products such as HNO_3. Ozone reacts with unsaturated hydrocarbons and with OH and HO_2 radicals.

Perhaps the most recent field study aimed at obtaining a better understanding of atmospheric chemical processes was the Second Texas Air Quality Field Study (TexAQS-II) conducted in Houston in August and September 2006 (Olaguer et al., 2009).

The TexAQS-II Radical and Aerosol Measurement Project (TRAMP) found evidence for the importance of short-lived radical sources such as HCHO and HONO in increasing O_3 productivity. During TRAMP, daytime HCHO pulses as large as 32 ppb were observed and attributed to industrial activities upwind in the Houston Ship Channel (HSC) and HCHO peaks as large as 52 ppb were detected by in-situ surface monitors in the HSC. Primary HCHO produced in flares from local refineries and petrochemical facilities could increase peak O_3 by ~30 ppb (Webster et al., 2007). Other findings from TexAQS-II included significant concentrations of HONO during the day, with peak concentrations approaching 1 ppb at local noon. These concentrations are well in excess of current air quality model predictions using gas phase mechanisms alone (Sarwar et al., 2008) and multiphase processes are needed to account for these observations. Olaguer et al. (2009) also noted that using measured HONO brings modeled O_3 concentrations into much better agreement with observations and could result in the production of an additional 10 ppb O_3. Large nocturnal vertical gradients indicating a surface or near-surface source of HONO, and large concentrations of night-time radicals (~30 ppt HO_2) were also found during TRAMP.

3.2.3 Multiphase 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. In addition to hydrometeors (e.g., cloud and fog droplets and snow and ice crystals) there are also potential reactions involving atmospheric particles of varying composition (e.g., wet [deliquesced] inorganic particles, mineral dust, carbon chain agglomerates and organic carbon particles) to consider. Multiphase reactions are involved in the formation of a number of species such as particulate nitrate, and gas phase HONO that can act to both increase and reduce the rate of O_3 formation in the polluted troposphere. Data collected in Houston as part of TexAQS-II summarized by Olaguer et al. (2009) indicate that concentrations of HONO are much higher than can be explained by gas phase chemistry and by tailpipe emissions; and that the photolysis of HONO formed in multiphase reactions in addition to the other sources can help narrow the discrepancy between observed and predicted production of O_3. However, removal of HO_X and NO_X onto hydrated particles will reduce the production of O_3.

Multi-phase processes have been associated with the release of gaseous halogen compounds from marine aerosol, mainly in marine and coastal environments. However, Thornton et al. (2010) found production rates of gaseous nitryl chloride near Boulder, CO from reaction of N_2O_5 with particulate Cl^-, similar to those found in coastal and marine

environments. $ClNO_2$ readily photolyzes to yield Cl. They also found that substantial quantities of N_2O_5 are recycled through $ClNO_2$ back into NO_X instead of forming HNO_3 (a stable reservoir for reactive nitrogen compounds). The oxidation of hydrocarbons by Cl radicals released from the marine aerosol could lead to the rapid formation of peroxy radicals and higher rates of O_3 production in selected coastal environments and in continental environments. It should be noted that in addition to production from marine aerosol, reactive halogen species are also produced by the oxidation of halogenated organic compounds (e.g., CH_3Cl, CH_3Br, and CH_3I). The atmospheric chemistry of halogens is complex because Cl, Br and I containing species can react among themselves and with hydrocarbons and other species and could also be important for O_3 destruction, as has been noted for the lower stratosphere (McElroy et al., 1986; Yung et al., 1980). For example, the reactions of Br and Cl containing radicals deplete O_3 in selected environments such as the Arctic during the spring (Barrie et al., 1988), the tropical marine boundary layer (Dickerson et al., 1999), and inland salt flats and salt lakes (Stutz et al., 2002). Mahajan et al. (2010) found that I and Br species acting together resulted in O_3 depletion that was much larger than would have been expected if they acted individually and did not interact with each other (see Section AX2.2.10.3). It should be stressed that knowledge of multiphase processes is still evolving and there are still many questions that remain to be answered. However, it is becoming clear that multiphase processes are important for O_3 chemistry.

Reactions of O_3 with monoterpenes have been shown to produce oxidants in the aerosol phase, principally as components of ultrafine particles. Docherty et al. (2005) found evidence for the substantial production of organic hydroperoxides in secondary organic aerosol (SOA) resulting from the reaction of monoterpenes with O_3. Analysis of the SOA formed in their environmental chamber indicated that the SOA consisted mainly of 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 and acids or revert back to the hydroperoxides. The aldehydes are also produced in large measure during the ozonolysis of the monoterpenes. Monoterpenes also react with OH radicals resulting in the production of more lower-molecular-weight products than in the reaction with monoterpenes and O_3. 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 could also produce organic hydroperoxides in SOA (Johnson et al., 2004). Recent measurements show that the abundance of oxidized SOA exceeds that of more reduced hydrocarbon like organic aerosol in Pittsburgh (Zhang et al., 2005) and in about 30 other cities across the Northern Hemisphere (Zhang et al., 2007b). Based on aircraft and ship-based sampling of organic aerosols over coastal waters downwind of

northeastern U.S. cities, de Gouw et al. (2008) reported that 40-70% of measured organic mass was water soluble and estimated that approximately 37% of SOA is attributable to aromatic precursors, using PM yields estimated for NO_X-limited conditions. Uncertainties still exist as to the pathways by which the oxidation of isoprene leads to the formation of SOA. Noziere et al. (2011) found that a substantial fraction of 2-methyltetrols are primary in origin, although these species have been widely viewed solely as products of the atmospheric oxidation of isoprene. This finding points to lingering uncertainty in reaction pathways in the oxidation of isoprene and in estimates of the yield of SOA from isoprene oxidation.

Reactions of O_3 on the surfaces of particles, in particular those with humic acid like composition, are instrumental in the processing of SOA and the release of low-molecular-weight products such as HCHO (D'Anna et al., 2009). However, direct reactions of O_3 and atmospheric particles appear to be too slow to represent a major O_3 sink in the troposphere (D'Anna et al., 2009).

3.2.3.1 Indoor Air

Except when activities such as photocopying or welding are occurring, the major source of O_3 to indoor air is through infiltration of outdoor air. Reactions involving ambient O_3 with NO either from exhaled breath or from gas-fired appliances, surfaces of furnishings and terpenoid compounds from cleaning products, air fresheners and wood products also occur in indoor air as was discussed in the previous O_3 AQCD. The previous O_3 AQCD also noted that the ozonolysis of terpenoid compounds could be a significant source of secondary organic aerosol in the ultrafine size fraction. Chen et al. (2011) examined the formation of secondary organic aerosol from the reaction of O_3 that has infiltrated indoors with terpenoid components of commonly used air fresheners. They focused on the formation and decay of particle bound reactive oxygen species (ROS) and on their chemical properties. They found that the ROS content of samples can be decomposed into fractions that differ in terms of reactivity and volatility, however the overall ROS content of samples decays and over 90% is lost within a day at room temperature. This result also suggests loss of ROS during sampling periods longer than a couple of hours.

3.2.4 Temperature and Chemical Precursor Relationships

As might be expected based on the temperature dependence of many reactions involved in the production and destruction of O_3 and the temperature dependence of emissions processes such as evaporation of hydrocarbon precursors and the emissions of

biogenically important precursors such as isoprene, ambient concentrations of O_3 also show temperature dependence. Bloomer et al. (2009) determined the sensitivity of O_3 to temperature at rural sites in the eastern U.S. They found that O_3 increased on average at rural (CASTNET) sites by ~3.2 ppbv/ºC before 2002, and after 2002 by ~2.2 ppbv/ºC. This change in sensitivity was largely the result of reductions in NO_X emissions from power plants. These results are in accord with model predictions by Wu et al. (2008a) showing that the sensitivity of O_3 to temperature decreases with decreases in precursor emissions. However, this study was basically confined to the eastern U.S., but results from sites downwind of Phoenix, AZ showed basically no sensitivity of O_3 to temperature (R^2=0.02) (U.S. EPA, 2006b). However, Wise and Comrie (2005) did find that meteorological parameters (mixing height and temperature) typically accounts for 40 to 70% of the variability in O_3 in the five southwestern cities (including Phoenix) they examined. It is likely that differences in the nature of sites chosen (urban vs. rural) accounted for this difference and is at least partially responsible for the difference in results. Jaffe et al. (2008) regressed O_3 on temperature at Yellowstone and Rocky Mountain NP and found weak associations (R^2 = 0.09 and 0.16). They found that associations with area burned by wildfires are much stronger. These results demonstrate that the associations of O_3 with temperature are not as clear in the West as they might be in the East. Other sources as discussed in Section 3.4 might also be more important in the West than in the East.

The warmer months of the year are generally regarded as being the most conducive to higher O_3 concentrations. However, Schnell et al. (2009) reported observations of high O_3 concentrations (maximum 1-h avg of 140 ppb; maximum 8-h avg of 120 ppb) in the Jonah-Pinedale gas fields in Wyoming during winter at temperatures of -17ºC. Potential factors contributing to these anomalously high concentrations include a highly reflective snow surface, emissions of short-lived radical reservoirs (e.g., HONO and HCHO) and a very shallow, stable boundary layer trapping these emissions (Schnell et al., 2009). Multiphase processes might also be involved in the production of these short-lived reservoirs. At a temperature of -17ºC, the production of hydroxyl radicals (by the photolysis of O_3 yielding O^1D followed by the reaction, $O(^1D) + H_2O$, needed to initiate hydrocarbon oxidation) is severely limited, suggesting that another source of free radicals is needed. Radicals can be produced by the photolysis of molecules such as HONO and HCHO which photolyze in optically thin regions of the solar spectrum. A similar issue, in part due to the under-prediction of free radicals, has arisen in the Houston airshed where chemistry transport models under-predict O_3 (Olaguer et al., 2009).

Rather than varying directly with emissions of its precursors, O_3 changes in a nonlinear fashion with the concentrations of its precursors. At the low NO_X concentrations found in remote continental areas to rural and suburban areas downwind of urban centers (low-

NO_X regime), the net production of O_3 typically increases with increasing NO_X. At the high NO_X concentrations found in downtown metropolitan areas, especially near busy streets and roads, and in power plant plumes, there is scavenging (titration) of O_3 by reaction with NO (high-NO_X regime). 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 low-NO_X regime described above, the overall effect of the oxidation of VOCs is to generate (or at least not consume) free radicals, and O_3 production varies directly with NO_X. 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 this regime, O_3 production is limited by the availability of free radicals. The production of free radicals is in turn limited by the availability of solar UV radiation capable of photolyzing O_3 (in the Hartley bands) or aldehydes and/or by the abundance of VOCs whose oxidation produce more radicals than they consume. There are a number of ways to refer to the chemistry in these two chemical regimes. Sometimes the terms VOC-limited and NO_X-limited are used. 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 involving VOCs. The terms NO_X-limited and NO_X-saturated (Jaegle et al., 2001) will be used wherever possible to more adequately describe these two regimes. However, the terminology used in original articles will also be used here. In addition to these two regimes, there is also a "very low NO_X regime" in the remote marine troposphere in which NO_X concentrations are less than about 20 ppt. Under these very low NO_X conditions, which are not likely to be found in the U.S, HO_2 and CH_3O_2 radicals react with each other and HO_2 radicals undergo self-reaction (to form H_2O_2), and OH and HO_2 react with O_3, leading to net destruction of O_3 and inefficient OH radical regeneration by comparison with much higher NO_X concentrations found in polluted areas. In polluted areas, 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 as noted in 2006 O_3 AQCD (U.S. EPA, 2006b) (Annex AX2.2.5). There are no sharp transitions between these regimes. For example, in the "low NO_X regime" there still may be significant peroxy-peroxy radical reactions depending on the local NO_X concentration. In any case, in all of these NO_X regimes, O_3 production is also limited by the abundance of HO_X radicals.

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 (Poppe et al., 1993; Zimmermann and Poppe, 1993; Hameed et al., 1979). These considerations introduce a high degree of uncertainty into attempts to relate changes in

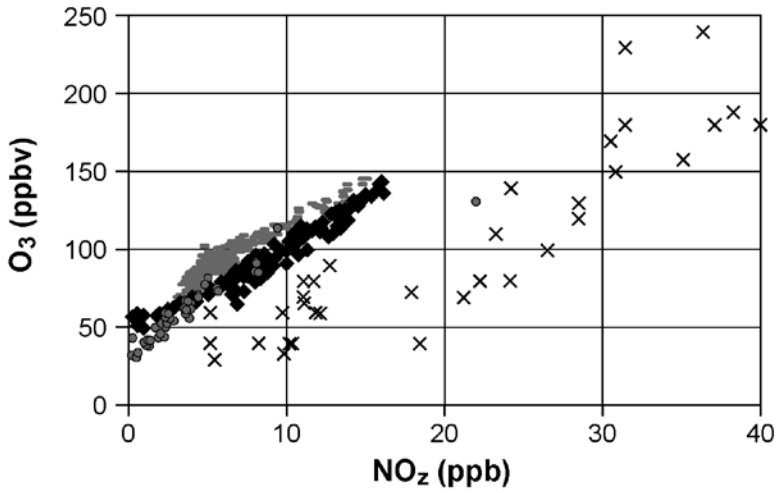
O_3 concentrations to emissions of precursors. There are no definitive rules governing the concentrations of NO_X at which the transition from NO_X-limited to NO_X-saturated conditions occurs. The transition between these two regimes is highly spatially and temporally dependent and depends also on the nature and abundance of the hydrocarbons that are present.

Trainer et al. (1993) and Olszyna et al. (1994) have shown that O_3 and NO_Y are highly correlated in rural areas in the eastern U.S. Trainer et al. (1993) also showed that O_3 concentrations correlate even better with NO_Z than with NO_Y, as may be expected because NO_Z represents the amount of NO_X that has been oxidized, forming O_3 in the process. NO_Z is equal to the difference between measured total reactive nitrogen (NO_Y) and NO_X and represents the summed products of the oxidation of NO_X. NO_Z is composed mainly of HNO_3, PAN and other organic nitrates, particulate nitrate, and HNO_4. Trainer et al. (1993) also suggested that the slope of the regression line between O_3 and NO_Z can be used to estimate the rate of O_3 production per NO_X oxidized (also known as the O_3 production efficiency [OPE]). Ryerson et al. (2001; 1998) used measured correlations between O_3 and NO_Z to identify different rates of O_3 production in plumes from large point sources. A number of studies in the planetary boundary layer over the continental U.S. have found that the OPE ranges typically from 1 to nearly 10. However, it may be higher in the upper troposphere and in certain areas, such as the Houston-Galveston area in Texas. Observations indicate that the OPE depends mainly on the abundance of NO_X and also on availability of solar UV radiation, VOCs and O_3 itself.

Various techniques have been proposed to use ambient NO_X and VOC measurements to derive information about the dependence of O_3 production on their concentrations. For example, 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 (NRC, 1991). In this approach, the ratio of summed (unweighted) VOC to NO_X is used to determine whether conditions were NO_X-limited or VOC-limited. This procedure is inadequate because it omits many factors that are important for O_3 production such as the impact of biogenic VOCs (which are typically not present in urban centers during early morning); important differences in the ability of individual VOCs to generate free radicals (rather than just total VOC) and other differences in O_3 forming potential for individual VOCs (Carter, 1995); and changes in the VOC to NO_X ratio due to photochemical reactions and deposition as air moves downwind from urban areas (Milford et al., 1994).

Photochemical production of O_3 generally occurs simultaneously with the production of various other species such as HNO_3, organic nitrates, and other oxidants such as

hydrogen peroxide. The relative rate of production of O_3 and other species varies depending on photochemical conditions, and can be used to provide information about O_3-precursor sensitivity. Sillman (1995) and Sillman and He (2002) identified several secondary reaction products that show different correlation patterns for NO_X-limited and NO_X-saturated conditions. The most important correlations are for O_3 versus NO_Y, O_3 versus NO_Z, O_3 versus HNO_3, and H_2O_2 versus HNO_3. The correlations between O_3 and NO_Y, and O_3 and NO_Z are especially important because measurements of NO_Y and NO_X are more widely available than for VOCs. Measured O_3 versus NO_Z (Figure 3-3) shows distinctly different patterns in different locations. In rural areas and in urban areas such as Nashville, TN, O_3 is highly correlated with NO_Z. By contrast, in Los Angeles, CA, O_3 is not as highly correlated with NO_Z, and the rate of increase of O_3 with NO_Z is lower and the O_3 concentrations for a given NO_Z value are generally lower. The different O_3 versus NO_Z relations in Nashville, TN and Los Angeles, CA reflects the difference between NO_X-limited conditions in Nashville versus an approach to NO_X-saturated conditions in Los Angeles.



Source: Adapted with permission of American Geophysical Union (Sillman and He, 2002; Sillman et al., 1998; Trainer et al., 1993)

Figure 3-3 Measured concentrations of O_3 and NO_Z (NO_Y–NO_X) during the afternoon at rural sites in the eastern U.S. (grey circles) and in urban areas and urban plumes associated with Nashville, TN (gray dashes); Paris, France (black diamonds); and Los Angeles, CA (Xs).

The difference between NO_X-limited and NO_X-saturated regimes is also reflected in measurements of H_2O_2. H_2O_2 production is highly sensitive to the abundance of free

radicals and is thus favored in the NO_X-limited regime. Measurements in the rural eastern U.S. (Jacob et al., 1995), Nashville, TN (Sillman et al., 1998), and Los Angeles, CA (Sakugawa and Kaplan, 1989), show large differences in H_2O_2 concentrations between likely NO_X-limited and NO_X-saturated locations.

The applications of indicator species mentioned above are limited to individual urban areas either because they are based on point measurements or by the range of the aircraft carrying the measurement instruments. Satellites provide a platform for greatly extending the range of applicability of the indicator technique and also have the resolution necessary to examine urban to rural differences. Duncan et al. (2010) used satellite data from OMI (Ozone Monitoring Instrument) for HCHO to NO_2 column ratios to diagnose NO_X-limited and radical-limited (NO_X-saturated) regimes. HCHO can be used as an indicator of VOCs as it is a common, short-lived, oxidation product of many VOCs that is a source of HO_X (Sillman, 1995). In adopting the satellite approach, chemistry-transport models (discussed further in Section 3.3) are used to estimate the fractional abundance of the indicator species in the planetary boundary layer. Duncan et al. (2010) found that O_3 formation over most of the U.S. became more sensitive to NO_X over most of the U.S. from 2005 to 2007 largely because of decreases in NO_X emissions. They also found that surface temperature is correlated with the ratio of HCHO to NO_2 especially in cities in the Southeast where emissions of isoprene (a major source of HCHO) are high due to high temperatures in summer.

3.3 Atmospheric Modeling

Chemistry-transport models (CTMs) have been widely used to compute the interactions among atmospheric pollutants and their transformation products, and the transport and deposition of pollutants. They have also been widely used to improve our basic understanding of atmospheric chemical processes and to develop control strategies. The spatial scales over which pollutant fields are calculated range from intra-urban to regional to global. Generally, these models are applied to problems on different spatial scales but efforts are underway to link across spatial scales for dealing with global scale environmental issues that affect population health within cities. Many features are common to all of these models and hence they share many of the same problems. On the other hand, there are significant differences in approaches to parameterizing physical and chemical processes that must be addressed in applying these models across spatial scales.

CTMs solve a set of coupled, non-linear partial differential equations, or continuity equations, for relevant chemical species. Jacobson (2005) described the governing partial differential equations, and the methods that are used to solve them. Because of limitations

imposed by the complexity and spatial-temporal scales of relevant physical and chemical processes, the CTMs must include parameterizations of these processes, which include atmospheric transport; the transfer of solar radiation through the atmosphere; chemical reactions; and removal to the surface by turbulent motions and precipitation. Development of parameterizations for use in CTMs requires data for three dimensional wind fields, temperatures, humidity, cloudiness, and solar radiation; emissions data for primary (i.e., directly emitted from sources) species such as NO_X, SO_2, NH_3, VOCs, and primary PM; and chemical reactions.

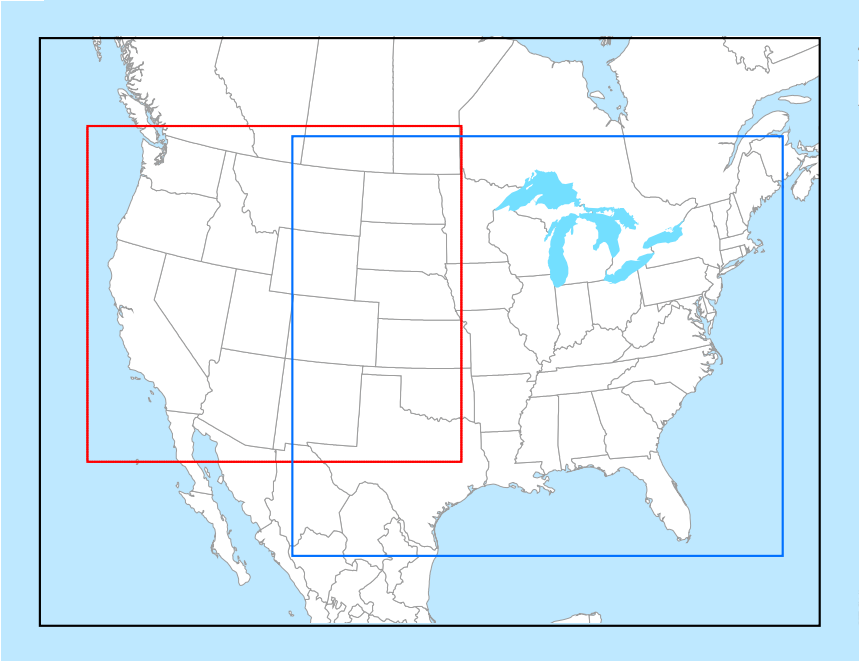


Figure 3-4 Sample CMAQ modeling domains. 36 km-grid-spacing; outer parent domain in black; 12 km western U.S. (WUS) domain in red; 12 km eastern U.S. (EUS) domain in blue.

The domains of CTMs extend from a few hundred kilometers on a side to the entire globe. Most major regional (i.e., sub-continental) scale air-related modeling efforts at EPA rely on the Community Multi-scale Air Quality modeling system (CMAQ) (Byun and Schere, 2006; Byun and Ching, 1999). CMAQ's horizontal domain typically extends over North America with efforts underway to extend it over the entire Northern Hemisphere. Note that CTMs can be 'nested' within each other as shown in Figure 3-4 which shows domains for CMAQ (Version 4.6.1); additional details on the model

configuration and application are found in (U.S. EPA, 2009e). The figure shows the outer domain (36 km horizontal grid spacing) and two 12 km spatial resolution (east and west) sub-domains. The upper boundary for CMAQ is typically set at about 100 hPa, or at about 16 km altitude on average, although in some recent applications the upper boundary has been set at 50 hPa. These domains and grid spacings are quite common and can also be found in a number of other models.

The main components of a CTM such as EPA's CMAQ are summarized in Figure 3-5. The capabilities of a number of CTMs designed to study local- and regional-scale air pollution problems were summarized by Russell and Dennis (2000) and in the 2006 O_3 AQCD. Historically, CMAQ has been driven most often by the MM5 mesoscale meteorological model (Seaman, 2000), though it could be driven by other meteorological models including the Weather Research Forecasting (WRF) model and the Regional Atmospheric Modeling System (RAMS) (ATMET, 2011).

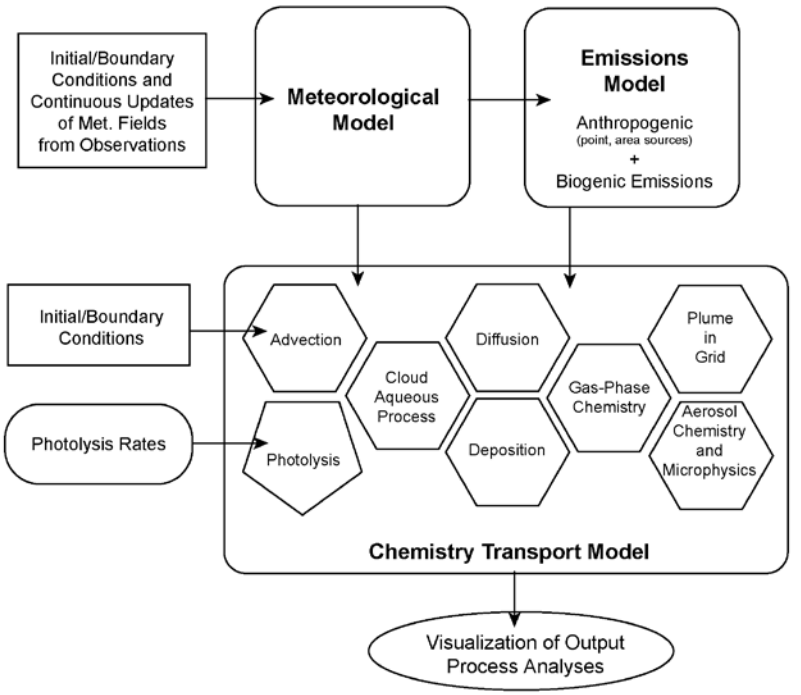


Figure 3-5 Main components of a comprehensive atmospheric chemistry modeling system, such as the U.S. EPA's Community Model for Air Quality (CMAQ) System.

Simulations of pollution episodes over regional domains have been performed with a horizontal resolution down to 1 km; see the application and general survey results

reported in Ching et al. (2006). However, simulations at such high resolution require better parameterizations of meteorological processes such as boundary layer fluxes, deep convection, and clouds (Seaman, 2000). Finer spatial resolution is necessary to resolve features such as urban heat island circulation; sea, bay, and land breezes; mountain and valley breezes; and the nocturnal low-level jet, all of which can affect pollutant concentrations. Other major air quality systems used for regional scale applications include the Comprehensive Air Quality Model with extensions (CAMx) (ENVIRON, 2005) and the Weather Research and Forecast model with Chemistry (WRF/Chem) (NOAA, 2010).

CMAQ and other grid-based or Eulerian air quality models subdivide the modeling domain into a three-dimensional array of grid cells. The most common approach to setting up the horizontal domain is to nest a finer grid within a larger domain of coarser resolution. The use of finer horizontal resolution in CTMs 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 and estimating their emissions. The vertical resolution of CTMs is variable and usually configured to have more layers in the PBL and fewer in the free troposphere.

The meteorological fields are produced either by other numerical prediction models such as those used for weather forecasting (e.g., MM5, WRF), and/or by assimilation of satellite data. The flow of information shown in Figure 3-5 has most often been unidirectional in the sense that information flows into the CTM (large box) from outside; feedbacks on the meteorological fields and on boundary conditions (i.e., out of the box) have not been included. However, CTMs now have the capability to consider these feedbacks as well; see, for example, Binkowski et al. (2007) and the Weather Research and Forecast model with Chemistry (WRF/Chem).

Because of the large number of chemical species and reactions that are involved in the oxidation of realistic mixtures of anthropogenic and biogenic hydrocarbons, condensed mechanisms must be used in atmospheric models. These mechanisms can be tested by comparison with smog chamber data. However, the existing chemical mechanisms often neglect many important processes such as the formation and subsequent reactions of long-lived carbonyl compounds, the incorporation of the most recent information about intermediate compounds, and heterogeneous reactions involving cloud droplets and aerosol particles.

The initial conditions, or starting concentration fields of all species computed by a model, and the boundary conditions, or 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. Both initial and boundary conditions can be estimated from models or data or, more generally, model + data hybrids. Because data for vertical

profiles of most species of interest are very sparse, results of model simulations over larger, usually global, domains are often used.

Chemical kinetics mechanisms representing the important reactions occurring in the atmosphere are used in CTMs to estimate the rates of chemical formation and destruction of each pollutant simulated as a function of time. The Master Chemical Mechanism (Univ of Leeds, 2010) is a comprehensive reaction database providing as near an explicit treatment of chemical reactions in the troposphere as is possible. The MCM currently includes over 12,600 reactions and 4,500 species. However, mechanisms that are this comprehensive are still computationally too demanding to be incorporated into CTMs for regulatory use. Simpler treatments of tropospheric chemistry have been assembled by combining chemical species into mechanisms that group together compounds with similar chemistry. It should be noted that because of different approaches to the lumping of organic compounds into surrogate groups for computational efficiency, chemical mechanisms can produce different results under similar conditions. Jimenez et al. (2003) provided brief descriptions of the features of the main mechanisms in use and compared concentrations of several key species predicted by seven chemical mechanisms in a box-model simulation over 24 hours. There are several of these mechanisms (CB04, CB05, SAPRC) that have been incorporated into CMAQ (Luecken et al., 2008) and Fuentes et al. (2007) for RACM2. The CB mechanism is currently undergoing extension (CB06) to include, among other things, longer lived species to better simulate chemistry in the remote and upper troposphere. These mechanisms were developed primarily for homogeneous gas phase reactions and treat multi-phase chemical reactions in a very cursory manner, if at all. As an example of the effects of their neglect, models such as CMAQ could have difficulties with capturing the regional nature of O_3 episodes, in part because of uncertainty in the chemical pathways converting NO_X to HNO_3 and recycling of NO_X (Godowitch et al., 2008; Hains et al., 2008). Much of this uncertainty also involves multi-phase processes as described in Section 3.2.

CMAQ and other CTMs incorporate processes and interactions of aerosol-phase chemistry (Zhang and Wexler, 2008; Gaydos et al., 2007; Binkowski and Roselle, 2003). There have also been several attempts to study the feedbacks of chemistry on atmospheric dynamics using meteorological models like MM5 and WRF (Liu et al., 2001; Park et al., 2001; Grell et al., 2000; Lu et al., 1997). This coupling is necessary to accurately simulate feedbacks from PM (Park et al., 2001; Lu et al., 1997) over areas such as Los Angeles or the Mid-Atlantic region. Photolysis rates in CMAQ can now be calculated interactively with model produced O_3, NO_2, and aerosol fields (Binkowski et al., 2007).

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, NH_3, and NO_X. Preprocessing of emissions data for CMAQ is done by the Spare-Matrix Operator Kernel Emissions (SMOKE) system (CEMPD, 2011). For many species, information concerning the temporal variability of emissions is lacking, so long-term annual averages are used in short-term, episodic simulations. Annual emissions estimates can be modified by the emissions model to produce emissions more characteristic of the time of day and season. Significant errors in emissions can occur if inappropriate time dependence is used.

Each of the model components described above has associated uncertainties; 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). While the effects of poorly specified boundary conditions propagate through the model's domain, the effects of these errors remain undetermined. Because many meteorological processes occur on spatial scales smaller than the model's vertical or horizontal grid spacing and thus are not calculated explicitly, parameterizations of these processes must be used. These parameterizations introduce additional uncertainty.

The performance of CTMs must be evaluated by comparison with field data as part of a cycle of model evaluations and subsequent improvements (NRC, 2007). However, they are too demanding of computational time to have the full range of their sensitivities examined by using Monte Carlo techniques (NRC, 2007). Models of this complexity are evaluated by comparison with field observations for O_3 and other species. Evaluations of the performance of CMAQ are given in Arnold et al. (2003), Eder and Yu (2005), Appel et al. (2005), and Fuentes and Raftery (2005). Discrepancies between model predictions and observations can be used to point out gaps in current understanding of atmospheric chemistry and to spur improvements in parameterizations of atmospheric chemical and physical processes. Model evaluation does not merely involve a straightforward comparison between model predictions and the concentration field of the pollutant of interest. Such comparisons may not be meaningful because it is difficult to determine if agreement between model predictions and observations truly represents an accurate treatment of physical and chemical processes in the CTM or the effects of compensating errors in complex model routines (in other words, it is important to know if the right answer is obtained for the right reasons). Each of the model components (emissions inventories, chemical mechanism, and meteorological driver) should be evaluated individually as has been done in to large extent in some major field studies such as TexAQS I and II. In addition to comparisons between concentrations of calculated and measured species, comparisons of correlations between measured primary VOCs and

NO_X and modeled VOCs and NO_X are especially useful for evaluating results from chemistry-transport models. Likewise, comparisons of correlations between measured species and modeled species can be used to provide information about the chemical state of the atmosphere and to evaluate model representations. A CTM that demonstrates the accuracy of both its computed VOC and NO_X in comparison with ambient measurements, and the spatial and temporal relations among the critical secondary species associated with $O_{3,}$ has a higher probability of representing O_3-precursor relations correctly than one that does not.

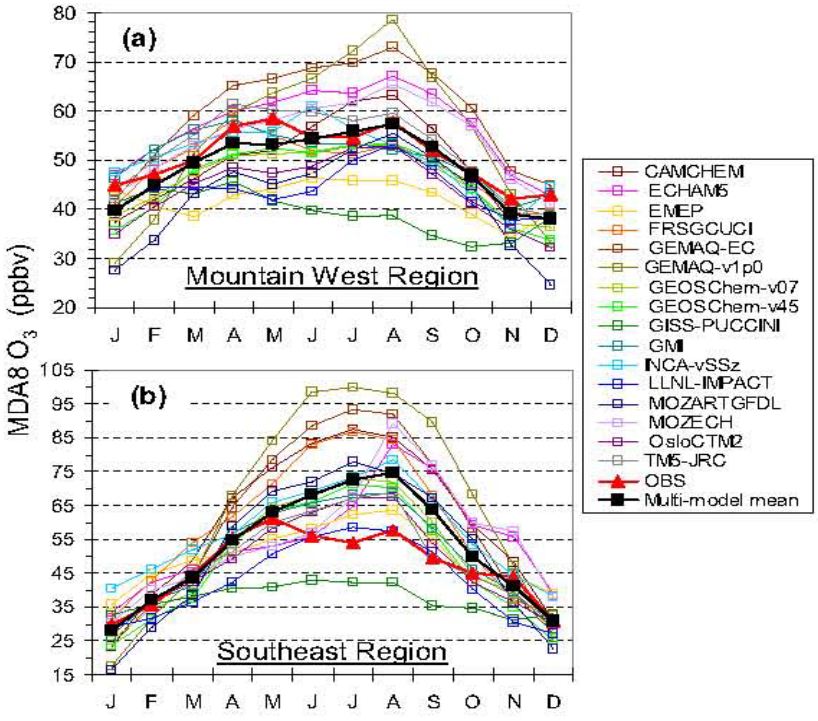
The above techniques are sometimes referred to as "static" in the sense that individual model variables are compared to observations. It is also crucial to understand the dynamic response to changes in inputs and to compare the model responses to those that are observed. These tests might involve changes in some natural forcing or in emissions from an anthropogenic source. As an example, techniques such as the direct decoupled method (DDM) (Dunker et al., 2002; Dunker, 1981) could be used. However, the observational basis for comparing a model's response is largely unavailable for many problems of interest, in large part because meteorological conditions are also changing while the emissions are changing. As a result, methods such as DDM are used mainly to address the effectiveness of emissions controls.

3.3.1 Global Scale CTMs

With recognition of the global nature of many air pollution problems, global scale CTMs have been applied to regional scale pollution problems (NRC, 2009). Global-scale CTMs are used to address issues associated with global change, to characterize long-range transport of air pollutants, and to provide boundary conditions for the regional-scale models. The upper boundaries of global scale CTMs extend anywhere from the tropopause (~8 km at the poles to ~16 km in the tropics) to the mesopause at ~80 km, in order to obtain more realistic boundary conditions for problems involving stratospheric dynamics and chemistry. The global-scale CTMs consider the same processes shown in Figure 3-5 for the regional scale models. In addition, many of the same issues that have arisen for the regional models have also arisen for the global scale models (Emmerson and Evans, 2009). For example, predictions of HNO_3 were found to be too high and predictions of PAN were found to be too low over the U.S. during summer in the MOZART model (Fang et al., 2010). Similar findings were obtained in a box model of upper tropospheric chemistry (Henderson et al., 2010).

The GEOS-Chem model is a community-owned, global scale CTM that has been widely used to study issues associated with the intra- and inter-hemispheric transport of pollution

and global change (Harvard University, 2010a). Comparisons of the capabilities of GEOS-Chem and several other models to simulate intra-hemispheric transport of pollutants are given in a number of articles (Fiore et al., 2009; Reidmiller et al., 2009). Reidmiller et al. (2009) showed comparisons among 18 global models and their ensemble average to spatially and monthly averaged observations of O_3 at CASTNET sites (see Figure 3-6). These results show that the multi-model ensemble agrees much better with the observations than do most of the individual models. The GEOS-Chem model was run for two grid spacings, 4°×4.5° and 2°×2.5° with very similar results that lie close to the ensemble average. In general, the model ensemble and the two GEOS-Chem simulations are much closer to the observations in the Intermountain West than in the Southeast. In particular, there are sizable over-predictions by most of the models in the Southeast during summer, the time when major O_3 episodes occur.



Source: Used with permission from Copernicus Publications (Reidmiller et al., 2009)

Figure 3-6 Comparison of global CTM predictions of maximum daily 8-h avg ozone concentrations and multi-model mean with monthly averaged CASTNET observations in the Intermountain West and Southeast regions of the U.S.

Global models are not alone in overestimating O_3 in the Southeast. Godowitch et al. (2008), Gilliland et al. (2008) and Nolte et al. (2008) found positive O_3 biases in regional models over the eastern U.S., as well, which they largely attributed to uncertainties in temperature, relative humidity and planetary boundary layer height. Agreement between monthly average values is expected to be better than with daily values because of a number of factors including the increasing uncertainty of emissions at finer time resolution. Kasibhatla and Chameides (2000) found that the accuracy of simulations improved as the averaging time of both the simulation and the observations increased.

Simulations of the effects of long-range transport at particular locations must be able to link multiple horizontal resolutions from the global to the local scale. Because of limitations on computational resources, global simulations are not made at the same horizontal resolutions found in the regional scale models, i.e., down to 1-4 km resolution on a side. They are typically conducted with a horizontal grid spacing of 1º-2º of latitude and longitude (or roughly 100-200 km at mid-latitudes). Some models such as GEOS-Chem have the capability to include nested models at a resolution of 0.5º×0.667º (Wang et al., 2009a) and efforts are underway to achieve even higher spatial resolution. Another approach is to nest regional models within GEOS-Chem. Caution must be exercised with nesting different models because of differences in chemical mechanisms and numerical schemes, and in boundary conditions between the outer and inner models. As an example of these issues, surface O_3 concentrations that are too high have been observed in models in which CMAQ was nested inside of GEOS-Chem. The high O_3 results in large measure from stratospheric O_3 intruding into the CMAQ domain [for one way to address this issue see Lam (2010)]. In addition, downward mixing of this O_3 in CMAQ that is too rapid might also be involved. Ozone has large vertical gradients in the upper troposphere that must be preserved if its downward transport is to be simulated correctly. Using a vertical resolution in CMAQ that is too coarse could be involved, coupled with using fewer layers in CMAQ than in the driving MM5 or WRF meteorological model. As a result of the above factors, O_3 gradients are eliminated and O_3 is mixed too rapidly in the upper troposphere. Efforts are also being made to extend the domain of CMAQ over the Northern Hemisphere. In this approach, the same numerical schemes are used for transporting species and the same chemistry is used throughout all spatial scales. Finer resolution in models of any scale can only improve scientific understanding to the extent that the governing processes are accurately described. Consequently, there is a crucial need for observations at the appropriate scales to evaluate the scientific understanding represented by the models.

3.4 Background Ozone Concentrations

Background concentrations of O_3 have been given various definitions in the literature over time. In the context of a review of the NAAQS, it is useful to define background O_3 concentrations in a way that distinguishes between concentrations that result from precursor emissions that are relatively less directly controllable from those that are relatively more directly controllable through U.S. policies. North American (NA) background O_3 can include contributions that result from emissions from natural sources (e.g., stratospheric intrusion, biogenic methane and more short-lived VOC emissions), emissions of pollutants that contribute to global concentrations of O_3 (e.g., anthropogenic methane) from countries outside North America. In previous NAAQS reviews, a specific definition of background concentrations was used and referred to as policy relevant background (PRB). In those previous reviews, PRB concentrations were defined by EPA as those concentrations that would occur in the U.S. in the absence of anthropogenic emissions in continental North America (CNA), defined here as the U.S., Canada, and Mexico. For this document, we have focused on the sum of those background concentrations from natural sources everywhere in the world and from anthropogenic sources outside CNA. North American background concentrations so defined facilitate separation of pollution that can be controlled directly by U.S. regulations or through international agreements with neighboring countries from that which would require more comprehensive international agreements, such as are being discussed as part of the United Nations sponsored Convention on Long Range Transboundary Air Pollution Task Force on Hemispheric Air Pollution. There is no chemical difference between background O_3 and O_3 attributable to CNA anthropogenic sources, and background concentrations can contribute to the risk of health effects. However, to inform policy considerations regarding the current or potential alternative standards, it is useful to understand how total O_3 concentrations can be attributed to different sources.

Contributions to NA background O_3 include photochemical reactions involving natural emissions of VOCs, NOX, and CO as well as the long-range transport of O_3 and its precursors from outside CNA, and the stratospheric-tropospheric exchange (STE) of O_3. These sources have the greatest potential for producing the highest background concentrations, and therefore are discussed in greater detail below. Natural sources of O_3 precursors include biogenic emissions, wildfires, and lightning. Biogenic emissions from agricultural activities in CNA are not considered in the formation of NA background O_3. Sources included in the definition of NA background O_3 are shown schematically in Figure 3-7. Definitions of background and approaches to derive background concentrations were reviewed in the 2006 O_3 AQCD and in Reid et al. (2008).

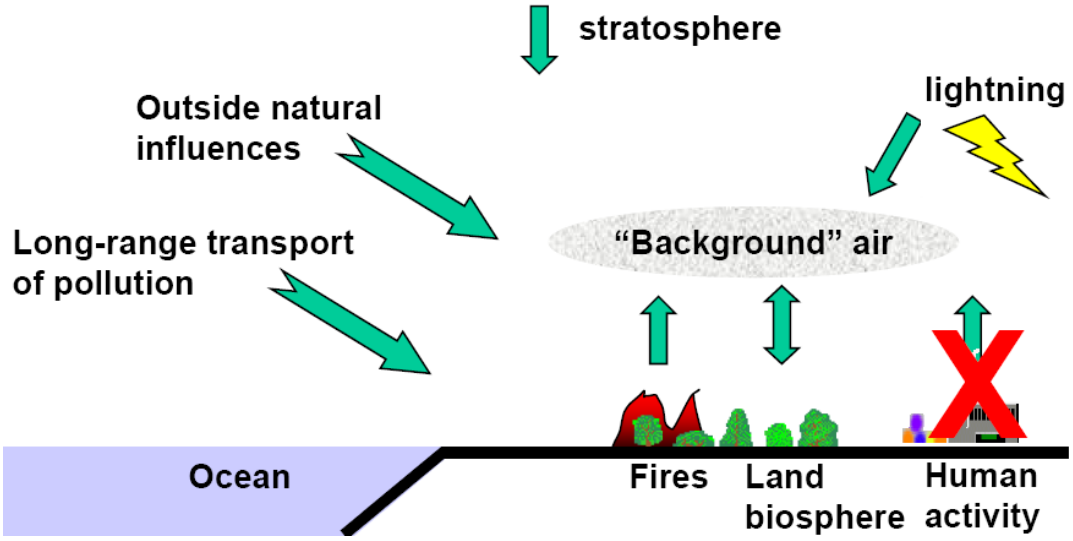


Figure 3-7 Schematic overview of contributions to North American background concentrations of ozone, i.e., ozone concentrations that would exist in the absence of anthropogenic emissions from the U.S., Canada, and Mexico.

3.4.1 Contributions from Anthropogenic Emissions outside North America

In addition to emissions from North America, emissions from Eurasia have contributed to the global burden of O_3 in the atmosphere and to the U.S. (NRC, 2009, and references therein). Because the mean tropospheric lifetime of O_3 is 30-35 days (Hsu and Prather, 2009), O_3 can be transported from continent to continent and around the globe in the Northern Hemisphere and O_3 produced by U.S. emissions can be recirculated around northern mid-latitudes back to the U.S. High elevation sites are most susceptible to the intercontinental transport of pollution especially during spring. An O_3 concentration of ~85 ppb was observed at Mt. Bachelor Observatory, OR (elevation 2,700 m) on April 22, 2006 with a number of occurrences of O_3 >60 ppb from mid-April to mid-May of 2006. Calculations using GEOS-Chem, a global-scale, chemistry-transport model, indicate that Asia contributed 9 ± 3 ppb to a modeled mean concentration of 53 ± 9 ppb O_3 at Mt. Bachelor during the same period compared to measured concentrations of 54 ± 10 ppb (Zhang et al., 2008). Zhang et al. (2008) also calculated a contribution of 5 to 7 ppb to surface O_3 over the western U.S. during that period from Asian anthropogenic emissions. They also estimated an increase in NO_X emissions of ~ 44% from Asia from 2001 to 2006 resulting in an increase of 1-2 ppb in O_3 over North America.

Cooper et al. (2010) analyzed all available O_3 measurements in the free troposphere above western North America at altitudes of 3-8 km (above sea level) during April and

May of 1995 to 2008 (i.e., times when intercontinental transport is most prominent). They derived a trend of +0.63 ± 0.34 ppb/year in median O_3 concentrations with indication of a similar rate of increase since 1984. Back trajectories that were likely to have been strongly and recently influenced by North American emissions were filtered out, resulting in a trend of +0.71 ± 0.45 ppb/year. Considering only trajectories with an Asian origin resulted in a trend of +0.80 ± 0.34 ppb/year. These results suggest that local North American emissions were not responsible for the measured O_3 increases. This O_3 could have been produced from natural and anthropogenic precursors in Asia and Europe with some contribution from North American emissions that have circled the globe. Cooper et al. (2010) also found that it is unlikely that the trends in tropospheric O_3 are associated with trends in stratospheric intrusions. Note, however, that these results relate to O_3 trends above ground level and not to surface O_3. Jaffe (2011) found associations between ozonesonde data and the average of 10 CASTNET Sites in the western U.S. with R^2 ranging between 0.048 in October and 0.45 in August for all days on a monthly basis for which there was an ozonesonde launch. Model results (Zhang et al., 2008) show that surface O_3 contributions from Asia are much smaller than those derived in the free troposphere because of dilution and chemical destruction during downward transport to the surface. These processes tend to reduce the strength of associations between free tropospheric and surface O_3 especially if air from other sources is sampled by the surface monitoring sites.

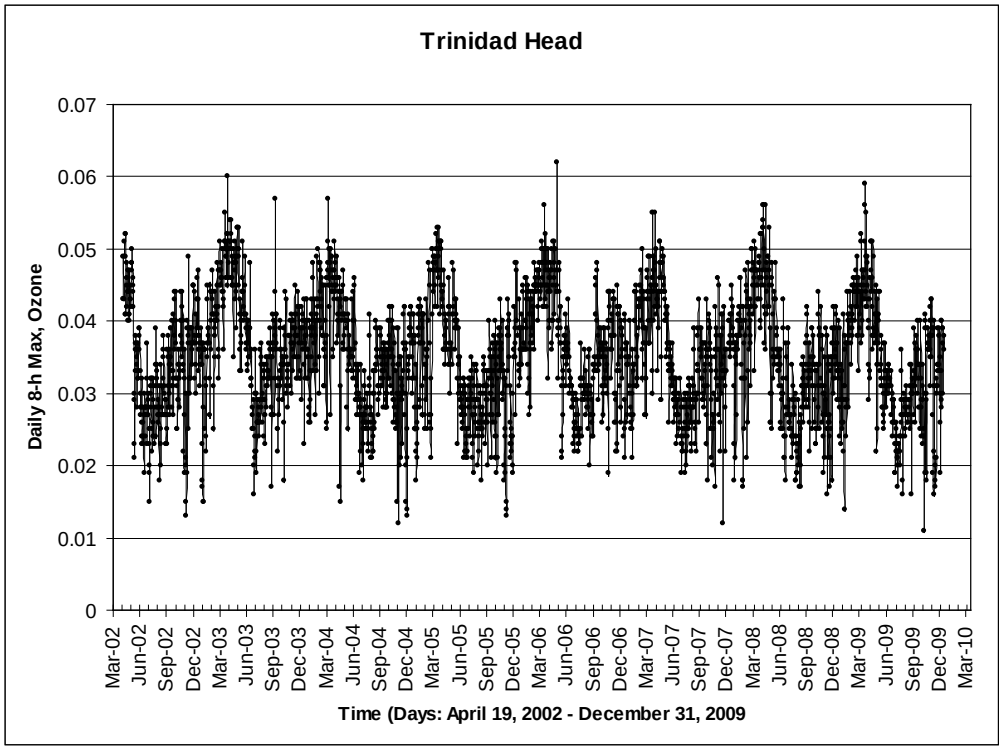
Sampling locations and times at which measurements might be expected to reflect in large measure North American background O_3 contributions include Trinidad Head, CA at times during spring (Oltmans et al., 2008; Goldstein et al., 2004). The monitoring station at Trinidad Head is on an elevated peninsula extending out from the mainland of northern California, and so might be expected at times to intercept air flowing in from the Pacific Ocean with little or no influence from sources on the mainland. Figure 3-8 shows the time series of daily maximum 8-h avg O_3 concentrations measured at Trinidad Head from April 18, 2002 through December 31, 2009. The data show pronounced seasonal variability with spring maxima and summer minima. Springtime concentrations typically range from 40 to 50 ppb with a number of occurrences >50 ppb. The two highest daily maxima were 60 and 62 ppb. The data also show much lower concentrations during summer, with concentrations typically ranging between 20 and 30 ppb. Oltmans et al. (2008) examined the time series of O_3 and back trajectories reaching Trinidad Head. They found that springtime maxima (April-May) were largely associated with back trajectories passing over the Pacific Ocean and most likely entraining emissions from Asia, with minimal interference from local sources. However, Parrish et al. (2009) noted that only considering trajectories coming from a given direction is not sufficient for ruling out local continental influences, as sea breeze circulations are complex phenomena involving vertical mixing and entrainment of long-shore components. They found that

using a wind speed threshold, in addition to a criterion for wind direction, allowed for determination of background trajectories not subject to local influence; as judged by measurements of chemical tracers such as CO_2, MTBE and radon. By applying the two criteria for wind speed and direction, they found that Trinidad Head met these criteria only 30% of the time during spring. Goldstein et al. (2004) used CO_2 as an indicator of exchange with the local continental environment and found that O_3 concentrations were higher by about 2-3 ppb when filtered against local influence indicating higher O_3 in air arriving from over the Pacific Ocean. At Trinidad Head during spring, O_3 is more likely to be titrated by local emissions of NO_X than to be photochemically produced (Parrish et al., 2009). At other times of the year, Trinidad Head is less strongly affected by air passing over Asia and many trajectories have long residence times over the semi-tropical and tropical Pacific Ocean, where O_3 concentrations are much lower than they are at mid-latitudes. The use of the Trinidad Head data to derive contributions from background sources requires the use of screening procedures adopted by Parrish et al. (2009) and the application of photochemical models to determine the extent either of titration of O_3 by fresh NO_X emissions and the extent of local production of O_3 from these emissions. As noted above, anthropogenic emissions from North America also contribute to hemispheric background and must be filtered out from observations even when it is thought that air sampled came directly from over the Pacific Ocean and was not influenced by local pollutant emissions.

Parrish et al. (2009) also examined data obtained at other marine boundary layer sites on the Pacific Coast. These include Olympic NP, Redwood NP, Point Arena, and Point Reyes. Using data from these sites, they derived trends in O_3 of +0.46 ppb/year (with a 95% confidence interval of 0.13 ppb/year) during spring and +0.34 ppb/year (0.09 ppb/year) for the annual mean O_3 increase in air arriving from over the Pacific during the past two decades. Although O_3 data are available from the Channel Islands, Parrish et al. (2009) noted that these data are not suitable for determining background influence because of the likelihood of circulating polluted air from the South Coast Basin.

Cooper et al. (In Press) further examined O_3 profiles measured above four coastal sites in California, including Trinidad Head. Based on comparison with the ozone profiles, they suggested that Asian pollution, stratospheric intrusions and international shipping made substantial contributions to lower tropospheric O_3 measured at inland California sites. These contributions tended to increase on a relative basis in going from south north. In particular, no increases in lower tropospheric O_3 in the northern Central Valley, and increases of 32 to 63% in the LA basin due to local pollution were found. It should be noted that the extent of photochemical production and loss, involving both anthropogenic and natural precursors, occurring in descending air still remains to be determined. Cooper et al. (In Press) also note that very little (8-10%) of the sources noted above and affecting

the vertical O_3 measurements reach the eastern U.S. However, this does not necessarily mean that the effects of the Asian sources were fully captured in the ozone profiles or that stratospheric intrusions do not occur over the eastern U.S.



Source: Used with permission from Elsevier Ltd. (Oltmans et al., 2008) and NOAA Climate Monitoring Diagnostics Laboratory for data from 2008-2009

Figure 3-8 Time series of daily maximum 8-h avg ozone concentrations (ppm) measured at Trinidad Head, CA, from April 18, 2002 through December 31, 2009.

3.4.2 Contributions from Natural Sources

3.4.2.1 Contributions from the Stratosphere

The basic atmospheric dynamics and thermodynamics of STE were outlined in the 2006 O_3 AQCD; as noted there, stratospheric air rich in O_3 is transported into the troposphere.

Ozone is produced naturally by photochemical reactions in the stratosphere as shown in Figure 3-1 in Section 3.2. Some of this O_3 is transported downward into the troposphere throughout the year, with maximum contributions at mid-latitudes during late winter and early spring mainly coming from a process known as tropopause folding. These folds occur behind most cold fronts, bringing stratospheric air with them. The tropopause should not be interpreted as a material surface through which there is no exchange. Rather these folds should be thought of as regions in which mixing of tropospheric and stratospheric air is occurring (Shapiro, 1980). This imported stratospheric air contributes to the natural background of O_3 in the troposphere, especially in the free troposphere during winter and spring. STE also occurs during other seasons including summer.

Methods for estimating the contribution of stratospheric intrusions rely on the use of tracers of stratospheric origin that can be either dynamical or chemical. Thompson et al. (2007), based on analysis of ozonesonde data found that roughly 20-25% of tropospheric O_3 over northeastern North America during July-August 2004 was of stratospheric origin. This O_3 can be mixed into the PBL where it can either be destroyed or transported to the surface. They relied on the combined use of low relative humidity and high (isentropic) potential vorticity (PV) (> 2 PV units) to identify stratospheric contributions. PV has been a widely used tracer for stratospheric air; see the 2006 O_3 AQCD. Lefohn et al. (2011) used these and additional criteria to assess stratospheric influence on sites in the intermountain West and in the Northern Tier. Additional criteria include consideration of trajectories originating at altitudes above the 380 K potential temperature surface with a residence time requirement at these heights. They identified likely stratospheric influence at the surface sites on a number of days during spring of 2006 to 2008. However, they noted that their analysis of stratospheric intrusions captures only the frequency and vertical penetration of the intrusions but does not provide information about the contribution of the intrusions to the measured O_3 concentration. These results are all generally consistent with what was noted in the 2006 O_3 AQCD. Fischer et al. (2004) analyzed the O_3 record during summer at Mount Washington and identified a stratospheric contribution to 5% of events during the summers of 1998 -2003 when O_3 was > 65 ppb; the air was dry and trajectories originated from altitudes where potential vorticity was elevated (PV > 1 PV unit). However, this analysis did not quantify the relative contributions of anthropogenic and stratospheric O_3 sources, because as they note identifying stratospheric influences is complicated by transport over industrialized/urban source regions. Stratospheric O_3 was hypothesized to influence the summit during conditions also potentially conducive to photochemical O_3 production, which make any relative contribution calculations difficult without additional measurements of anthropogenic and stratospheric tracers.

Although most research has been conducted on tropopause folding as a source of stratosphere to troposphere exchange, this is not the only mechanisms by which stratospheric ozone can be brought to lower altitudes. Tang et al. (2011) estimated that deep convection capable of penetrating the tropopause can increase the overall downward flux of O_3 by ~ 20%. This mechanism operates mainly during summer in contrast with tropopause folding which is at a maximum from late winter through spring and at lower latitudes. Yang et al. (2010) estimated that roughly 20% of free tropospheric O_3 above coastal California in 2005 and 2006 was stratospheric in origin. Some of this O_3 could also contribute to O_3 at the surface.

It should be noted that there is considerable uncertainty in the magnitude and distribution of this potentially important source of tropospheric O_3. Stratospheric intrusions that reach the surface are much less frequent than intrusions which penetrate only to the middle and upper troposphere. However, O_3 transported to the upper and middle troposphere can still affect surface concentrations through various exchange mechanisms that mix air from the free troposphere with air in the PBL.

Several instances of STE producing high concentrations of O_3 around Denver and Boulder, CO were analyzed by Langford et al. (2009) and several likely instances of STE, including one of the cases analyzed by Langford et al. (2009) were also cited in the 2006 O_3 AQCD (U.S. EPA, 2006b) (Annex AX23, Section AX3.9). Clear examples of STE have also been observed in southern Quebec province by Hocking et al. (2007), in accord with previous estimates by Wernli et al. (2002) and James et al. (2003). As also noted in the 2006 O_3 AQCD, the identification of stratospheric O_3, let alone the calculation of its contributions, is highly problematic and requires data for other tracers.

3.4.2.2 Contributions from Other Natural Sources

Biomass burning consists of wildfires and the intentional burning of vegetation to clear new land for agriculture and for population resettlement; to control the growth of unwanted plants on pasture land; to manage forest resources with prescribed burning; to dispose of agricultural and domestic waste; and as fuel for cooking, heating, and water sterilization. Globally, most wildfires may be ignited directly as the result of human activities, leaving only 10-30% initiated by lightning (Andreae, 1991). However, because fire management practices suppress natural wildfires, the buildup of fire fuels increases the susceptibility of forests to more severe but less frequent fires in the future. Thus there is considerable uncertainty in attributing the fraction of wildfire emissions to human activities because the emissions from naturally occurring fires that would have been present in the absence of fire suppression practices are not known. Contributions to NO_X,

CO and VOCs from wild fires and prescribed fires are considered as precursors to background O_3 formation.

Biomass burning also exhibits strong seasonality and interannual variability (van der Werf et al., 2006), with most biomass burned during the local dry season. This is true for both prescribed burns and wildfires. Jaffe et al. (2008) examined the effects of wildfires on O_3 in the western U.S. They found a strong association ($R^2 = 0.60$) between O_3 measured at various national park and CASTNET sites and area burned within surrounding 5°×5° and 10°×10° areas. However, no such association was found when considering the surrounding 1°×1° area, reflecting near source consumption of O_3 and the time necessary for photochemical processing of emissions to form O_3. Jaffe et al. (2008) estimate that burning 1 million acres results in an increase of O_3 of 2 ppb, on average; and that O_3 increased by 3.5 and 8.8 ppb during mean and maximum fire years. The unusually warm and dry weather in central Alaska and western Yukon in the summer of 2004, for example, contributed to the burning of 11 million acres there. Subsequent modeling by Pfister et al. (2005) showed that the CO contribution from these fires in July 2004 was 33.1 (± 5.5) MT that summer, roughly comparable to total U.S. anthropogenic CO emissions during the same period. These results underscore the importance of wildfires as a source of important O_3 precursors. In addition to emissions from forest fires in the U.S., emissions from forest fires in other countries can be transported to the U.S., for example from boreal forest fires in Canada (Mathur, 2008), Siberia (Generoso et al., 2007) and tropical forest fires in the Yucatan Peninsula and Central America (Wang et al., 2006). These fires have all resulted in notable increases in O_3 concentrations in the U.S.

Estimates of biogenic VOC and CO emissions are made using the BEIS model with data from the BELD and annual meteorological data. VOC emissions from vegetation were described in Section 3.2. As noted earlier, NO_X is produced by lightning. Kaynak et al. (2008) found contributions of 2 to 3 ppb background O_3 centered mainly over the southeastern U.S. during summer. Although total column estimates of lightning-produced NO_X are large compared to anthropogenic NO_X during summer, lightning-produced NO_X does not contribute substantially to the NO_X burden in the continental boundary layer. This is because only 2% of NO_X production by lightning occurs within the boundary layer and most occurs in the free troposphere (Fang et al., 2010). In addition, much of the NO_X produced in the free troposphere is converted to more oxidized N species during downward transport.

3.4.3 Estimating Background Concentrations

Historically, two approaches to estimating North American background concentrations (previously referred to as PRB) have been considered in previous O_3 assessments. In the 1996 and earlier O_3 AQCDs, measurements from remote monitoring sites were used. In the 2006 O_3 AQCD, the use of chemistry-transport models was adopted, because as noted in Section 3.9 of the 2006 O_3 AQCD (U.S. EPA, 2006b), estimates of background concentrations cannot be obtained directly by examining measurements of O_3 obtained at relatively remote monitoring sites in the U.S. because of the long-range transport from anthropogenic source regions within North America. The 2006 O_3 AQCD also noted that it is impossible to determine sources of O_3 without ancillary data that could be used as tracers of sources or to calculate photochemical production and loss rates. As further noted by Reid et al. (2008), the use of monitoring data for estimating background concentrations is essentially limited to the edges of the domain of interest. This is because background O_3 entering from outside North America can only be destroyed over North America either through chemical reactions or by deposition to the surface. Within North America, background O_3 is only produced by interactions between natural sources and between North American natural sources and precursors from other continents. The current definition of North American background implies that only CTMs (see Section 3.3 for description and associated uncertainties) can be used to estimate the range of background concentrations. An advantage to using models is that the entire range of O_3 concentrations measured in different environments can be used to evaluate model performance. In this regard, data from the relatively small number of monitoring sites, at which large contributions to background are expected, are best used to evaluate model predictions.

Estimates of North American background concentrations in the 2006 O_3 AQCD were based on output from the GEOS-Chem model (Fiore et al., 2003). The GEOS-Chem model estimates indicated that background O_3 concentrations in eastern U.S. surface air are 25 ± 10 ppb (or generally 15-35 ppb) from June through August, based on conditions for 2001. These values and all subsequent values given for background concentrations refer to daily 8-h maximum O_3 concentrations. Background concentrations decline from spring to summer. Background O_3 concentrations may be higher, especially at high altitude sites during the spring, due to enhanced contributions from (1) pollution sources outside North America; and (2) stratospheric O_3 exchange. Only one model (GEOS-Chem, Harvard University, 2010b) was documented in the literature for calculating background O_3 concentrations (Fiore et al., 2003). The simulated monthly mean concentrations in different quadrants of the U.S. are typically within 5 ppbv of observations at CASTNET sites, with no significant bias, except in the Southeast in summer when the model is 8-12 ppbv too high. This bias might be due to excessive

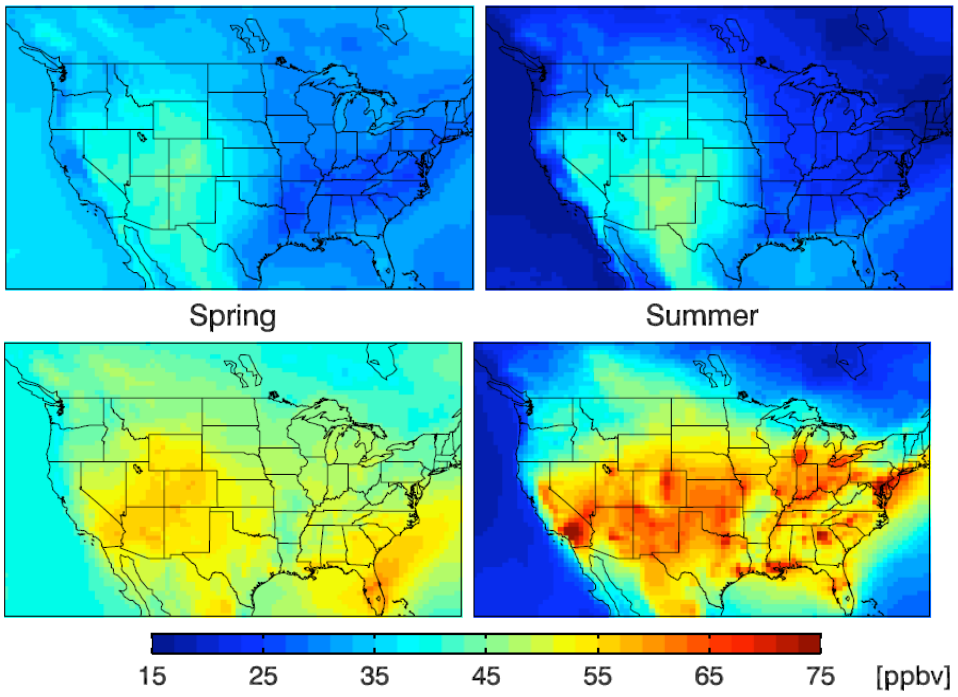
background O_3 transported in from the Gulf of Mexico and the tropical Atlantic Ocean in the model and/or to inaccuracies in emissions inventories within the U.S.

Although many of the features of the day-to-day variability in O_3 at relatively remote monitoring sites in the U.S. were simulated reasonably well by Fiore et al. (2003), uncertainties in the calculation of the temporal variability of O_3 originating from different sources on shorter time scales must be recognized. The uncertainties stem in part from an underestimate in the seasonal variability in the STE of O_3 (Fusco and Logan, 2003), the geographical variability of this exchange, and the variability in the exchange between the free troposphere and the PBL in the model. In addition, the relatively coarse spatial resolution in that version of GEOS-Chem (2°×2.5°) limited the ability to provide separate estimates for cities located close to each other, and so only regional estimates were provided for the 2006 O_3 AQCD based on the results of Fiore et al. (2003).

Wang et al. (2009a) recomputed North American background concentrations for 2001 using GEOS-Chem at higher spatial resolution (1°×1°) over North America and not only for afternoon hours but for the daily maximum 8-h O_3 concentration. These GEOS-Chem calculations represent the latest results documented in the literature. The resulting background concentrations, 26.3 ± 8.3 ppb for summer, are consistent with those of 26 ± 7 ppb reported by Fiore et al. (2003), suggesting horizontal resolution was not a significant factor limiting the accuracy of the earlier results. In addition to computing North American background contributions, Wang et al. (2009a) also computed U.S. background concentrations (i.e., including anthropogenic contributions from everywhere outside the U.S., including Canada and Mexico) of 29.6 ± 8.3 ppb with higher contributions near the Canadian and Mexican borders.

Zhang et al. (In Press) computed North American background, United States background and natural background (including only contributions from natural sources everywhere in the world) O_3 concentrations using an even finer grid spacing of (0.5°×0.667°) over North America for 2006 through 2008. For March through August 2006, mean North American background O_3 concentrations of 27 ± 8 ppb at low elevation (< 1,500 m) and 40 ± 7 ppb at high elevation (> 1,500 m) were predicted. These model predicted values can be compared to the baseline O_3 concentrations estimated by Chan and Vet (2010) of 37 ± 9 ppb for the continental eastern U.S., 51 ± 6 ppb for the continental western U.S., 44 ± 10 ppb for the coastal western U.S. from March to May; and 32 ± 2 ppb for the continental eastern U.S., 25 ± 10 ppb for the continental western U.S. and 39 ± 12 ppb for the coastal western U.S. from June to August (baseline as defined by Chan and Vet (2010) refers to concentrations at locations that are not likely to be near anthropogenic sources or to have been affected by anthropogenic emissions within the past few days).

As noted above, increases in Asian emissions only accounted for an average increase of between 1 to 2 ppb in background O_3 across the U.S. even though Asian emissions have increased by about 44% from 2001 to 2006. United States background concentrations (i.e., O_3 concentrations based on including Canadian and Mexican emissions as background contributions) are on average 2 ppb higher than North American background concentrations, with higher contributions close to the borders. Zhang et al. (In Press) also investigated the effects of model resolution on the results and found that North American background concentrations are ~ 4 ppb higher, on average, in the 0.5°×0.667° version than in the coarser 2°×2.5° version.



Source: Zhang et al. (In Press).

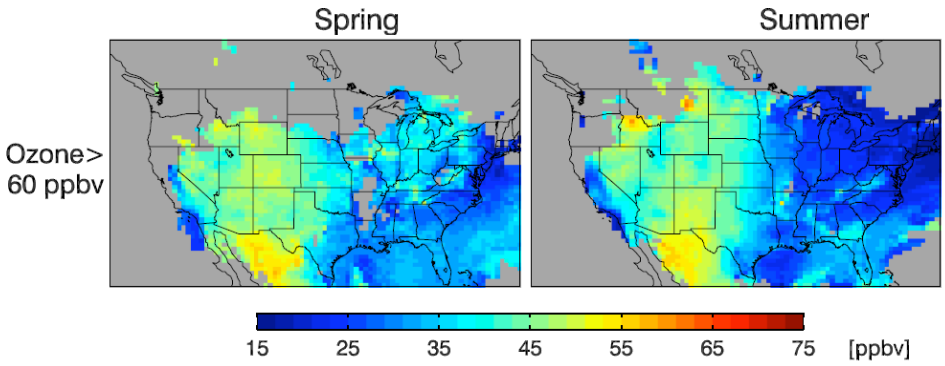
Figure 3-9 North American background ozone concentration in surface air for spring and summer 2006 (top). GEOS-Chem calculated concentrations for the base case, i.e., including all sources in surface air for the U.S., Canada and Mexico for spring and summer of 2006 (bottom).

North American background and base case (calculated including U.S. anthropogenic sources) O_3 concentration in surface air for spring and summer 2006 calculated with GEOS-Chem by Zhang et al. (In Press) are shown in the upper and lower panels of

Figure 3-9. As can be seen from the upper panels, North American background concentrations tend to be higher in the West, particularly in the intermountain West and in the Southwest than in the East in both spring and summer. North American background concentrations tend to be highest in the Southwest during summer, however, in large measure due to wildfires. Intercontinental transport and stratospheric intrusions are major contributors to the high elevation, intermountain West during spring with wildfires becoming more important sources during summer. The base case O_3 concentrations (lower panels) show two broad maxima with highest concentrations extending throughout the Southwest, intermountain West and the East in both spring and summer. These maxima extend over many thousands of kilometers demonstrating that O_3 is a regional pollutant. Low-level outflow from the Northeast out over the Atlantic Ocean and from the Southeast out over the Gulf of Mexico is also apparent.

Lower bounds to North American background concentrations tend to be higher by several ppb at high elevations than at low elevations, reflecting the increasing importance of background sources such as STE and intercontinental transport with altitude. In addition, background concentrations tend to increase with increasing base model (and measured) concentrations at higher elevation sites, particularly during spring.

Figure 3-10 shows that when model predicted O_3 is > 60 ppb, North American background concentrations are generally higher in both the higher-elevation West and in the lower-elevation East compared to their seasonal means. Although results are broadly consistent with results from earlier coarser resolution versions of GEOS-Chem mentioned above, there are some differences of note. Concentrations of O_3 for both the base case and the North American background case are higher in the intermountain West than in earlier versions. Also of note, in many areas in the East, background concentrations tend to be higher on days when predicted O_3 is >60 ppb or at least do not decrease with increasing O_3. This result contrasts somewhat with Fiore et al. (2003) who found that background concentrations in the East tend to decrease with increasing O_3.

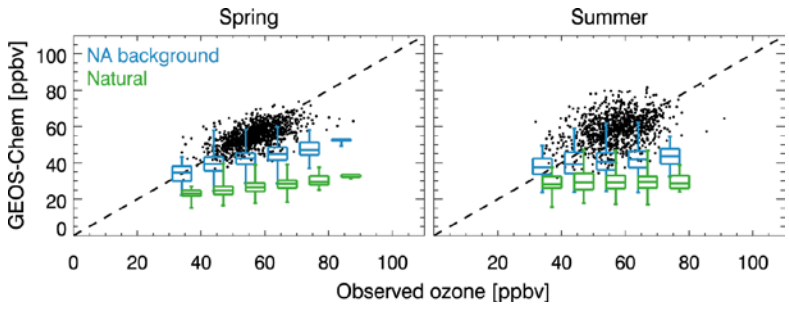


Source: Zhang et al. (In Press).

Figure 3-10 North American background ozone concentrations calculated when base case ozone is > 60 ppb.

Figures 3-11a and b show comparison among observed and base case GEOS-Chem results and corresponding North American and natural backgrounds in 10 ppb bins as box plots. Comparisons between GEOS-Chem and measurements at individual CASTNET sites are shown in Figures 3-49 to 3-55 as supplemental material in Section 3.8. In general, the modeled mean concentrations agree to within ~ 5 ppb at the majority of sites (26 out of 28) and the model agrees more closely with observations in the intermountain West than earlier versions (see Section 3-8 Figures 3-52 to 3-53). Substantial over predictions are found in Florida but not at other sites in the Southeast (see Figure 3-50 in Section 3.8). Comparison between results in Wang et al. (2009a) for 2001with data obtained at the Virgin Islands indicate that the model over-predicts summer mean O_3 concentrations there by 10 ppb (28 vs. 18 ppb). The Virgin Islands NP site appears not to have been affected by U.S. emissions, as was found from the close agreement between the base case and the PRB case. Wind roses calculated for the Virgin Islands site indicate that flows affecting this site are predominantly easterly/southeasterly in spring and summer. The over-predictions at the Virgin Islands site imply that modeled O_3 over the tropical Atlantic Ocean is too high. As a result, inflow of O_3 over Florida and into the Gulf of Mexico is also likely to be too high as winds are predominantly easterly at these low latitudes. Similar considerations apply to the results of Zhang et al. (In Press). The most likely explanation involves deficits in model chemistry, for example, reactions involving halogens are not included. It is not yet clear why the model under-predicts mean O_3 at Yosemite (elevation 1,680 m) by ~ 10 ppb (see Figure 3-55 in Section 3.8). However, predictions are within a few ppb at an even higher elevation site in California (Converse Station, elevation 1,837 m) or at the low elevation sites.

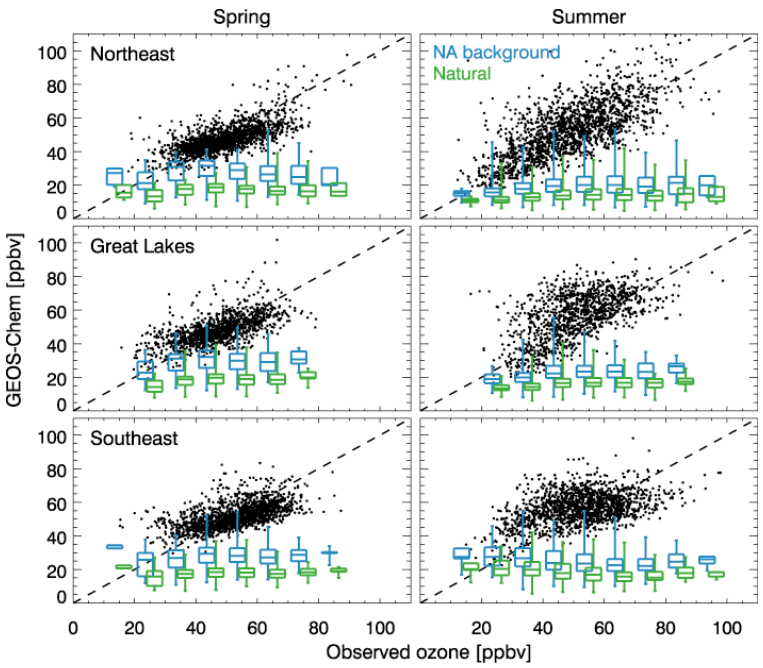
Figures 3-56 a-b in Section 3.8 show a comparison of GEOS-Chem output with measurements at Mt. Bachelor, OR from March-August, 2006. In general, mean concentrations are simulated reasonably well at both coarse and finer grid resolutions with mean values 2 ppb higher in the finer resolution model. Although the finer resolution version provides some additional day to day variability, it still does not capture peak concentrations. Figure 3-57 in Section 3.8 shows a comparison of vertical profiles (mean ± 1σ) calculated by GEOS-Chem with ozonesondes launched at Trinidad Head and Boulder, CO. As can be seen from the figure, variability in both model and measurements increases with altitude, but variability in the model results is much smaller at high altitudes than seen in the observations. This may be due in large measure to the inability of grid-point models to capture the fine-scale, layered structure often seen in O_3 in the mid and upper troposphere (Rastigejev et al., 2010; Newell et al., 1999).



Source: Zhang et al. (In Press).

Also shown is the 1:1 line and North American background and natural background model statistics for 10-ppbv bins of observed ozone concentrations: the minimum, 25th, 50th, 75th percentile, and maximum.

Figure 3-11a Simulated vs. observed daily 8-h max ozone concentrations for spring (March-May) and summer (June-August) 2006 for the ensemble of CASTNET sites in the intermountain West.

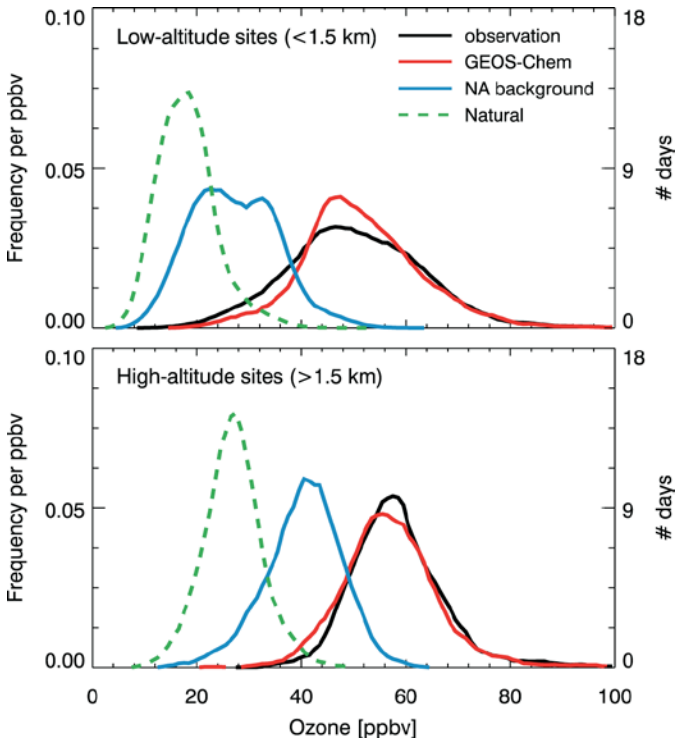


Source: Zhang et al. (In Press).

Also shown is the 1:1 line and North American background and natural background model statistics for 10-ppbv bins of observed ozone concentrations: the minimum, 25th, 50th, 75th percentile, and maximum.

Figure 3-11b Simulated vs. observed daily 8-h max ozone concentrations for spring (March-May) and summer (June-August) 2006 for the ensembles of CASTNET sites in the Northeast U.S., Great Lakes, and the Southeast U.S.

The natural background for O_3 averages 18 ± 6 ppbv at the low-elevation sites and 27 ± 6 ppbv at the high-elevation sites. The difference between North American background and natural background concentrations reflects contributions from intercontinental pollution and anthropogenic methane (given by the difference between values in 2006 and the pre-industrial era, or 1,760 ppb and 700 ppb). The difference between the two backgrounds averages 9 ppbv at the low-elevations sites and 13 ppbv at sites in the intermountain West. The United States background is on average 1-3 ppbv higher than the North American background, reflecting anthropogenic sources in Canada and Mexico, with little variability except in border regions.



Source: Zhang et al. (In Press).

Model results (red) are compared to observations (black). Also shown are frequency distributions for the North American background (solid blue) and natural background (dashed green).

Figure 3-12 Frequency distributions of daily 8-h max ozone concentrations in March- August 2006 for the ensemble of low-altitude (<1.5 km) and high-altitude CASTNET sites in the U.S.

Figure 3-12 shows frequency distributions for measurements at low-altitude and high-altitude CASTNET sites, GEOS-Chem results for the base case, North American background and the natural background. Most notable is the shift to higher concentrations and the narrowing of the concentration distributions for all three simulations and the observations in going from low to high altitudes. However, maximum concentrations show little if any dependence on altitude, except for the natural background which tends to be slightly higher at lower altitudes.

As noted in Section 3.3, CTMs are subject to uncertainty in model inputs for emissions, meteorology, and chemistry. For example, many of the chemical processes described in Section 3.2 have not yet been included in GEOS-Chem.

Another approach to modeling background concentrations involves using a regional CTM such as CMAQ or CAMx with boundary conditions taken from a global scale CTM such as GEOS-Chem. Mueller and Mallard (2011a), while not calculating North American

background values exactly as defined here, calculated contributions from natural sources and inflow from the boundaries to O_3 for 2002 using MM5 and CMAQ for the outermost domain (36 km resolution) shown in Figure 3-4 with boundary conditions from GEOS-Chem. The overall bias based on comparison with AQS monitors for the base case is about 3 ppb; the annual mean fractional bias and mean fractional error were 7% and 21% for the O_3 season across the U.S. Note that Figure 2 in their paper is mislabeled, as it should refer to the case with total emissions - not to natural emissions in North America only (Mueller and Mallard, 2011b). However, boundary conditions are fixed according to monthly averages based on an earlier version of GEOS-Chem and do not reflect shorter term variability or trends in Northern Hemispheric emissions of pollution. In addition, fluxes of O_3 from the stratosphere are not defined. Note that their natural background includes North American natural background emissions only and influence from boundary conditions and thus is not a global natural background. Calculated values including natural emissions from North America and from fluxes through the boundaries are somewhat larger than given in Zhang et al. (In Press), in large measure because of much larger contributions from wildfires and lightning. Wildfire contributions reach values of ~ 140 ppb in Redwoods National Park and higher elsewhere in the U.S. and in Quebec. However as noted by Singh et al. (2010b) significant enhancements of O_3 in California fire plumes are found only when mixed with urban pollution. Lightning contributions (ranging up to ~ 30 ppb) are substantially larger than estimated by Kaynak et al. (2008) (see Section 3.4.2.1). The reasons for much larger contributions from wildfires and lightning are not clear and need to be investigated further.

3.4.4 Summary of Background Results

In general, the GEOS-Chem predictions tend to show smaller disagreement with observations at the high-altitude sites than at the low-altitude sites. Overall agreement between model results for the base case and measurements is within a few ppb for spring-summer means in the Northeast (see Figure 3-49 in Section 3.8) and the Southeast (see Figure 3-50 in Section 3.8), except in and around Florida where the base case over predicts O_3 by 10 ppb at one site, at least. In the Upper Midwest (see Figure 3-51 in Section 3.8), the model predictions are within 5 ppb of measurements, the same is true for sites in the intermountain West (see Figures 3-52 and 3-53) and at lower elevations sites in the West (see Figure 3-54 in Section 3.8) including California (see Figure 3-55 in Section 3.8). However, the model under predicts O_3 by 10 ppb at the Yosemite site. These results suggest that the model is capable of calculating March to August mean O_3 to within ~ 5 ppb at most (26 out of 28) sites chosen. Currently, there are no simulations of North American background concentrations available in the literature apart from those

using GEOS-Chem alone. However, as noted in the 2006 O_3 AQCD, an ensemble approach as is done in many other applications of atmospheric models is to be preferred.

The GEOS-Chem calculations presented here represent the latest results documented in the literature. However, all models undergo continuous updating of inputs, parameterizations of physical and chemical processes, and inputs and improvements in model resolution. Inputs that might be considered most relevant include emissions inventories, chemical reactions and meteorological fields. This leads to uncertainty in model predictions in part because there is typically a lag between updated information for these above inputs, as outlined in Section 3.2 for chemical processes and emissions and in Section 3.3 for model construction, and their implementation in CTMs including GEOS-Chem. Examples might include updated emissions for year specific shipping, wildfires and updates to the 2005 NEI; updates to the chemistry of isoprene and multi-phase processes, including those affecting the abundance of halogens; and updates to species such as methane. To the extent that results from an updated model become available, they will be presented and used to help inform NAAQS setting.

Supplemental material given in Section 3.9 summarizes results of modeling work using GEOS-Chem that is still in progress. Results for the current definition of North American background, U.S. background and natural background are given for January 2006 to December 2008. Major differences from the work of Zhang et al. (In Press) include the use of a later model version which incorporates updates to the chemistry of isoprene nitrates and to the generation of lightning NO_x. In addition, anthropogenic emissions were updated for each model year from the NEI 2005 inventory. The complete draft report is available on-line (U.S. EPA, 2011c).

3.5 Monitoring

3.5.1 Routine Monitoring Techniques

The FRM for O_3 measurement is called the Chemiluminescence Method (CLM) and is based on the detection of chemiluminescence resulting from the reaction of O_3 with ethylene gas. The UV absorption photometric analyzers were approved as FEMs in 1977 and gained rapid acceptance for NAAQS compliance purposes due to ease of operation, relatively low cost, and reliability. The UV absorption method is based on the principle that O_3 molecules absorb UV radiation at a wavelength of 254 nm from a mercury lamp. The concentration of O_3 is computed from Beer's law using the radiation absorbed across a fixed path length, the absorption coefficient, and the measured pressure and temperature

in the detection cell. UV absorption photometry is the predominant method for assessing compliance with the NAAQS for O_3. Almost all of the state and local air monitoring stations (SLAMS) that reported data to EPA AQS from 2005 to 2009 used UV absorption photometer FEMs. No CLM monitors, approved as FRMs or FEMs, reported O_3 data to AQS from 2005 to 2009 and only one monitor reported data using a long-path or open path Differential Optical Absorption Spectrometer (DOAS) FEM during this period.

The rationale, history, and calibration of O_3 measurements were summarized in the 1996 O_3 AQCD and the 2006 O_3 AQCD and focused on the state of ambient O_3 measurements at that time as well as evaluation of interferences and new developments. This discussion will continue with the current state of O_3 measurements, interferences, and new developments for the period 2005 to 2010.

UV O_3 monitors use mercury lamps as the source of UV radiation and employ an O_3 scrubber (typically manganese dioxide) to generate an ozone-free air flow to serve as a reference channel for O_3 measurements. There are known interferences with UV O_3 monitors. The 2006 O_3 AQCD reported on the investigation of the effects of water vapor, aromatic compounds, ambient particles, mercury vapor and alternative materials in the instrument's O_3 scrubber. The overall conclusions from the 2006 O_3 AQCD review of the scientific literature are briefly summarized below.

Kleindienst et al. (1993) found water vapor to have no significant impact and aromatic compounds to have a minor impact (as much as 3% higher than the FRM extrapolated to ambient conditions) on UV absorption measurements. UV O_3 monitor response evaluated by chamber testing using cigarette smoke, reported an elimination of the O_3 monitor response to the smoke when a particle filter was used that filtered out particles less than 0.2 µm in diameter (Arshinov et al., 2002). One study (Leston et al., 2005) in Mexico City compared a UV O_3 FEM to a CLM FRM. The UV FEM commonly reported consistently higher O_3 than the CLM FRM. The typical difference was 20 ppb with a range up to 50 ppb. Leston et al. (2005) also presented smog chamber data which demonstrated that heated metal and heated silver wool scrubbers perform better in the presence of aromatic hydrocarbon irradiations than manganese dioxide scrubbers when compared to the FRM. They also suggested the use of humidified calibration gas and alternative scrubber materials to improve UV O_3 measurements. Some O_3 monitor manufacturers now offer heated silver wool scrubbers as an alternative to manganese dioxide. Another possible solution to the O_3 scrubber problem may be the use of a gas phase scrubber such as NO. A commercial version of this has recently been introduced by 2B Technologies as an option on their model 202 FEM; however, it has not been field tested or approved for use as an FEM.

Review of the recent literature is summarized below. Study of UV monitors by Williams et al. (2006) concluded that well maintained monitors showed no significant interferences when operated in locations with significant concentrations of potentially interfering VOCs including Nashville, Houston, and the Gulf of Maine. Monitors were tested in urban and suburban environments, as well as on board a ship in both polluted and clean marine air. Comparisons of UV measurements to a non-FRM/FEM NO based CLM demonstrated agreement to within 1%. At the Houston location, they did observe a brief period on one day for about 30 minutes where the UV measurements exceeded the CLM by about 8 ppb (max). This was attributed to probable instrument malfunction.

Wilson and Birks (2006) investigated water vapor interference in O_3 measurements by four different UV monitors. In extreme cases where a rapid step change in relative humidity between 0 and 90% was presented, large transitory responses (tens to hundreds of ppb) were found for all monitors tested. Rapid changes in relative humidity such as this would not be expected during typical ambient O_3 measurements and could only be expected during measurement of vertical profiles from balloon or aircraft. The magnitude of the interference and the direction (positive or negative) was dependent on the manufacturer and model. Wilson and Birks (2006) also hypothesized that water vapor interference is caused by physical interactions of water vapor on the detection cell. The O_3 scrubber was also thought to act as a reservoir for water vapor and either added or removed water vapor from the air stream, subsequently affecting the detector signal and producing either a positive or negative response. They demonstrated that the use of a Nafion permeation membrane just before the O_3 detection cell to remove water vapor eliminated this interference.

Dunlea et al. (2006) evaluated multiple UV O_3 monitors with two different O_3 scrubber types (manganese dioxide and heated metal wool) in Mexico City. Large spikes in O_3 concentrations were observed while measuring diesel exhaust where large increases in particle number density were observed. The interference due to small particles passing through the Teflon filter and scattering/absorbing light in the detection cell were estimated to cause at most a 3% increase in measurements in typical ambient air environments. This estimate pertains to measurements in the immediate vicinity of fresh diesel emissions and most monitor siting guidelines would not place the monitor close to such sources, so actual interferences are expected to be much less than 3%. Dunlea et al. (2006) also observed no evidence for either a positive or negative interference or dependence due to variations in aromatics during their field study.

Li et al. (2006c) verified early reports of gas phase mercury interference with the UV O_3 measurement. They found that 300 ng/m^3 of mercury produced an instrument response of

about 35 ppb O_3. Background concentrations of mercury are around 1-2 ng/m^3 and expected to produce an O_3 response that would be <1 ppb.

Spicer et al. (2010) examined potential UV O_3 monitor interferences by water vapor, mercury, aromatic compounds, and reaction products from smog chamber simulations. Laboratory tests showed little effect of changing humidity on conventional FEM UV O_3 monitors with manganese dioxide or heated metal wool scrubbers in the absence of other interferences. Mercury vapor testing produced an O_3 response by the UV monitors that was <1 ppb O_3 per 1 ppt (about 8 ng/m^3) mercury vapor. Interference by aromatic compounds at low (3% RH) and high (80% RH) humidity showed some positive responses that varied by UV monitor and ranged from 0 to 2.2 ppb apparent O_3 response, per ppb of aromatic compound tested. The authors acknowledged that the aromatic compounds most likely to interfere are rarely measured in the atmosphere and therefore, make it difficult to assess the impact of these compounds during ambient air monitoring. Comparison of UV and CLM responses to photochemical reaction products in smog chamber simulations at 74 to 85% RH showed varied responses under low (0.125 ppmv/0.06 ppmv) to high (0.50 ppmv/0.19 ppmv) hydrocarbon/NO_X conditions. The conventional UV monitors were as much as 2 ppb higher than the CLM under low hydrocarbon/NO_X conditions and 6 ppb higher under the high hydrocarbon/NO_X conditions. Two FEM UV monitors were also co-located at six sites in Houston from May to October, 2007 with one UV monitor equipped with Nafion permeation membrane. The average difference between 8-h daily max O_3 concentrations using the UV and the UV with Nafion permeation membrane ranged from -4.0 to 4.1 ppb.

3.5.2 Precision and Bias

In order to provide decision makers with an assessment of data quality, EPA's Quality Assurance (QA) group derives estimates of both precision and bias for O_3 and the other gaseous criteria pollutants from the biweekly single point quality control (QC) checks using calibration gas, performed at each site by the monitoring agency. The single-point QC checks are typically performed at concentrations around 90 ppb. Annual summary reports of precision and bias can be obtained for each monitoring site at http://www.epa.gov/ttn/amtic/qareport.html. The assessment of precision and bias are based on the percent-difference values, calculated from single-point QC checks. The percent difference is based on the difference between the pollutant concentration indicated by monitoring equipment and the known (actual) concentration of the standard used during the QC check. The monitor precision is estimated from the 90% upper confidence limit of the coefficient of variation (CV) of relative percent difference (RPD) values. The bias is estimated from the 95% upper confidence limit on the mean of the

absolute values of percent differences. The data quality goal for O_3 precision and bias at the 90 and 95% upper confidence limits is 7% (40 CFR Part 58, Appendix A). Table 3-1 presents a summary of the number of monitors that meet the precision and bias goal of 7% for 2005 to 2009. Greater than 96% of O_3 monitors met the precision and bias goal between 2005 and 2009.

Table 3-1 Summary of ozone monitors meeting 40 CFR Part 58, Appendix A Precision and Bias Goals

Year	Number of Monitors	Monitors with Acceptable Precision (%)	Monitors with Acceptable Bias (%)
2005	879	96.5	96.7
2006	881	98.1	97.6
2007	935	98.1	98.1
2008	955	97.1	96.7
2009	958	97.4	97.5

Another way to look at the precision (CV) and bias (percent difference) information using the single-point QC check data from the monitoring network is to present box plots of the monitors' individual precision and percent-difference data; Figure 3-13 and Figure 3-14 include this information for O_3 monitors operating from 2005 to 2009.

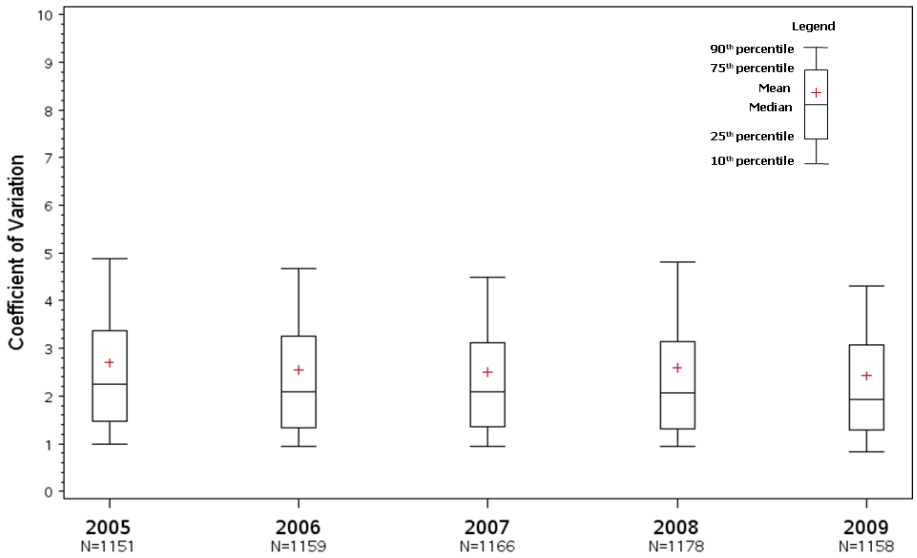


Figure 3-13 Box plots of precision data by year (2005-2009) for all ozone monitors reporting single-point QC check data to AQS.

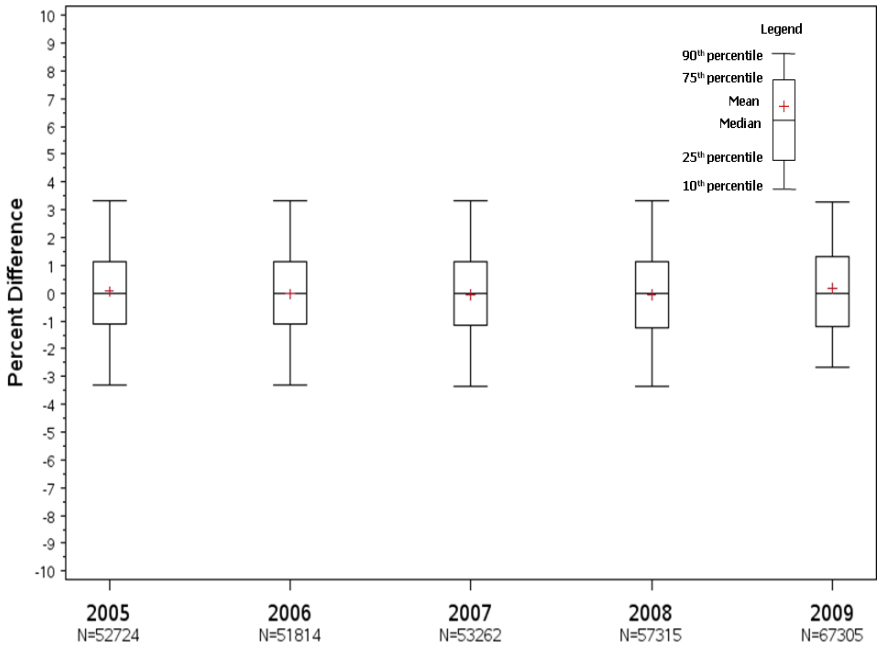


Figure 3-14 Box plots of percent-difference data by year (2005-2009) for all ozone monitors reporting single-point QC check data to AQS.

3.5.2.1 Precision from Co-located UV Ozone Monitors in Missouri

The Missouri Department of Natural Resources (MODNR) maintains a network of co-located UV O_3 analyzers. The MODNR provided co-located data from four monitors: two co-located at the same monitoring site in Kansas City (AQS ID 290370003) and two co-located at the same monitoring site in St. Louis (AQS ID 291831002). Hourly observations for the co-located measurements at these two sites between April and October, 2006-2009 were used to evaluate precision from co-located UV monitors. These data were then compared with the precision obtained by the biweekly single point QC checks for all sites reporting single-point QC check data to AQS between 2005 and 2009; the method normally used for assessing precision. Box plots of the RPD between the primary and co-located hourly O_3 measurements in Missouri are shown in Figure 3-15 and box plots of the RPD between the actual and indicated QC check for all U.S. sites are shown in Figure 3-16. As mentioned above, the average concentration of the single-point QC check is 90 ppb, whereas the average ambient O_3 concentration measured at the two sites in Missouri was 34 ppb. The mean RPD for the co-located monitors in Missouri and the single-point QC check data from all sites were less than 1 percent.

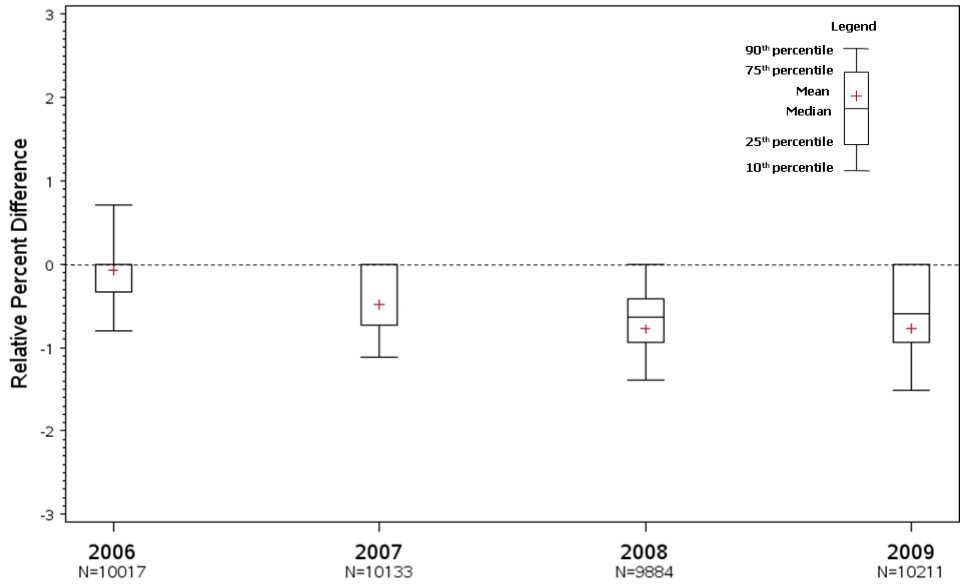


Figure 3-15 Box plots of RPD data by year for the co-located ozone monitors at two sites in Missouri from 2006-2009.

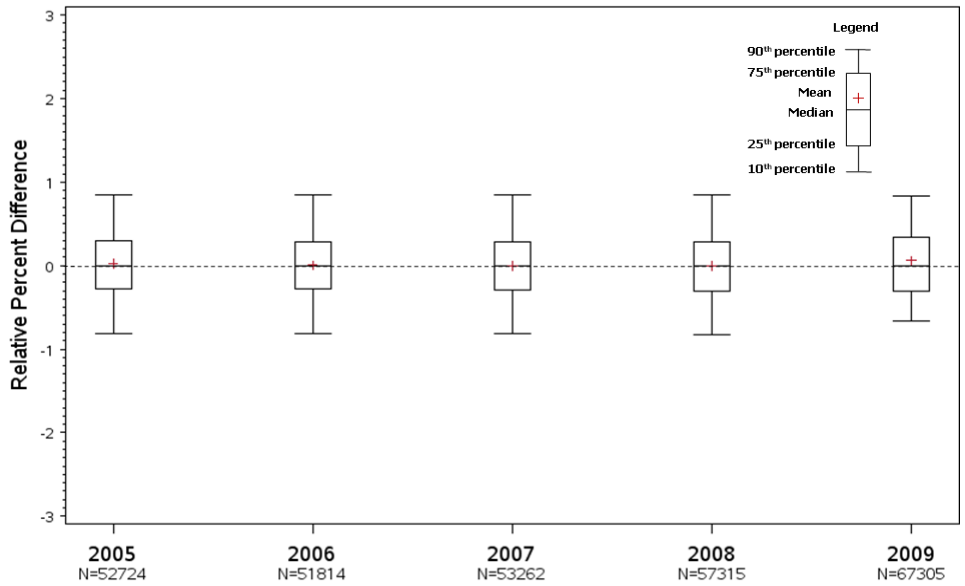


Figure 3-16 Box plots of RPD data by year for all U.S. ozone sites reporting single-point QC check data to AQS from 2005-2009.

3.5.3 Performance Specifications

The performance specifications for evaluating and approving new FEMs in accordance with 40 CFR Part 53 are provided in Table 3-2. These specifications were developed and originally published in the Federal Register in 1975. Modern, commercially-available instruments can now perform much better than the requirements specified below. For example, the lower detectable limit (LDL) performance specification is 10 ppb and the typical vendor-stated performance for the LDL is now less than 0.60 ppb. The amount of allowable interference equivalent for total interference substances is 60 ppb, and the current NAAQS for O_3 is 75 ppb, with an averaging time of 8 hours. Improvements in new measurement technology have occurred since these performance specifications were originally developed. These specifications should be revised to more accurately reflect the necessary performance requirements for O_3 monitors used to support the current NAAQS.

Table 3-2 Performance specifications for ozone based in 40 CFR Part 53

Parameter	Specification
Range	0 – 0.5 ppm (500 ppb)
Noise	0.005 ppm (5 ppb)
LDL – defined as two times the noise	0.01 ppm (10 ppb)
Interference equivalent	
Each interfering substance	± 0.02 ppm (20 ppb)
Total interfering substances	0.06 ppm (60 ppb)
Zero drift	
12 h	± 0.02 ppm (20 ppb)
24 h	± 0.02 ppm (20 ppb)
Span Drift, 24 h	
20% of upper range limit	± 20.0%
80% of upper range limit	± 5.0%
Lag time	20 min
Rise time	15 min
Fall time	15 min
Precision	
20% of upper range limit	0.01 ppm (10 ppb)
80% of upper range limit	0.01 ppm (10 ppb)

3.5.4 Monitor Calibration

The calibration of O_3 monitors was summarized in detail in the 1996 O_3 AQCD. The calibration of O_3 monitors is done using an O_3 generator and UV photometers. UV photometry is the prescribed procedure for the calibration of reference methods to

measure O_3 in the atmosphere. Because O_3 is unstable and cannot be stored, the O_3 calibration procedure specifically allows the use of transfer standards for calibrating ambient O_3 monitors. A transfer standard is calibrated against a standard of high authority and traceability and then moved to another location for calibration of O_3 monitors. The EPA and the National Institute of Standards and Technology (NIST) have established a network of standard reference photometers (SRPs) that are used to verify transfer standards. The International Bureau of Weights and Measures (BIPM) maintain one NIST SRP (SRP27) as the World's O_3 reference standard. NIST maintains two SRPs (SRP0 and SRP2) that are used for comparability to ten other SRPs maintained by the EPA's Regional QA staff.

SRPs have been compared to other reference standards. Tanimoto et al. (2006) compared NIST SRP35, owned by the National Institute for Environmental Studies in Japan, to gas phase titration (GPT). The SRP was found to be 2% lower than GPT. GPT is no longer used as a primary or transfer standard in the U.S. Viallon et al. (2006) compared SRP27 built at BIPM to four other NIST SRPs maintained by BIPM (SRP28, SRP31, SRP32, and SRP33). A minimum bias of +0.5% was found for all SRP measurement results, due to use of the direct cell length measurement for the optical path length; this bias was accounted for by applying the appropriate correction factor. Study of the bias-corrected SRPs showed systematic biases and measurement uncertainties for the BIPM SRPs. A bias of -0.4% in the instrument O_3 mole fraction measurement was identified and attributed to non-uniformity of the gas temperature in the instrument gas cells, which was compensated by a bias of +0.5% due to an under-evaluation of the UV light path length in the gas cells. The relative uncertainty of the O_3 absorption cross section was 2.1% at 253.65 nm and this was proposed as an internationally accepted consensus value until sufficient experimental data is available to assign a new value.

In November, 2010, the EPA revised the Technical Assistance Document for *Transfer Standards for Calibration of Air Monitoring Analyzers for Ozone* (2010f) that was first finalized in 1979 (U.S. EPA, 1979b). The revision removed methods no longer in use and updated definitions and procedures where appropriate. In the revised document, the discussion of transfer standards for O_3 applies to the family of standards that are used beyond SRPs or Level 1 standards. To reduce confusion, EPA reduced the number of common terms that were used in the past such as: primary standard, local primary standard, transfer standard, and working standard. Beyond the SRPs, all other standards are considered transfer standards.

3.5.5 Other Monitoring Techniques

3.5.5.1 Portable UV Ozone Monitors

Small, lightweight, and portable UV O_3 monitors with low power consumption are commercially available. These monitors are based on the same principle of UV absorption by O_3 at 254 nm. Monitors of this type are typically used for vertical profiling using balloons, kites, or light aircraft where space and weight are limited. They have also been used for monitoring at remote locations such as National Parks. Burley and Ray (2007) compared portable O_3 monitor measurements to those from a conventional UV monitor in Yosemite National Park. Calibrations of the portable O_3 monitors against a transfer standard resulted in an overall precision of ± 4 ppb and accuracy of ± 6%. Field measurement comparisons between the portable and conventional monitor at Turtleback Dome showed the portable monitor to be 3.4 ppb lower on average, with daytime deviation typically on the order of 0-3 ppb. Agreement between the portable and conventional monitor during daylight hours (9:00 a.m. to 5:00 p.m. PST) resulted in an R^2 of 0.95, slope of 0.95, and intercept of 0.36 ppb. Significant deviations were observed in the predawn hours where the portable monitor was consistently low. These deviations were attributed to the difference in sampling inlet location. The portable monitor was located at 1.3 m above ground and the conventional monitor was located at 10 m above ground. Agreement between the portable and conventional monitors for all hours sampled resulted in an R^2 of 0.88, slope of 1.06, and intercept of -6.8 ppb. Greenberg et al. (2009) also compared a portable UV O_3 monitor to a conventional UV monitor in Mexico City and obtained good agreement for a 14 day period with an R^2 of 0.97, slope of 0.97, and intercept of 6 ppb. One portable O_3 monitor was recently approved as an FEM (EQOA-0410-190) on April 27, 2010 (75 FR 22126).

3.5.5.2 NO-based Chemiluminescence Monitors

One commercially available NO-based chemiluminescence monitor is currently undergoing FEM testing (Teledyne Advanced Pollution Instrumentation, Douglassville, GA). It may also be designated as a second or replacement FRM since the ethene based FRMs are no longer manufactured. Although this is a relatively new monitor, other NO-based CLM instruments have been custom built for various field studies since the early 1970s. A commercial version that measured both O_3 and NO_X was offered in the early 1970s but failed to gain commercial acceptance. Initial testing with SO_2, NO_2, Cl_2, C_2H_2, C_2H_4 and C_3H_6 (Stedman et al., 1972) failed to identify any interferences. In the intervening years, custom built versions have not been found to have any interference;

however, they do experience a slight decrease in response with increasing relative humidity (due to quenching of the excited species by the water molecules). The new NO-based CLM solves this problem with the use of a Nafion membrane dryer. A custom built NO-based CLM similar to the monitor undergoing FEM testing was used by Williams et al. (2006) in Houston, TX; Nashville, TN; and aboard ship along the New England coast. It was found to be in good agreement with a standard UV based FEM and with a custom built DOAS.

3.5.5.3 Passive Air Sampling Devices and Sensors

A passive O_3 sampling device depends on the diffusion of O_3 in air to a collecting or indicating medium. In general, passive samplers are not adequate for compliance monitoring because of the limitations in averaging time (typically one week or more), particularly for O_3. However, these devices are valuable for personal human exposure estimates and for obtaining long-term data in rural areas where conventional UV monitors are not practical or feasible to deploy. The 1996 O_3 AQCD provided a detailed discussion of passive samplers, along with the limitations and uncertainties of the samplers evaluated and published in the literature from 1989 to 1995. The 2006 O_3 AQCD provided a brief update on available passive samplers developed for use in direct measurements of personal exposure published through 2004. The 2006 O_3 AQCD also noted the sensitivity of these samplers to wind velocity, badge placement, and interference by other co-pollutants that may result in measurement error.

Subsequent evaluations of passive diffusion samplers in Europe showed good correlation when compared to conventional UV O_3 monitors, but a tendency for the diffusion samplers to overestimate the O_3 concentration (Gottardini et al., 2010; Vardoulakis et al., 2009; Buzica et al., 2008). The bias of O_3 diffusion tubes were also found to vary with concentration, season, and exposure duration (Vardoulakis et al., 2009). Development of simple, inexpensive, passive O_3 measurement devices that rely on O_3 detection papers and a variety of sensors with increased time resolution (sampling for hours instead of weeks) and improved sensitivity have been reported (Maruo et al., 2010; Ebeling et al., 2009; Miwa et al., 2009; Ohira et al., 2009; Maruo, 2007; O-Keeffe et al., 2007; Utembe et al., 2006). Limitations for some of these sensors and detection papers include air flow dependence and relative humidity interference.

3.5.5.4 Differential Optical Absorption Spectrometry

Optical remote sensing methods can provide direct, sensitive, and specific measurements of O_3 over a broad area or open path in contrast with conventional single-point UV monitors. The 1996 O_3 AQCD provided a brief discussion of DOAS for O_3 measurements and cited references to document the sensitivity (1.5 ppb for a 1-minute averaging time), correlation (r = 0.89), and agreement (on the order of 10%) with UV O_3 monitors (Stevens et al., 1993). The 2006 O_3 AQCD provided an update on DOAS where a positive interference due to an unidentified absorber was noted (Reisinger, 2000).

More recent study of the accuracy of UV absorbance monitors by Williams et al. (2006) compared UV and DOAS measurements at two urban locations. In order to compare the open path measurements and UV, the data sets were averaged to 30-minute periods and only data when the boundary layer was expected to be well mixed (between 10:00 a.m. and 6:00 p.m. CST) were evaluated. The comparisons showed variations of no more than ± 7% (based on the slope of the linear least squares regression over a concentration range from about 20 to 200 ppb) and good correlation (R^2 = 0.96 and 0.98). Lee et al. (2008b) evaluated DOAS and UV O_3 measurements in Korea and found the average DOAS concentration to be 8.6% lower than the UV point measurements with a good correlation (R^2 = 0.94).

DOAS has also been used for the measurement of HNO_2 (or HONO). DOAS was compared to chemical point-measurement methods for HONO. Acker et al. (2006) obtained good results when comparing wet chemical and DOAS during well mixed atmospheric conditions (wet chemical = 0.009 + 0.92 x DOAS; r = 0.7). Kleffmann and Wiesen (2008) noted that interferences with the HONO wet chemical methods can affect results from inter-comparison studies if not addressed. In an earlier study, Kleffman et al. (2006) demonstrated that when the interferences were addressed, excellent agreement with DOAS can be obtained. Stutz et al. (2009) found good agreement (15% or better) between DOAS and a wet chemical method (Mist Chamber/Ion Chromatography) in Houston, TX except generally during mid-day when the chemical method showed a positive bias that may have been related to concentrations of O_3. DOAS remains attractive due to its sensitivity, speed of response, and ability to simultaneously measure multiple pollutants; however, further inter-comparisons and interference testing are recommended.

3.5.5.5 Satellite Remote Sensing

Satellite observations for O_3 are growing as a resource for many purposes, including model evaluation, assessing emissions reductions, pollutant transport, and air quality management. Satellite remote sensing instruments do not directly measure the composition of the atmosphere. Satellite retrievals are conducted using the solar backscatter or thermal infrared emission spectra and a variety of algorithms. Most satellite measurement systems have been developed for stratospheric measurement of the total O_3 column. Mathematical techniques have been developed and must be applied to derive information from these systems about tropospheric O_3 (Tarasick and Slater, 2008; Ziemke et al., 2006). Direct retrieval of global tropospheric O_3 distributions from solar backscattered UV spectra have been reported from the Ozone Monitoring Instrument (OMI) and Global Ozone Monitoring Experiment (GOME) (Liu et al., 2006). Another satellite measurement system, Tropospheric Emission Spectrometer (TES), produces global-scale vertical concentration profiles of tropospheric O_3 from measurements of thermal infrared emissions. TES has been designed specifically to focus on mapping the global distribution of tropospheric O_3 extending from the surface to about 10-15 km altitude (Beer, 2006).

In order to improve the understanding of the quality and reliability of the data, satellite-based observations of total column and tropospheric O_3 have been validated in several studies using a variety of techniques, such as aircraft observations, ozonesondes, CTMs, and ground-based spectroradiometers. Antón et al. (2009) compared satellite data from two different algorithms (OMI-DOAS and OMI-TOMS) with total column O_3 data from ground-based spectroradiometers at five locations. The satellite total column O_3 data underestimated ground-based measurements by less than 3%. Richards et al. (2008) compared TES tropospheric O_3 profiles using airborne differential absorption lidar (DIAL) and found TES to have a 7 ppbv positive bias relative to DIAL throughout the troposphere. Nasser et al. (2008) compared TES O_3 profiles and ozonesonde coincidences and found a positive bias of 3-10 ppbv for TES. Worden et al. (2007a) also compared TES with ozonesondes and found TES O_3 profiles to be biased high in the upper troposphere (average bias of 16.8 ppbv for mid-latitudes and 9.8 ppbv for the tropics) and biased low in the lower troposphere (average bias of -2.6 ppbv for mid-latitudes and -7.4 ppbv for the tropics). Comparisons of TES and OMI with ozonesondes by Zhang et al. (2010b) showed a mean positive bias if 5.3 ppbv (10%) for TES and 2.8 ppbv (5%) for OMI at 500 hPa. In addition, Zhang et al. (2010b) used a CTM (GEOS-Chem) to determine global differences between TES and OMI. They found differences between TES and OMI were generally ±10 ppbv except at northern mid-latitudes in summer and over tropical continents. Satellite observations have also been

combined (e.g., OMI and TES) to improve estimates of tropospheric O_3 (Worden et al., 2007b).

3.5.6 Ambient Ozone Network Design

3.5.6.1 Monitor Siting Requirements

To monitor compliance with the NAAQS, state and local monitoring agencies operate O_3 monitoring sites at various locations depending on the area size (population and geographic characteristics[2]) and typical peak concentrations (expressed in percentages below, or near the O_3 NAAQS). SLAMS make up the ambient air quality monitoring sites that are primarily needed for NAAQS comparisons, but may also serve some other basic monitoring objectives that include: providing air pollution data to the general public in a timely manner; emissions strategy development; and support for air pollution research. SLAMS include National Core (NCore), Photochemical Assessment Monitoring Stations (PAMS), and all other State or locally-operated stations except for the monitors designated as special purpose monitors (SPMs).

The SLAMS minimum monitoring requirements to meet the O_3 design criteria are specified in 40 CFR Part 58, Appendix D. Although NCore and PAMS are a subset of SLAMS, the monitoring requirements for those networks are separate and discussed below. The minimum number of O_3 monitors required in a Metropolitan Statistical Area (MSA) ranges from zero for areas with a population of at least 50,000 and under 350,000 with no recent history of an O_3 design value[3] greater than 85 percent of the NAAQS, to four for areas with a population greater than 10 million and an O_3 design value greater than 85 percent of the NAAQS. Within an O_3 network, at least one site for each MSA, or Combined Statistical Area (CSA) if multiple MSAs are involved, must be designed to record the maximum concentration for that particular metropolitan area. More than one maximum concentration site may be necessary in some areas. The spatial scales for O_3 sites are neighborhood, urban and regional.

- Neighborhood scale: represents concentrations within some extended area of the city that has relatively uniform land use with dimensions in the 0.5-4.0 km range. The neighborhood and urban scales listed below have the potential to

[2] Geographic characteristics such as complexity of terrain, topography, land use, etc.

[3] A design value is a statistic that describes the air quality status of a given area relative to the level of the NAAQS. Design values are typically used to classify nonattainment areas, assess progress towards meeting the NAAQS, and develop control strategies. See http://epa.gov/airtrends/values.html (U.S. EPA, 2010a) for guidance on how these values are defined.

overlap in applications that concern secondary or homogeneously distributed primary air pollutants.

- Urban scale: represents concentrations within an area of city-like dimensions, on the order of 4-50 km. Within a city, the geographic placement of sources may result in there being no single site that can be said to represent air quality on an urban scale.
- Regional scale: usually defines a rural area of reasonably homogeneous geography without large sources, and extends from tens to hundreds of kilometers.

Since O_3 concentrations decrease significantly in the colder parts of the year in many areas, O_3 is required to be monitored at SLAMS monitoring sites only during the "ozone season." Table D-3 of 40 CFR Part 58, Appendix D lists the beginning and ending month of the ozone season for each U.S. state or territory. Most operate O_3 monitors only during the ozone season. Those that operate some or all of their O_3 monitors on a year-round basis include Arizona, California, Hawaii, Louisiana, Nevada, New Mexico, Puerto Rico, Texas, American Samoa, Guam and the Virgin Islands.

The total number of SLAMS O_3 sites needed to support the basic monitoring objectives includes more sites than the minimum numbers required in 40 CFR Part 58, Appendix D. In 2010, there were 1250 O_3 monitoring sites reporting values to the EPA AQS database (Figure 3-17). Monitoring site information for EPA's air quality monitoring networks is available in spreadsheet format (CSV) and keyhole markup language format (KML or KMZ) that is compatible with Google Earth™ and other software applications on the AirExplorer website (U.S. EPA, 2011d). States may operate O_3 monitors in non-urban or rural areas to meet other objectives (e.g., support for research studies of atmospheric chemistry or ecosystem impacts). These monitors are often identified as SPMs and can be operated up to 24 months without being considered in NAAQS compliance determinations. The current monitor and probe siting requirements have an urban focus and do not address the siting for SPMs or monitors in non-urban, rural areas to support ecosystem impacts and the secondary standards.

NCore is a new multi-pollutant monitoring network implemented to meet multiple monitoring objectives. Those objectives include: timely reporting of data to the public through AirNow (U.S. EPA, 2011a); support for the development of emission reduction strategies; tracking long-term trends of criteria pollutants and precursors; support to ongoing reviews of the NAAQS and NAAQS compliance; model evaluation; support for scientific research studies; and support for ecosystem assessments. Each state is required to operate at least one NCore site. The NCore monitoring network began January 1, 2011 at about 80 stations (about 60 urban and 20 rural sites). NCore has leveraged the use of

sites in existing networks; for example, some IMPROVE sites also serve as rural NCore sites. In addition to O_3, other components including CO, NO_X, NO_Y, SO_2, and basic meteorology are also measured at NCore sites. The spatial scale for urban NCore stations is urban or neighborhood; however, a middle-scale[4] site may be acceptable in cases where the site can represent many such locations throughout a metropolitan area. Rural NCore sites are located at a regional or larger scale, away from any large local emission sources so that they represent ambient concentrations over an extensive area. Ozone monitors at NCore sites are operated year round.

PAMS provides more comprehensive data on O_3 in areas classified as serious, severe, or extreme nonattainment for O_3. In addition to O_3, PAMS provides data for NO_X, NO_Y, VOCs, carbonyls, and meteorology. The PAMS network design criteria are based on locations relative to O_3 precursor source areas and predominant wind directions associated with high O_3 concentrations. The overall network design is location specific and geared toward enabling characterization of precursor emission sources in the area, O_3 transport, and photochemical processes related to O_3 nonattainment. Minimum monitoring for O_3 and its precursors is required annually during the months of June, July, and August when peak O_3 concentrations are expected. In 2006, the EPA reduced the minimum PAMS monitoring requirements (71 FR 61236). There were a total of 92 PAMS sites reporting values to the AQS data base in 2010.

[4] Middle scale defines an area up to several city blocks in size with dimensions ranging from about 100 to 500 m.

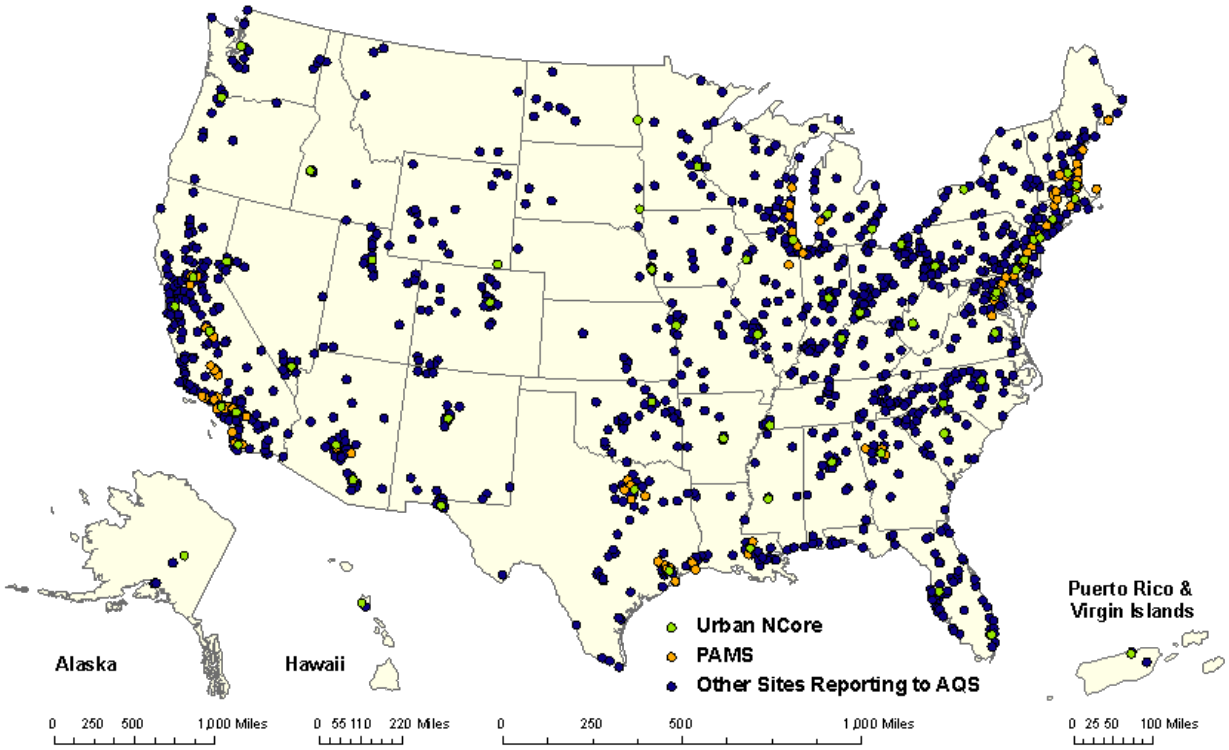


Figure 3-17 U.S. ozone sites reporting data to AQS in 2010.

The Clean Air Status and Trends Network (CASTNET) is a regional monitoring network established to assess trends in acidic deposition due to emission reduction regulations. CASTNET also provides concentration measurements of air pollutants involved in acidic deposition, such as sulfate and nitrate, in addition to the measurement of O_3. CASTNET O_3 monitors operate year round and are primarily located in rural areas. In 2010, there were 80 CASTNET sites located in, or near, rural areas. As part of CASTNET, the National Park Service (NPS) operates 23 sites located in national parks and other Class-I areas. Ozone data collected at the 23 NPS sites is compliant with the SLAMS QA requirements in 40 CFR Part 58, Appendix A. Ozone measurements at the remaining CASTNET sites were not collected with the QA requirements for SLAMS outlined in 40 CFR Part 58, Appendix A, and therefore, these O_3 data cannot be used for NAAQS compliance purposes. The SLAMS QA requirements and procedures are currently being implemented at the remaining sites.

The NPS also operates a Portable Ozone Monitoring Systems (POMS) network. The POMS couples the small, low-power O_3 monitor with a data logger, meteorological measurements, and solar power in a self contained system for monitoring in remote

locations. Typical uses for the POMS data include research projects, survey monitoring, and assessments of spatial O_3 distribution. The portable O_3 monitor in use by the NPS was recently designated as an equivalent method for O_3 (75 FR 22126). Seventeen NPS POMS monitors were operating in 2010 (NPS, 2011). A map of the rural NCore sites, along with the CASTNET, and the NPS POMS sites are shown in Figure 3-18.

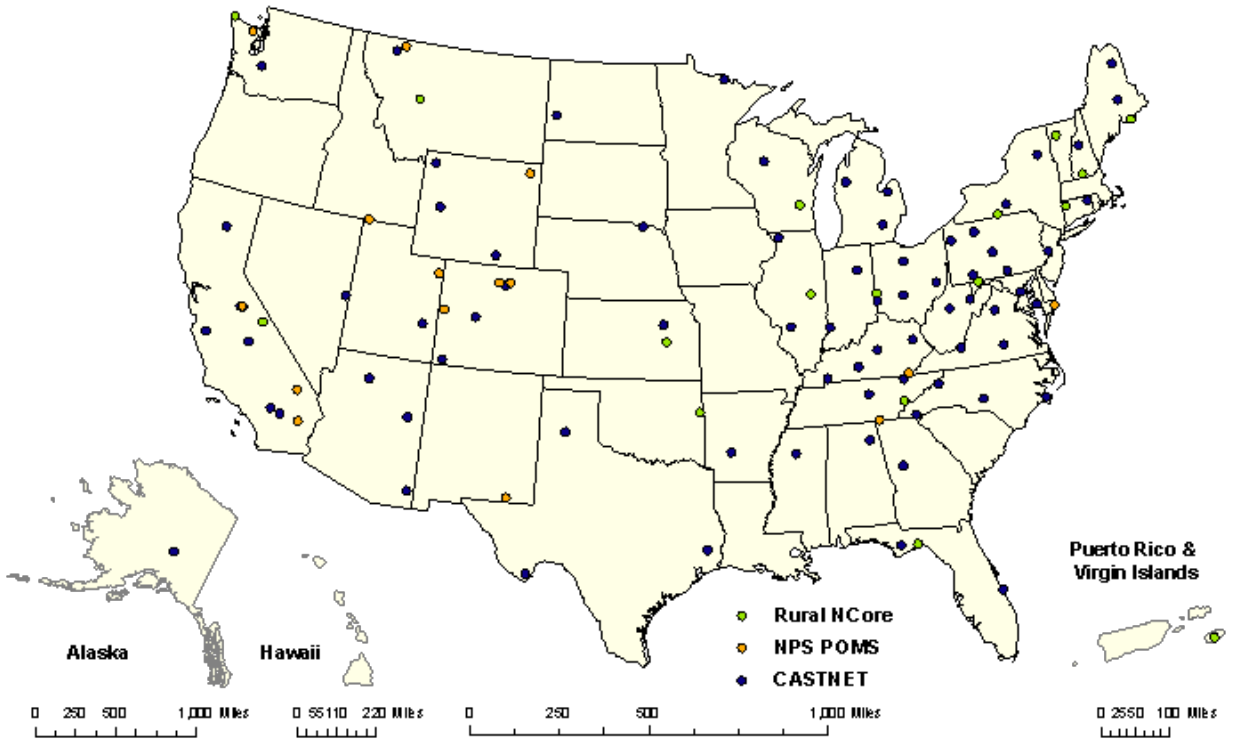


Figure 3-18 U.S. Rural NCore, CASTNET and NPS POMS ozone sites in 2010.

3.5.6.2 Probe/Inlet Siting Requirements

Probe and monitoring path siting criteria for ambient air quality monitoring are contained in 40 CFR Part 58, Appendix E. For O_3, the probe must be located between 2 and 15 m above ground level and be at least 1 m away (both in the horizontal and vertical directions) from any supporting structure, walls, etc. If it is located on the side of a building, it must be located on the windward side, relative to prevailing wind direction during the season of highest potential O_3 concentration. Ozone monitors are placed to determine air quality in larger areas (neighborhood, urban, or regional scales) and therefore, placement of the monitor probe should not be near local, minor sources of NO, O_3-scavenging

hydrocarbons, or O_3 precursors. The probe or inlet must have unrestricted air flow in an arc of at least 180 degrees and be located away from any building or obstacle at a distance of at least twice the height of the obstacle. The arc of unrestricted air flow must include the predominant wind direction for the season of greatest O_3 concentrations. Some exceptions can be made for measurements taken in street canyons or sites where obstruction by buildings or other structures is unavoidable. The scavenging effect of trees on O_3 is greater than other pollutants and the probe/inlet must be located at least 10 m from the tree drip line to minimize interference with normal air flow. When siting O_3 monitors near roadways, it is important to minimize the destructive interfereences from sources of NO, since NO reacts readily with O_3. For siting neighborhood and urban scale O_3 monitors, guidance on the minimum distance from the edge of the nearest traffic lane is based on roadway average daily traffic count (40 CFR Part 58, Appendix E, Table E-1). The minimum distance from roadways is 10 m (average daily traffic count $\leq$ 1,000) and increases to a maximum distance of 250 m (average daily traffic count $\geq$ 110,000).

3.6 Ambient Concentrations

This section investigates spatiotemporal variability in ambient O_3 concentrations and associations between O_3 and co-pollutants. To set the stage for the rest of the section, common O_3 measurement units, metrics, and averaging times are described and compared in Section 3.6.1. Spatial variability is covered in Section 3.6.2 and is divided into urban-focused variability and rural-focused variability. Urban-focused variability is organized by scale, extending from national-scale down to neighborhood-scale and the near-road environment. Rural-focused variability is organized by region and includes observations of ground-level vertical O_3 gradients where available. Temporal variability is covered in Section 0 and is organized by time, extending from multiyear trends down to hourly (diel) variability. In many instances, spatial and temporal variability are inseparable (e.g., seasonal dependence to spatial variability), resulting in some overlap between Sections 3.6.2 and 0. Finally, Section 0 covers associations between O_3 and co-pollutants including CO, SO_2, NO_2, $PM_{2.5}$ and PM_{10}.

As noted in the 2006 O_3 AQCD, 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 other photochemical oxidants (e.g., PAN, H_2O_2, etc.) typically have been obtained only as part of special field studies. Consequently, no data on nationwide patterns of occurrence are available for these other oxidants; nor are extensive data available on the relationships of concentrations and patterns of these oxidants to those of O_3. As a result, this section focuses solely on O_3, the NAAQS indicator for photochemical oxidants. The majority of ambient O_3 data reported in this section were

obtained from AQS, EPA's repository for detailed, hourly data that has been subject to EPA quality control and assurance procedures (see Section 3.1 for a description of the AQS network).

3.6.1 Measurement Units, Metrics, and Averaging Times

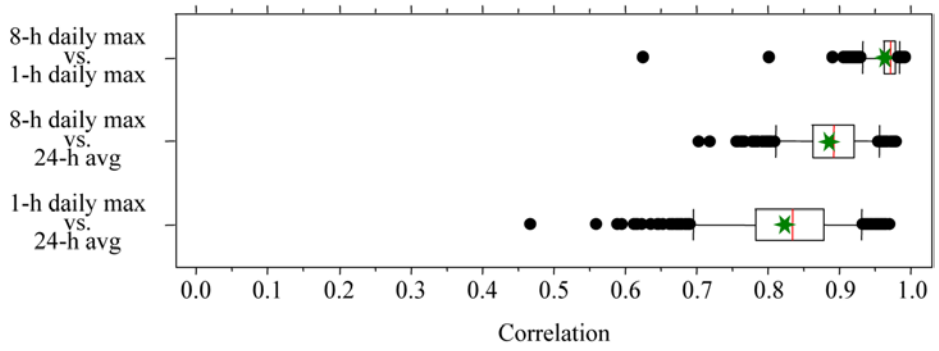
Several approaches are commonly used for reporting O_3 data. In atmospheric sciences and epidemiology, O_3 is frequently reported as a concentration, expressed as a volume-to-volume mixing ratio, commonly measured in ppm or ppb. In human exposure, O_3 is frequently reported as a cumulative exposure, expressed as a mixing ratio times time (e.g., ppm-h). In ecology, cumulative exposure indicators are frequently used that extend over longer time periods, such as growing season or year. This section focuses on ambient concentrations derived primarily from hourly average O_3 measurements and concentrations are reported in ppb wherever possible. Further details on human and ecological exposure metrics can be found in Chapter 4 and Chapter 9, respectively.

As discussed in Section 3.1, most continuous O_3 monitors report hourly average concentrations to AQS with a required precision of 10 ppb and LDL of 10 ppb (see Table 3-2). This data can be used as reported (1-h avg), or further summarized in one of several ways to focus on important aspects of the data while simultaneously reducing the volume of information. Three common daily reporting metrics include: (1) the average of the hourly observations over a 24-h period (24-h avg); (2) the maximum hourly observation occurring in a 24-h period (1-h daily max); and (3) the maximum 8-h running average of the hourly observations occurring in a 24-h period (8-h daily max)[5]. Throughout this ISA and the literature, O_3 concentrations are reported using different averaging times as appropriate, making it important to recognize the differences between these metrics.

Nation-wide, year-round 1-h avg O_3 data reported to AQS from 2007-2009 was used to compare these different daily metrics. Correlations between the 24-h avg, 1-h daily max and 8-h daily max metrics were generated on a site-by-site basis. Figure 3-19 contains box plots of the distribution in correlations from all sites. The top comparison in Figure 3-19 is between 8-h daily max and 1-h daily max O_3. Not surprisingly, these two metrics are very highly correlated (median r = 0.97, IQR = 0.96-0.98). There are a couple outlying sites, with correlations between these two metrics as low as 0.63, but 95% of sites have correlations above 0.93. The middle comparison in Figure 3-19 is between 8-h daily max and 24-h avg O_3. For these metrics, the distribution in correlations is shifted down and broadened out (median r = 0.89, IQR = 0.86-0.92). Finally, the bottom

[5] For O_3 regulatory monitoring purposes, the 8-h daily max is calculated by first generating all 8-h running averages and storing these averages hourly by the first hour in the 8-h period. The 8-h daily max is then set equal to the maximum of the 24 individual 8-h avg occurring in a given day.

comparison in Figure 3-19 is between 1-h daily max and 24-h avg O_3. Again, for these metrics the distribution in correlations is shifted down and broadened out relative to the other two comparisons (median r = 0.83, IQR = 0.78-0.88). The correlation between the two daily maximum metrics (1-h daily max and 8-h daily max) are quite high for most sites, but correlations between the daily maximum metrics and the daily average metric (24-h avg) are lower. This illustrates the influence of the overnight period on the 24-h avg O_3 concentration. In contrast, the 1-h daily max and 8-h daily max are more indicative of the daytime, higher O_3 periods. The correlation between these metrics, however, can be very site-specific, as is evident from the broad range in correlations in Figure 3-19 for all three comparisons. Therefore, understanding which O_3 metric is being used in a given study is very important since they capture different aspects of O_3 temporal variability.



Shown are the median (red line), mean (green star), inner-quartile range (box), 5th and 95th percentiles (whiskers), and extremes (black circles).

Figure 3-19 Distribution in nation-wide year-round site-level correlations between daily ozone metrics including 24-h avg, 1-h daily max and 8-h daily max using AQS data, 2007-2009.

The median 1-h daily max, 8-h daily max, and 24-h avg O_3 concentrations across all sites included in the 3-year nation-wide data set were 44, 40, and 29 ppb, respectively. Representing the upper end of the distribution, the 99th percentiles of these same metrics across all sites were 94, 80, and 60 ppb, respectively. While the ratio of these metrics will vary by location, typically the 1-h daily max will be the highest value representing peak concentrations and the 24-h avg will be considerably lower representing daily average concentrations incorporating the overnight period. The 8-h daily max typically represents

the higher mid-day concentrations and will generally lie somewhere between the other two metrics[6].

3.6.2 Spatial Variability

3.6.2.1 Urban-Focused Variability

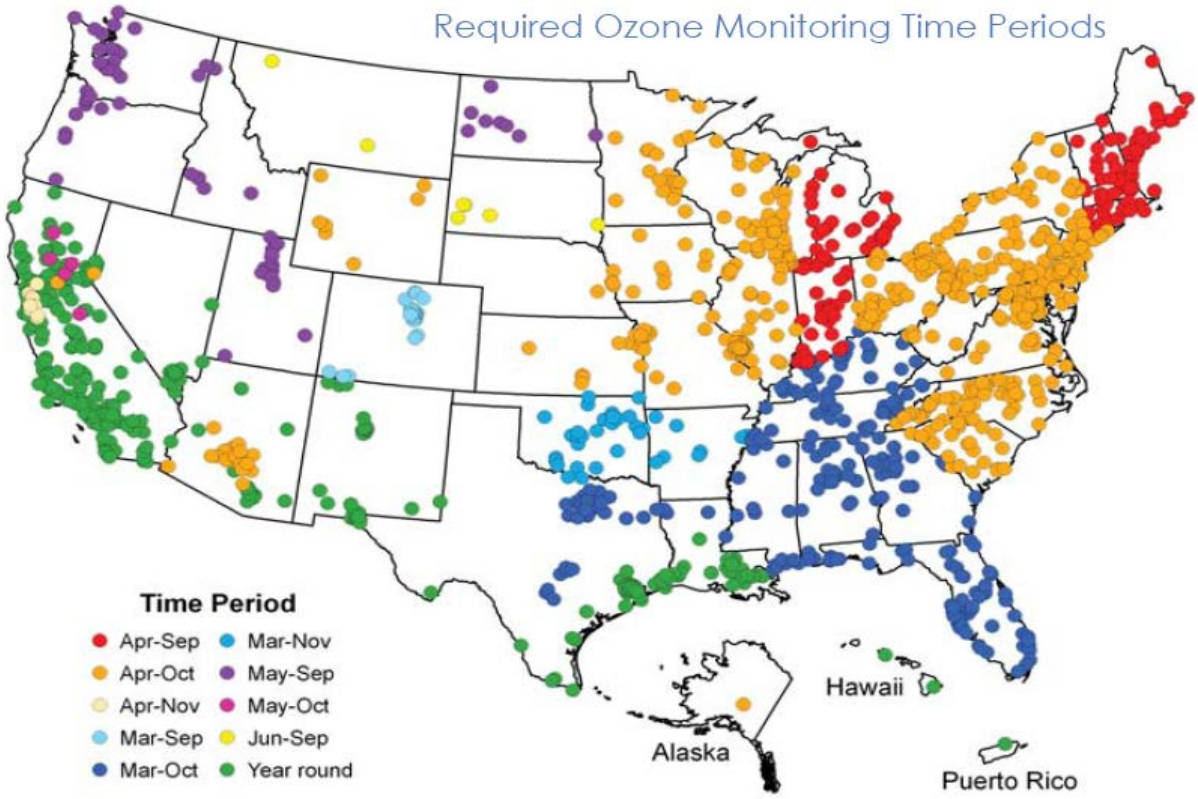
National-Scale Variability

AQS contains a large depository of national O_3 data collected to meet the monitoring objectives described in Section 3.5.6.1. In many areas, O_3 concentrations decrease significantly during months with lower temperatures and decreased sunlight. As a result, year-round O_3 monitoring is only required in certain areas. Table D-3 of 40 CFR Part 58, Appendix D lists the beginning and ending month of the ozone season (defined in Section 3.5.6.1) by geographic area and Figure 3-20 illustrates these time periods on a monitor-by-monitor basis. Monitoring is optional outside the ozone season and many states elect to operate their monitors year-round or for time periods outside what is strictly mandated.

Hourly FRM and FEM O_3 data reported to AQS for the period 2007 - 2009 were used to investigate national-scale spatial variability in O_3 concentrations. Given the variability in O_3 monitoring time periods available in AQS as a result of the regionally-varying ozone seasons, the analyses in this section were based on two distinct data sets:

- a **year-round** data set: data only from monitors reporting year-round;
- a **warm-season** data set: data from all monitors reporting May through September.

[6] The 8-h daily max is not strictly limited to lie between the 1-h daily max and the 24-h avg since the 8-h averaging period used to calculate the 8-h daily max can extend into the morning hours of the subsequent day. However, the 8-h daily max typically incorporates the middle of the day when O_3 concentrations are at their highest, resulting in an 8-h daily max somewhere between the 1-h daily max and the 24-h avg calculated for that day.



Source: U.S. EPA (2008d)

Figure 3-20 Required ozone monitoring time periods (ozone season) identified by monitoring site.

The warm-season data set was used to capture the majority of ozone season data while providing a consistent time-frame for comparison across states. All available monitoring data including data from year-round monitors was included in the warm-season data set after removing observations outside the 5-month window. Data were retrieved from AQS on February 25, 2011 for these two data sets, and all validated data was included regardless of flags or regional concurrence[7]. A summary of the two O_3 data sets including the applied completeness criteria is provided in Table 3-3. Figure 3-21 and Figure 3-22 show the location of the 457 year-round and 1,064 warm-season monitors meeting the completeness criteria for all three years (2007-2009).

[7] Concentrations that might have been affected by exceptional events (and contribute to a violation of the NAAQS) can be flagged in the Air Quality System (AQS) by the reporting organization. Exceptional events are defined as unusual or naturally occurring events that can affect air quality but are not reasonably controllable using techniques that tribal, state or local air agencies may implement in order to attain and maintain the National Ambient Air Quality Standards (NAAQS). The corresponding EPA Regional Office is responsible for reviewing the data and evidence of the event, and deciding whether to concur with the flag. Flagged data that has been concurred by the Regional office is typically excluded for regulatory purposes.

Table 3-3 Summary of ozone data sets originating from AQS

	Year-Round Data Set	Warm-Season Data Set
Years	2007-2009	2007-2009
Months	January - December (12 mo)	May - September (5 mo)
Completeness Criteria	75% of hours in a day	75% of hours in a day
	75% of days in a calendar quarter	75% of days between May - September
	all 4 quarters per year	
Number of monitors meeting completeness criteria	618 containing at least one valid year in 2007-2009	1,267 containing at least one valid year in 2007-2009
	550 containing at least two valid years in 2007-2009	1,169 containing at least two valid years in 2007-2009
	457 containing all three valid years in 2007-2009	1,064 containing all three valid years in 2007-2009

Tabulated statistics generated from the year-round and warm-season data sets are included in Table 3-4 and Table 3-5, respectively. This information was used to compare (1) the year-round and warm-season data sets; (2) the O_3 distribution variability across years (2005-2009); and (3) four different averaging times (1-h avg, 24-h avg, 1-h daily max, and 8-h daily max). Summary statistics for 2005 and 2006 were added to these tables in order to gain a broader view of year-to-year variability, but the year-round and warm-season data sets used for analyses in the rest of this section are limited to 2007-2009 as described above and in Table 3-3. The 8-h daily max pooled by site was also included in these tables to show the distribution of the annual and 3-year (2007-2009) site-averages of the 8-h daily max statistic.

The year-round data set includes data from roughly half the number of monitors as the warm-season data set and a larger fraction of the year-round monitors are located in the southern half of the U.S. due to extended monitoring requirements in these areas. Despite these differences, the mean, SD and percentiles of the nation-wide O_3 concentrations were quite similar for the year-round data presented in Table 3-4 and the warm-season data presented in Table 3-5. In both data sets, there was very little variability across years in the central statistics; for example, the median 1-h avg concentrations between 2005 and 2009 ranged from 28 to 29 ppb for the year-round data and from 29 to 30 ppb for the warm-season data. The 8-h daily max showed similar uniformity in median across the five years, with concentrations ranging from 39 to 41 ppb for the year-round data and from 40 to 43 for the warm-season data. The upper percentiles (95th and above) showed a general downward trend from 2005 to 2009 in both nation-wide data sets. For example, the 99th percentile of the 8-h daily max observed in the warm-season data dropped from 85 ppb in 2005 to 75 ppb in 2009. Trends in O_3 concentrations investigated over a longer time period are included in Section 3.6.3.1.

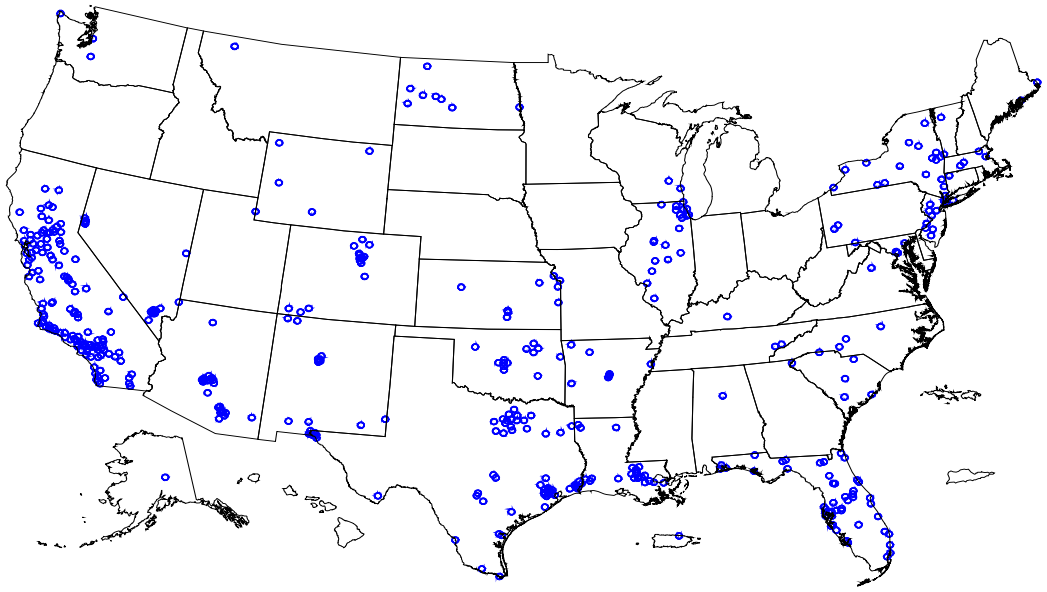


Figure 3-21 Location of the 457 ozone monitors meeting the year-round data set completeness criterion for all 3 years between 2007 and 2009.

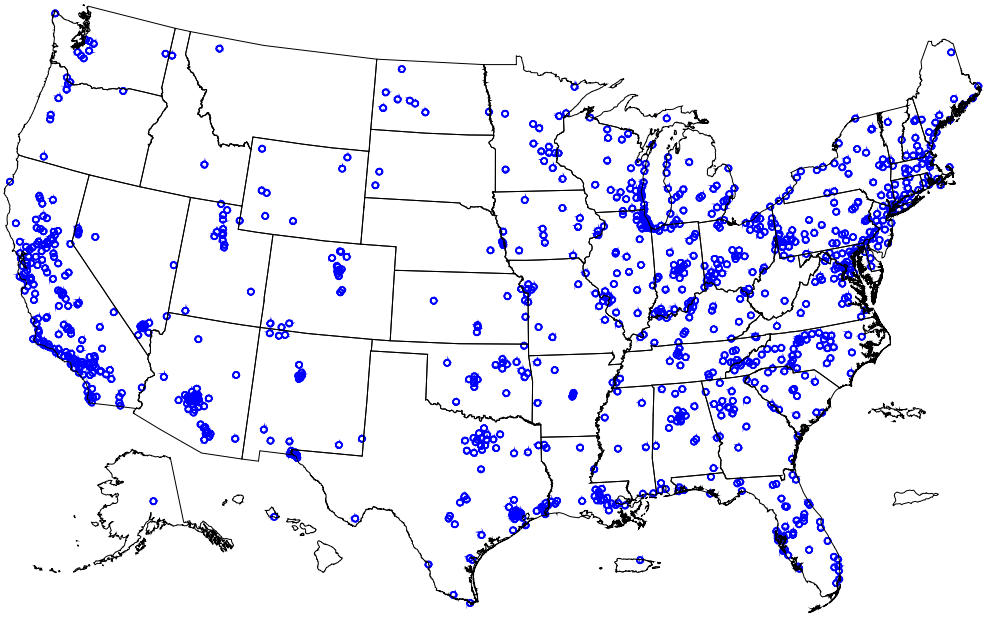


Figure 3-22 Location of the 1,064 ozone monitors meeting the warm-season data set completeness criteria for all 3 years between 2007 and 2009.

Table 3-4 Nationwide distributions of ozone concentrations (ppb) from the year-round data set

Time Period	N Monitors	N Obs	Mean	SD	Min	1	5	10	25	50	75	90	95	98	99	Max	Max Site ID[a]
1-h avg																	
2005	499	4,284,219	29	18	2	2	2	2	15	28	41	53	61	71	78	182	060710005
2006	532	4,543,205	30	18	2	2	2	5	16	29	42	54	61	71	78	175	060370016
2007	522	4,547,280	29	18	2	2	2	5	16	29	41	52	60	68	75	237	450790021
2008	520	4,470,065	30	17	2	2	2	6	17	29	41	52	59	67	74	222	450210002
2009	551	4,716,962	29	16	2	2	2	6	17	29	40	50	56	64	70	188	720770001
2007-2009	599	13,734,307	29	17	2	2	2	6	17	29	40	51	58	67	73	237	450790021
24-h avg																	
2005	504	183,815	29	13	2	4	9	13	20	28	37	46	51	57	61	103	060719002
2006	536	194,884	30	13	2	5	10	14	21	29	38	47	52	58	62	102	061070009
2007	531	194,873	29	12	2	5	11	14	20	29	37	45	50	56	60	96	060651016
2008	528	191,875	30	12	2	5	11	14	21	29	38	46	50	56	61	98	060710005
2009	556	202,142	29	11	2	6	11	14	21	28	37	44	48	53	57	95	060710005
2007-2009	611	588,890	29	12	2	5	11	14	21	29	37	45	49	55	60	98	060710005
1-h daily max																	
2005	504	183,815	48	18	2	11	21	26	35	46	58	71	80	91	100	182	060710005
2006	536	194,884	48	18	2	13	23	28	36	46	58	71	80	91	100	175	060370016
2007	531	194,873	47	17	2	14	23	28	36	45	57	69	77	87	94	237	450790021
2008	528	191,875	47	17	2	14	23	27	35	45	56	67	76	87	96	222	450210002
2009	556	202,142	45	15	2	14	22	27	35	44	54	64	72	83	91	188	720770001
2007-2009	611	588,890	46	16	2	14	23	27	35	44	55	67	75	86	94	237	450790021
8-h daily max																	
2005	504	183,279	42	16	2	7	16	21	30	40	52	63	70	78	84	145	060710005
2006	536	194,285	42	16	2	9	18	23	31	41	52	63	70	79	85	142	060710005
2007	528	194,266	41	15	2	10	19	23	31	40	51	61	68	75	81	137	060710005
2008	528	191,283	41	15	2	11	19	23	31	40	51	60	66	75	82	172	450210002
2009	556	201,536	40	14	2	11	18	23	30	39	49	57	63	71	77	128	060712002
2007-2009	608	587,085	41	15	2	10	19	23	31	40	50	60	66	74	80	172	450210002
8-h daily max (pooled by site)																	
2005	508	508	42	6	23	27	32	34	38	42	45	48	51	53	55	61	060710005
2006	538	538	42	6	12	28	31	34	38	43	46	50	52	54	55	61	060719002
2007	538	538	41	6	17	27	31	34	38	41	45	49	51	54	55	63	060719002
2008	529	529	41	6	20	28	31	34	37	40	45	50	52	55	57	61	060719002
2009	558	558	40	6	20	26	30	33	36	39	44	48	50	53	54	60	060719002
2007-2009	457	457	41	6	19	29	32	34	38	40	45	49	51	54	55	61	060719002

[a]AQS Site ID corresponding to the observation in the Max column

Table 3-5 Nationwide distributions of ozone concentrations (ppb) from the warm-season data set

Time Period	N Monitors	N Obs	Mean	SD	Min	1	5	10	25	50	75	90	95	98	99	Max	Max Site ID
1-h avg																	
2005	1,023	7,455,018	30	19	2	2	2	5	16	29	43	55	64	73	79	182	060710005
2006	1,036	7,590,796	31	18	2	2	2	6	17	30	43	55	62	71	77	175	060370016
2007	1,021	7,711,463	31	18	2	2	2	6	18	30	43	55	63	71	77	237	450790021
2008	1,034	7,701,597	31	17	2	2	2	7	18	30	42	53	60	68	74	222	450210002
2009	1,029	7,835,074	29	16	2	2	2	7	17	29	40	50	56	63	69	259	311090016
2007-2009	1,103	23,248,134	30	17	2	2	2	7	18	30	42	53	60	68	74	259	311090016
24-h avg																	
2005	1,103	319,410	30	12	2	5	10	14	22	30	39	46	51	57	61	103	060719002
2006	1,110	324,993	31	12	2	6	12	15	22	30	39	47	52	58	61	102	061070009
2007	1,100	330,197	31	12	2	6	12	16	23	31	39	47	51	57	61	96	060651016
2008	1,120	329,918	31	12	2	6	12	16	22	30	38	46	50	56	60	98	060710005
2009	1,141	335,669	29	11	2	6	12	15	21	29	37	44	48	53	56	95	060710005
2007-2009	1,197	995,784	30	12	2	6	12	16	22	30	38	45	50	55	59	98	060710005
1-h daily max																	
2005	1,103	319,410	50	18	2	12	23	28	38	49	61	74	81	91	99	182	060710005
2006	1,110	324,993	50	17	2	15	25	29	38	48	60	72	80	90	98	175	060370016
2007	1,100	330,197	50	17	2	16	25	30	38	48	60	72	80	88	95	237	450790021
2008	1,120	329,918	48	16	2	16	25	29	37	47	58	69	76	86	93	222	450210002
2009	1,141	335,669	46	15	2	15	23	28	36	45	54	64	71	80	87	259	311090016
2007-2009	1,197	995,784	48	16	2	16	24	29	37	47	58	68	76	85	93	259	311090016
8-h daily max																	
2005	1,104	318,771	44	16	2	9	18	23	32	43	55	66	72	79	85	145	060710005
2006	1,112	324,327	44	16	2	11	20	25	33	43	54	64	70	78	84	142	060710005
2007	1,097	329,482	44	15	2	12	20	25	33	43	54	65	71	78	82	137	060710005
2008	1,120	329,223	43	15	2	12	20	25	33	42	52	61	67	74	80	172	450210002
2009	1,141	334,972	40	13	2	12	19	24	31	40	49	57	63	69	75	128	060712002
2007-2009	1,194	993,677	42	15	2	12	20	24	32	42	52	61	67	75	80	172	450210002
8-h daily max (pooled by site)																	
2005	1,141	1,141	45	6	14	28	34	36	41	46	49	52	54	56	57	61	040139508
2006	1,152	1,152	44	6	12	29	34	37	41	45	48	51	54	58	59	65	060170020
2007	1,164	1,164	45	7	17	28	34	36	40	45	50	54	56	58	59	64	471550102
2008	1,163	1,163	43	6	20	29	33	36	39	44	48	50	53	56	58	61	060719002
2009	1,173	1,173	41	5	20	28	32	35	38	41	44	47	50	53	55	63	060651016
2007-2009	1,064	1,064	43	6	19	29	34	36	39	43	47	50	52	55	57	61	060719002

Given the strong diurnal pattern in O_3 concentrations, the selection of averaging time has a substantial effect on the magnitude of concentration reporting. The nation-wide median 1-h avg, 24-h avg, 1-h daily max, and 8-h daily max concentrations for the year-round data set in 2009 were 29, 28, 44 and 39 ppb, respectively. The median concentrations for the warm-season data set in 2009 were: 29, 29, 45 and 40 ppb, respectively. The 1-h avg

and 24-h avg both include the lowest concentrations typically observed in the overnight period which lowers their values relative to the daily maximum statistics.

A strong seasonal pattern in O_3 concentrations can also be seen in the year-round data. Table 3-6 shows the 8-h daily max stratified by season, with the seasons defined as:

- winter: December-February;
- spring: March-May;
- summer: June-August; and
- fall: September-November.

In addition, warm-season (May-Sept) and cold-season (Oct-Apr) stratifications of the year-round data set are included in the table for comparison with the four seasonal stratifications. Substantial seasonal variability in the 8-h daily max concentration for the period 2007-2009 was evident with lower concentrations present in fall (median = 36 ppb) and winter (median = 32 ppb) and higher concentrations in spring (median = 47 ppb) and summer (median = 46 ppb). The seasonal differences were even more pronounced in the upper percentiles. For example, the 99th percentile in the 8-h daily max over the 2007-09 time period ranged from 52 ppb in winter to 90 ppb in summer. The distribution in 8-h daily max O_3 during the warm-season (as defined above) and during summer were very similar, which is not surprising given their close overlap in months. The distribution during the cold-season (as defined above) is shifted toward higher 8-h daily max O_3 concentrations compared with the distribution during winter. This is a result of including the four transition months (Oct, Nov, Mar and Apr) in the cold-season when high O_3 concentrations can occur. Further investigation of temporal variability including multiyear trends and diel behavior is included in Section 0.

Table 3-6 Seasonally stratified distributions of 8-h daily max ozone concentrations (ppb) from the year-round data set (2007-2009)

Time Period	N Monitors	N Obs	Mean	SD	Min	1	5	10	25	50	75	90	95	98	99	Max	Max Site ID
8-h daily max (2007-2009)																	
Year-round	608	587,085	41	15	2	10	19	23	31	40	50	60	66	74	80	172	450210002
8-h daily max by season (2007-2009)																	
Winter (Dec-Feb)	608	143,855	31	10	2	6	14	18	25	32	38	43	46	49	52	172	450210002
Spring (Mar-May)	612	148,409	47	12	2	20	28	33	40	47	55	62	67	72	77	118	060370016
Summer (Jun-Aug)	613	148,280	47	16	2	16	22	26	35	46	57	67	75	84	90	137	060710005
Fall (Sep-Nov)	608	146,541	37	13	2	10	17	21	28	36	45	54	61	68	75	116	060370016
Warm-season (May-Sep)	616	246,233	47	16	2	16	22	27	35	46	57	66	73	81	87	137	060710005
Cold-season (Oct-Apr)	608	340,852	36	12	2	8	16	21	28	36	44	52	57	63	67	172	450210002

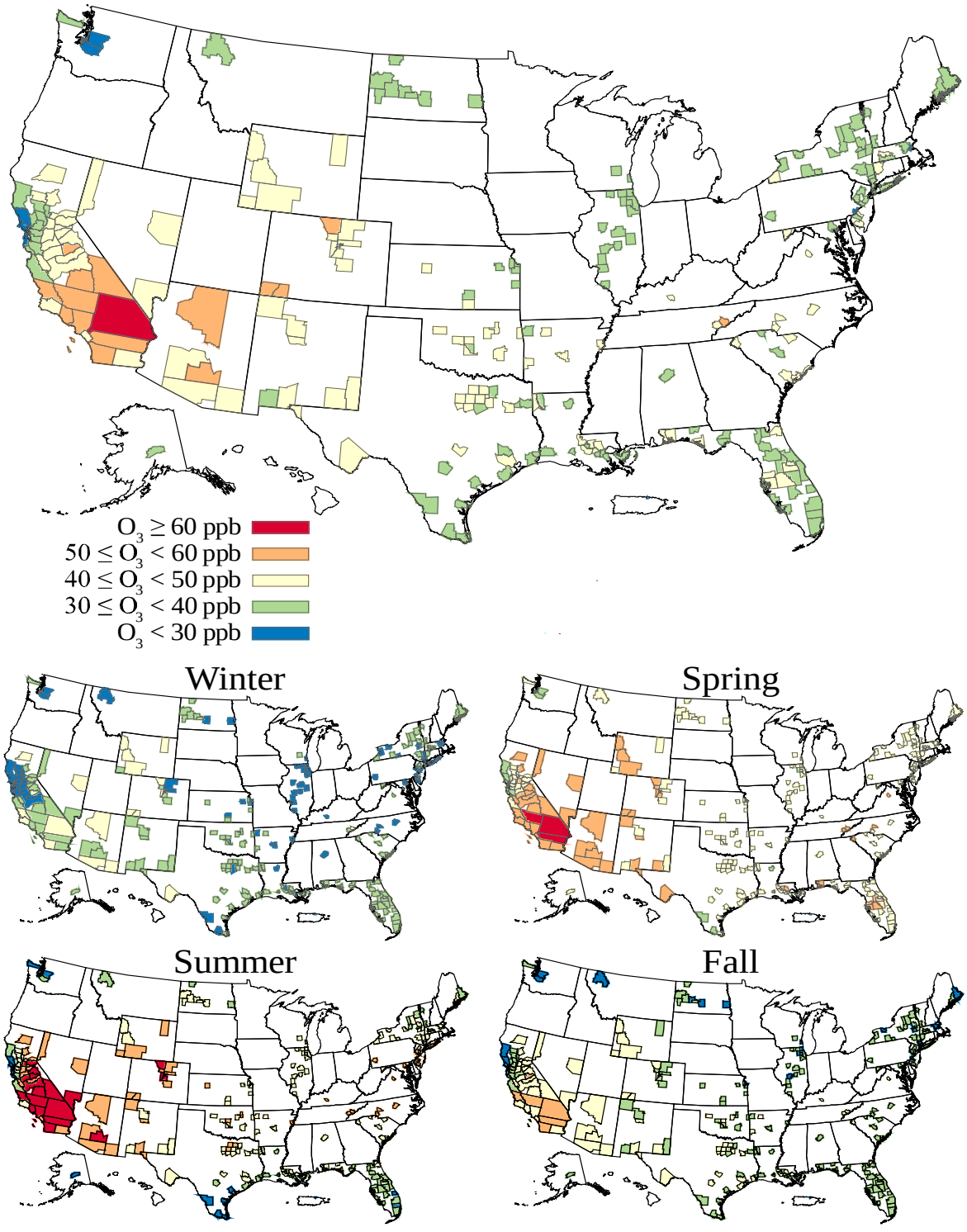


Figure 3-23 Highest monitor (by county) 3-year avg (2007-2009) of the 8-h daily max ozone concentration based on the year-round data set (top map) with seasonal stratification (bottom 4 maps).

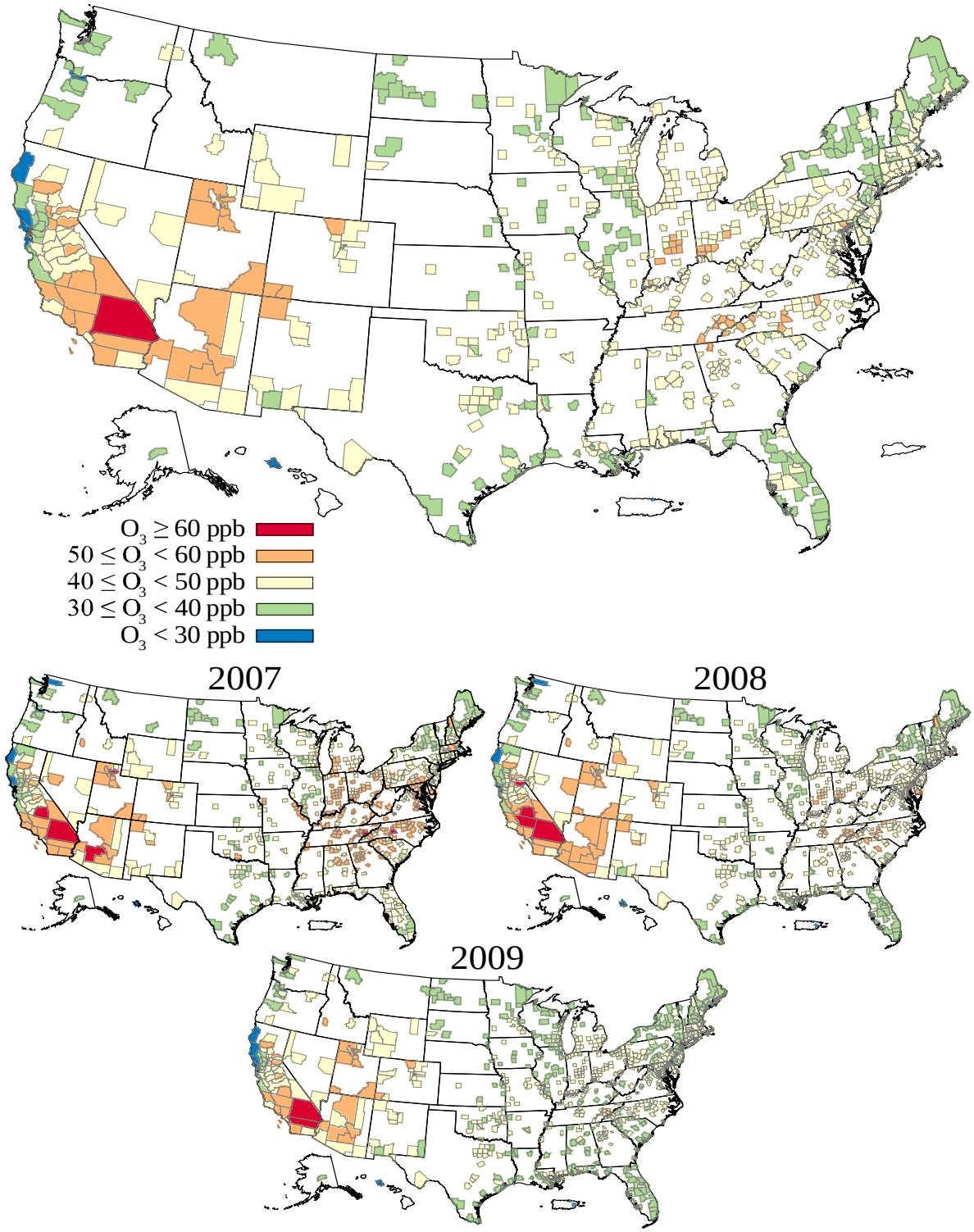


Figure 3-24 Highest monitor (by county) 3-year avg (2007-2009) of the 8-h daily max ozone concentration based on the warm-season data set (top map) with annual stratification (bottom 3 maps).

A national picture of AQS O_3 concentrations was generated from the year-round and warm-season data sets by aggregating the 8-h daily max observations by U.S. county. For this purpose, the 8-h daily max concentrations at each site were averaged over one or more calendar years and then the highest site in each county was selected for that county. Figure 3-23 contains the county-scale 8-h daily max O_3 concentrations from the year-round data set for 2007-2009 (top map) with seasonal stratification (bottom four maps). Figure 3-24 contains the county-scale 8-h daily max O_3 concentrations from the warm-season data set for 2007-2009 (top map) along with individual maps for each calendar year between 2007 and 2009 (bottom three maps). These maps are meant to illustrate the general national-scale distribution in long-term average 8-h daily max O_3 concentrations and are not representative of O_3 concentrations at all locations or times within the counties shown; considerable spatial variability can exist within a county. This is particularly important in the West where counties are larger on average than in the East. These maps are limited by monitor availability, resulting in the majority of U.S. counties not having available data (the white regions in Figure 3-23 and Figure 3-24).

As shown in the top county-scale map generated from the 2007-2009 year-round data set in Figure 3-23, the highest 3-year avg 8-h daily max O_3 concentrations ($\geq$ 50 ppb) occur in counties in central and southern California, Arizona, Colorado and high elevation counties in Tennessee. The highest year-round average concentration of 61 ppb over this period comes from Site #060719002 located at an elevation of 1,244 m in Joshua Tree National Monument, San Bernardino County, CA. The lowest 3-year avg 8-h daily max O_3 concentrations (<30 ppb) occur in Pacific Coast counties in northern California and Washington as well as in two northeastern counties in Pennsylvania and Massachusetts. The seasonally-stratified county-scale maps in Figure 3-24 reinforce the strong seasonality in 8-h daily max O_3 concentrations shown in Table 3-6. The highest wintertime concentrations ($\geq$ 40 ppb) occur in the West with the highest 3-year wintertime avg of 46 ppb calculated for Site #080690007 located at an elevation of 2,743 m near Rocky Mountain National Park, Larimer County, CO. In spring and summer, the concentrations increase considerably across all counties, with the highest concentrations ($\geq$ 60 ppb) occurring during the summer in 15 counties in California, 3 counties in Colorado and 1 county each in Nevada and Arizona. Many counties in rural Wyoming, Montana, North Dakota, Maine, and along the Gulf Coast peak in the spring instead of the summer. In the fall, 8-h daily max O_3 concentrations drop back down below their spring and summer concentrations.

The top county-scale map in Figure 3-24 based on the 2007-2009 warm-season data set looks similar to the corresponding map in Figure 3-23 based on the year-round data set. The warm-season map, however, incorporates approximately twice as many monitors across the U.S., providing more spatial coverage. Several counties in Utah, New Mexico,

Indiana, Ohio, Maryland, North Carolina, and Georgia in addition to California, Arizona, Colorado and Tennessee identified above have 3-year avg (2007-2009) 8-h daily max O_3 concentrations ≥ 50 ppb based on the warm-season data set. The individual yearly average county-maximum 8-h daily max O_3 concentrations in the lower half of Figure 3-23 show a general decrease in most counties from 2007 to 2009. The number of counties containing a monitor reporting an annual average 8-h daily max O_3 concentration above 50 ppb dropped from 230 counties in 2007 to 30 counties in 2009. This is consistent with the general decrease across these years shown in Table 3-4 and Table 3-5 for the upper percentiles of the 8-h daily max O_3 concentration.

Urban-Scale Variability

Statistical analysis 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 monitoring sites in a given metropolitan area. The validity of relying on central monitoring sites is strongly dependent on the spatial variability in concentrations within a given metropolitan area. To investigate urban-scale variability, 20 focus cities were selected for closer analysis of O_3 concentration variability; these cities are listed in Table 3-7 and were selected based on their importance in O_3 epidemiology studies and on their geographic distribution across the U.S. In order to provide a well-defined boundary around each city, the combined statistical area (CSA) encompassing each city was used. If the city was not within a CSA, the smaller core-based statistical area (CBSA) was selected. The CSAs/CBSAs are defined by the U.S. Census Bureau (2011)[8] and have been used to establish analysis regions around cities in previous ISAs for particulate matter (U.S. EPA, 2009d) and carbon monoxide (U.S. EPA, 2010c).

[8]A CBSA represents a county-based region surrounding an urban center of at least 10,000 people determined using 2000 census data and replaces the older Metropolitan Statistical Area (MSA) definition from 1990. The CSA represents an aggregate of adjacent CBSAs tied by specific commuting behaviors. The broader CSA definition was used when selecting monitors for the cities listed above with the exception of Phoenix and San Antonio, which are not contained within a CSA. Therefore, the smaller CBSA definition was used for these metropolitan areas.

Table 3-7 Focus cities used in this and previous assessments

Focus City	Short Name	CSA/CBSA Name[a]	Year-Round O_3 Monitoring Sites[b]	Warm-Season O_3 Monitoring Sites[c]	Included in Prior ISAs[d]
Atlanta, GA	Atlanta CSA	Atlanta-Sandy Springs-Gainesville	0	11	CO, PM, SO_X, NO_X
Baltimore, MD	Baltimore CSA	Washington-Baltimore-northern VA	9	19	NO_X
Birmingham, AL	Birmingham CSA	Birmingham-Hoover-Cullman	1	9	PM
Boston, MA	Boston CSA	Boston-Worcester-Manchester	3	18	CO, PM, NO_X
Chicago, IL	Chicago CSA	Chicago-Naperville-Michigan City	11	15	PM, NO_X
Dallas, TX	Dallas CSA	Dallas-Fort Worth	19	0	
Denver, CO	Denver CSA	Denver-Aurora-Boulder	12	3	CO, PM
Detroit, MI	Detroit CSA	Detroit-Warren-Flint	0	9	PM
Houston, TX	Houston CSA	Houston-Baytown-Huntsville	21	0	CO, PM, NO_X
Los Angeles, CA	Los Angeles CSA	Los Angeles-Long Beach-Riverside	47	3	CO, PM, SO_X, NO_X
Minneapolis, MN	Minneapolis CSA	Minneapolis-St. Paul-St. Cloud	2	6	
New York, NY	New York CSA	New York-Newark-Bridgeport	20	10	CO, PM, SO_X, NO_X
Philadelphia, PA	Philadelphia CSA	Philadelphia-Camden-Vineland	9	8	PM, NO_X
Phoenix, AZ	Phoenix CBSA	Phoenix-Mesa-Scottsdale	14	17	CO, PM
Pittsburgh, PA	Pittsburgh CSA	Pittsburgh-New Castle	2	12	CO, PM
Salt Lake City, UT	Salt Lake City CSA	Salt Lake City-Ogden-Clearfield	2	10	
San Antonio, TX	San Antonio CBSA	San Antonio	5	0	
San Francisco, CA	San Francisco CSA	San Jose-San Francisco-Oakland	25	6	
Seattle, WA	Seattle CSA	Seattle-Tacoma-Olympia	5	5	CO, PM
St Louis, MO	St Louis CSA	St. Louis-St. Charles-Farmington	3	13	CO, PM, SO_X

[a]Defined based on 2000 Census data from the U.S. Census Bureau (2011).
[b]The number of sites within each CSA/CBSA with AQS monitors meeting the year-round data set inclusion criteria.
[c]The number of sites within each CSA/CBSA with AQS monitors meeting the warm-season data set inclusion criteria; the warm-season data set includes May - September data from both the warm-season and year-round monitors meeting the warm-season data set inclusion criteria.
[d]Boundaries for the CO ISA (U.S. EPA, 2010c) and PM ISA (U.S. EPA, 2009d) focus cities were based on CSA/CBSA definitions; boundaries for the SOX ISA (U.S. EPA, 2008c) and NOX ISA (U.S. EPA, 2008b) focus cities were based on similar metropolitan statistical area (MSA) definitions from the 1990 U.S. Census.

The distribution of the 8-h daily max O_3 concentrations from 2007-2009 for each of the 20 focus cities is included in Table 3-8. These city-specific distributions were extracted from the warm-season data set and can be compared to the nationwide warm-season 8-h daily max distribution for 2007-2009 in Table 3-5 (and repeated in the first line of Table 3-8 for reference). The median 8-h daily max concentration in these focus cities was 41 ppb, similar to the nationwide median of 42 ppb. Seattle had the lowest median (31 ppb) and Salt Lake City had the highest median (53 ppb) of the 20 cities investigated. The 99th percentile of the 8-h daily max concentration in the focus cities was 84 ppb; similar once again to the nationwide 99th percentile of 80 ppb. Seattle had the lowest 99th percentile (64 ppb) and Los Angeles had the highest 99th percentile (98 ppb) of the 20 cities investigated. In aggregate, the 20 focus cities selected are similar in distribution to the nationwide data set, but there is substantial city-to-city variability in the individual distributions of the 8-h daily max concentrations based on the warm-season data set.

Table 3-8 City-specific distributions of 8-h daily max ozone concentrations (ppb) from the warm-season data set (2007-2009)

Time Period	N Monitors	N Obs	Mean	SD	Min	1	5	10	25	50	75	90	95	98	99	Max	Max Site ID
8-h daily max (2007-2009)																	
Nationwide	1,194	993,677	42	15	2	12	20	24	32	42	52	61	67	75	80	172	450210002
8-h daily max by CSA/CBSA (2007-2009)																	
Atlanta CSA	11	7,844	47	16	2	15	22	27	36	47	58	67	72	81	87	124	130890002
Baltimore CSA	28	20,999	43	16	2	9	18	23	31	43	54	64	70	78	83	118	240030014
Birmingham CSA	10	7,676	44	15	2	14	21	25	34	44	54	63	68	76	83	108	010732006
Boston CSA	21	12,603	41	14	2	13	21	25	31	40	49	59	67	75	81	104	250270015
Chicago CSA	27	20,764	37	14	2	9	15	19	27	37	47	57	62	69	74	108	170310042
Dallas CSA	19	19,858	41	15	2	11	20	24	31	39	50	61	67	74	79	121	484390075
Denver CSA	15	12,217	44	15	2	8	18	24	34	44	55	63	68	72	76	98	080590006
Detroit CSA	9	5,016	45	14	2	15	23	28	35	44	52	62	69	77	83	100	260990009
Houston CSA	21	22,305	36	15	2	8	15	19	25	34	46	57	64	72	78	110	482011034
Los Angeles CSA	49	49,295	47	18	2	10	20	26	35	45	58	72	81	91	98	137	060710005
Minneapolis CSA	8	5,315	40	12	2	15	21	25	31	40	48	54	58	63	67	86	270031002
New York CSA	21	26,304	39	16	2	6	15	20	28	37	47	59	68	77	83	123	090050005
Philadelphia CSA	14	12,673	41	17	2	8	17	21	29	39	52	64	70	78	83	125	240150003
Phoenix CBSA	22	26,129	49	12	2	18	27	32	41	50	58	65	68	72	75	85	040137021
Pittsburgh CSA	13	9,814	43	15	2	12	19	24	32	43	53	62	68	74	78	100	420050001
Salt Lake City CSA	12	5,146	51	14	2	8	23	32	44	53	61	67	71	77	80	96	490353008
San Antonio CSA	5	4,701	39	13	2	13	20	23	29	37	46	56	62	67	72	90	480290032
San Francisco CSA	31	28,325	34	12	2	8	16	20	26	33	41	48	55	63	68	110	060010007
Seattle CSA	5	6,148	31	12	2	4	12	17	23	31	39	46	51	59	64	91	530330023
St Louis CSA	19	11,569	43	15	2	12	19	23	32	43	53	61	68	76	81	113	295100086
All CSAs/CBSAs listed	360	314,701	42	16	2	9	18	22	31	41	52	63	69	78	84	137	060710005

Maps showing the location of central monitoring sites with O_3 monitors reporting to AQS for each of the 20 focus cities are included as supplemental material in Section 3.10.1, Figure 3-61 through Figure 3-80; examples for Atlanta, Boston and Los Angeles are shown in Figure 3-25 through Figure 3-27. The sites are delineated in the maps as year-round or warm-season based on their inclusion in the year-round data set and the warm-season data set (the warm-season data set includes May-September data from both the warm-season monitors and the year-round monitors meeting the warm-season data inclusion criteria). The maps also include the CSA/CBSA boundary selected for monitor inclusion, the location of urban areas and water bodies, the major roadway network, as well as the population gravity center based on the entire CSA/CBSA and the individual focus city boundaries. Population gravity center is calculated from the average longitude and latitude values for the input census tract centroids and represents the mean center of the population in a given area. Census tract centroids are weighted by their population during this calculation.

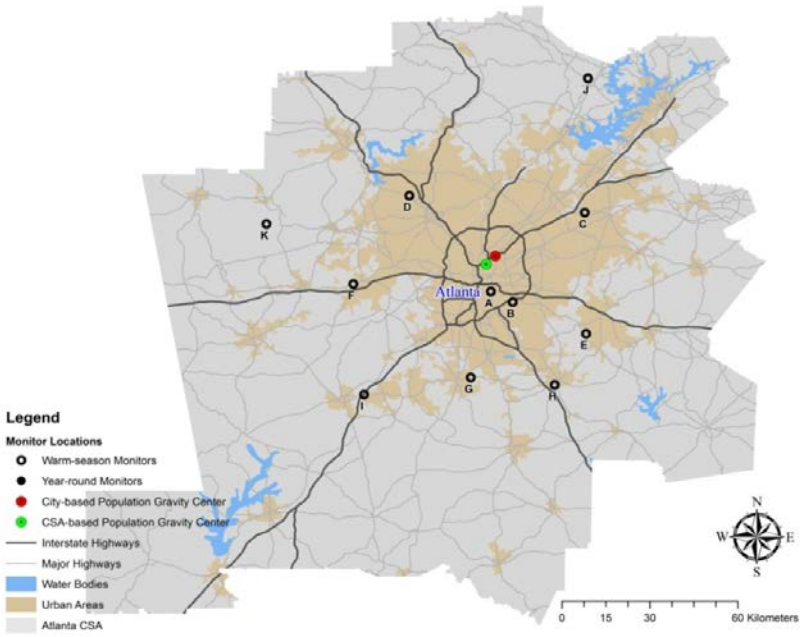


Figure 3-25 Map of the Atlanta CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

Figure 3-26 Map of the Boston CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

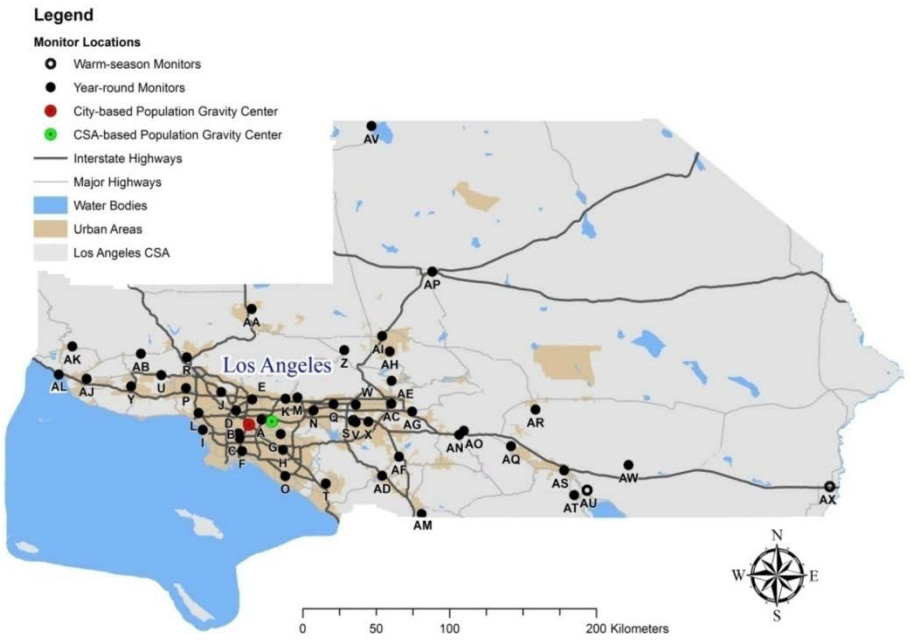


Figure 3-27 Map of the Los Angeles CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

The Atlanta CSA contains 11 warm-season monitors distributed evenly yet sparsely around the city center (Figure 3-25). The population gravity center for the city and the larger CSA are only separated by 4 km, indicating that the majority of the population lives within or evenly distributed around the city limits. Atlanta is landlocked with a radial network of interstate highways leading to the city center. The Boston CSA contains 3 year-round and 18 warm-season monitors spread evenly throughout the CSA. Boston is a harbor city with the Atlantic Ocean to the east, resulting in the city-based population gravity center being located 17 km east of the CSA-based population gravity center. The Los Angeles CSA contains the largest number of monitors of the 20 CSA/CBSAs investigated with 47 year-round and 3 warm-season monitors. These monitors are primarily concentrated in the Los Angeles urban area with relatively few monitors extending out to the northern and eastern reaches of the CSA. These unmonitored areas are very sparsely populated, resulting in only 15 km separating the city-based and the CSA-based population gravity centers despite the vast area of the Los Angeles CSA.

Other CSAs/CBSAs (see Section 3.10.1) with monitors concentrated within the focus city limits include Birmingham, Chicago, Denver, Houston, Phoenix, San Antonio, and Salt Lake City. The remaining CSAs/CBSAs have monitors distributed more evenly throughout the CSA/CBSA area. Baltimore is contained within the same CSA as Washington DC

and suburbs, resulting in a 50-km separation (the largest of the focus cities investigated) between the city-based population gravity center for Baltimore and the CSA-based population gravity center for the Washington-Baltimore-Northern Virginia CSA.

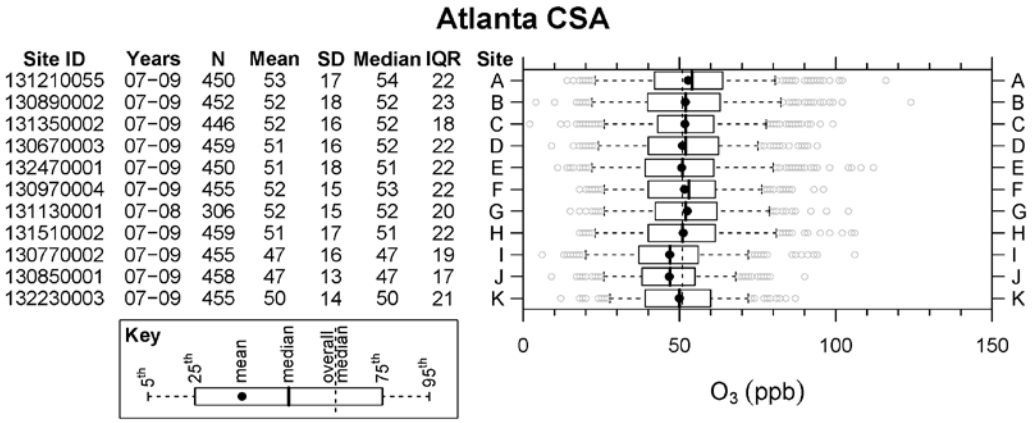


Figure 3-28 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Atlanta CSA.

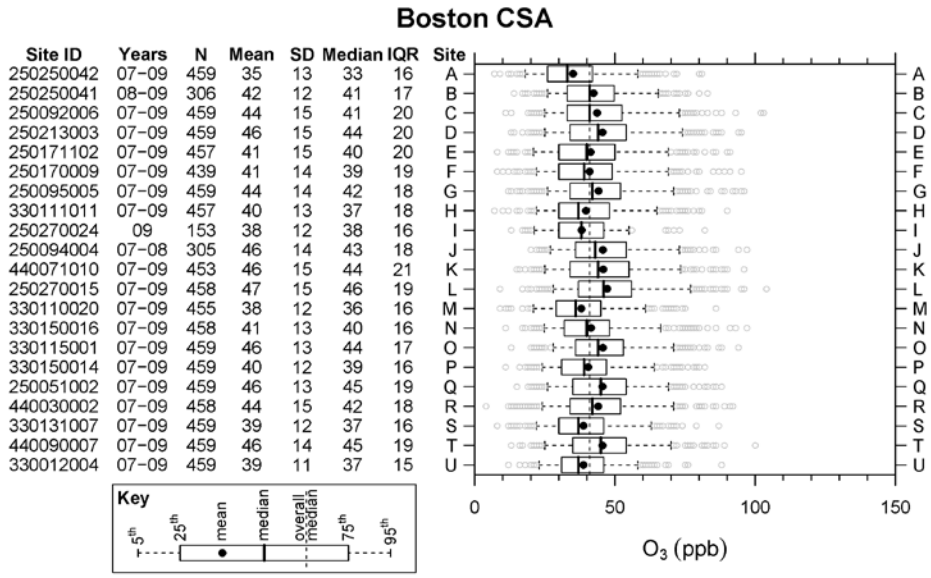


Figure 3-29 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Boston CSA.

Box plots depicting the distribution of 2007-2009 warm-season 8-h daily max O_3 data from each individual monitor in the 20 focus cities are included as supplemental material in Section 3.10.2, Figure 3-81 through Figure 3-100; examples for Atlanta, Boston and Los Angeles are shown in Figure 3-28 through Figure 3-30. The Atlanta CSA has very little spatial variability in 8-h daily max O_3 concentrations with median concentrations ranging from 47 ppb at Sites I and J located far from the city center to 54 ppb at Site A located closest to the city center. The variation in warm-season 8-h daily max concentrations are also relatively similar across monitors with IQRs ranging from 17 ppb at Site J to 23 ppb at Site B. The Boston CSA has more spatial variability in 8-h daily max O_3 concentrations than the Atlanta CSA with median concentrations ranging from 33 ppb at Site A nearest to the city center to 46 ppb at Site L located 84 km west of the city center. For monitors located within and just adjacent to the Boston city limits (Sites A-D), the O_3 concentrations can vary over relatively short distances owing to differing degrees of NO_X titration and influence from the local topography. Like the Atlanta CSA, the variation in warm-season 8-h daily max concentrations are relatively similar across monitors within the Boston CSA with IQRs ranging from 15 ppb at Site U to 21 ppb at Site K. The Los Angeles CSA exhibits the most variability in O_3 concentrations between monitors of all the CSAs/CBSAs investigated. The median 8-h daily max O_3 concentration in the Los Angeles CSA ranged from 20 ppb at Site AM in the south-central extreme of the CSA to 80 ppb at Site AE near Crestline, CA in the San Bernardino National Forest just north of San Bernardino, CA. These two sites are at approximately the same longitude and are separated by only 85 km, but the Crestline site is downwind of the Los Angeles basin, resulting in substantially higher O_3 concentrations. Site AM also contains data for only 2009, which could explain some of the deviation when comparing this site with others in the Los Angeles CSA. Sites AM and AE also had the lowest (8 ppb) and highest (28 ppb) IQR, respectively. The remaining focus cities exhibited spatial variability ranging from uniform as in the Atlanta CSA to non-uniform as observed in the Los Angeles CSA (see supplemental figures in Section 3.10.2).

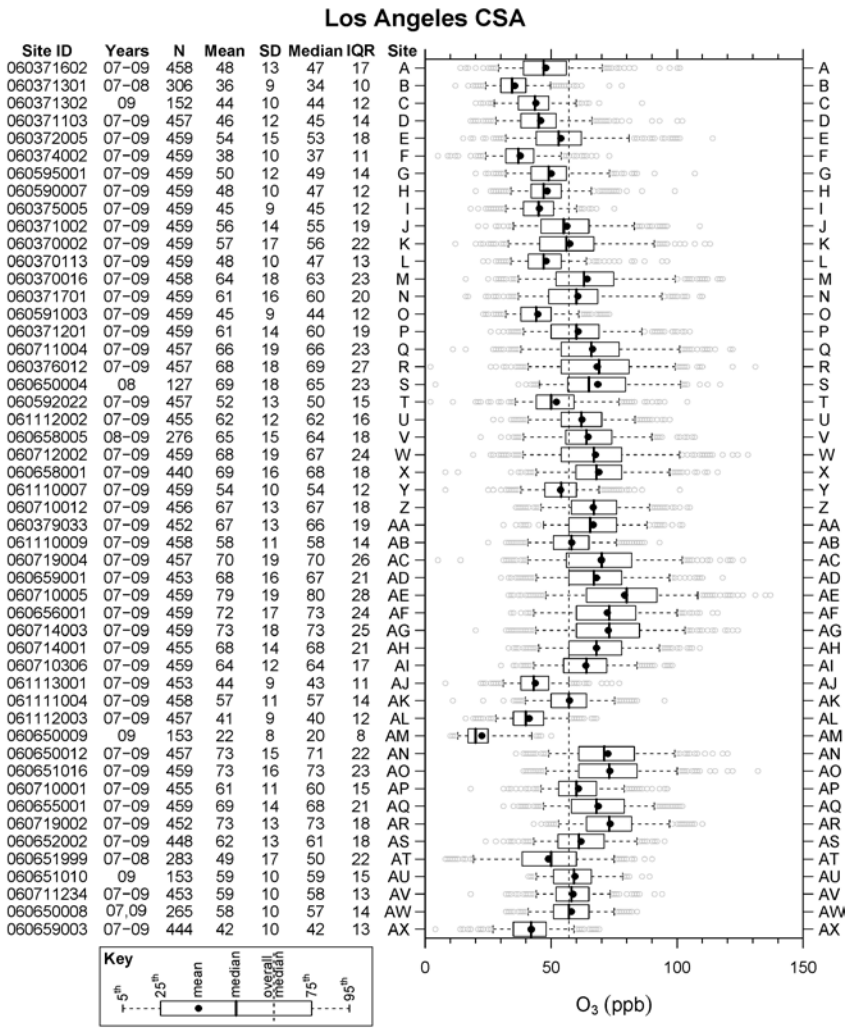


Figure 3-30 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Los Angeles CSA.

Pair-wise monitor comparisons were used to further evaluate spatial variability between monitors within the 20 focus cities. In the particular case of ground-level O_3, central-site monitoring has been justified as a regional measure of exposure mainly on the grounds that correlations between concentrations at neighboring sites measured over time are usually high. In areas with multiple monitoring sites, averages over the monitors have often been used to characterize population exposures. However, substantial differences in concentrations between monitors can exist even though concentrations measured at the monitoring sites are highly correlated, thus leading to the potential for exposure misclassification error. Therefore, both the Pearson correlation coefficient and the coefficient of divergence (COD) were calculated for each monitor pair within the

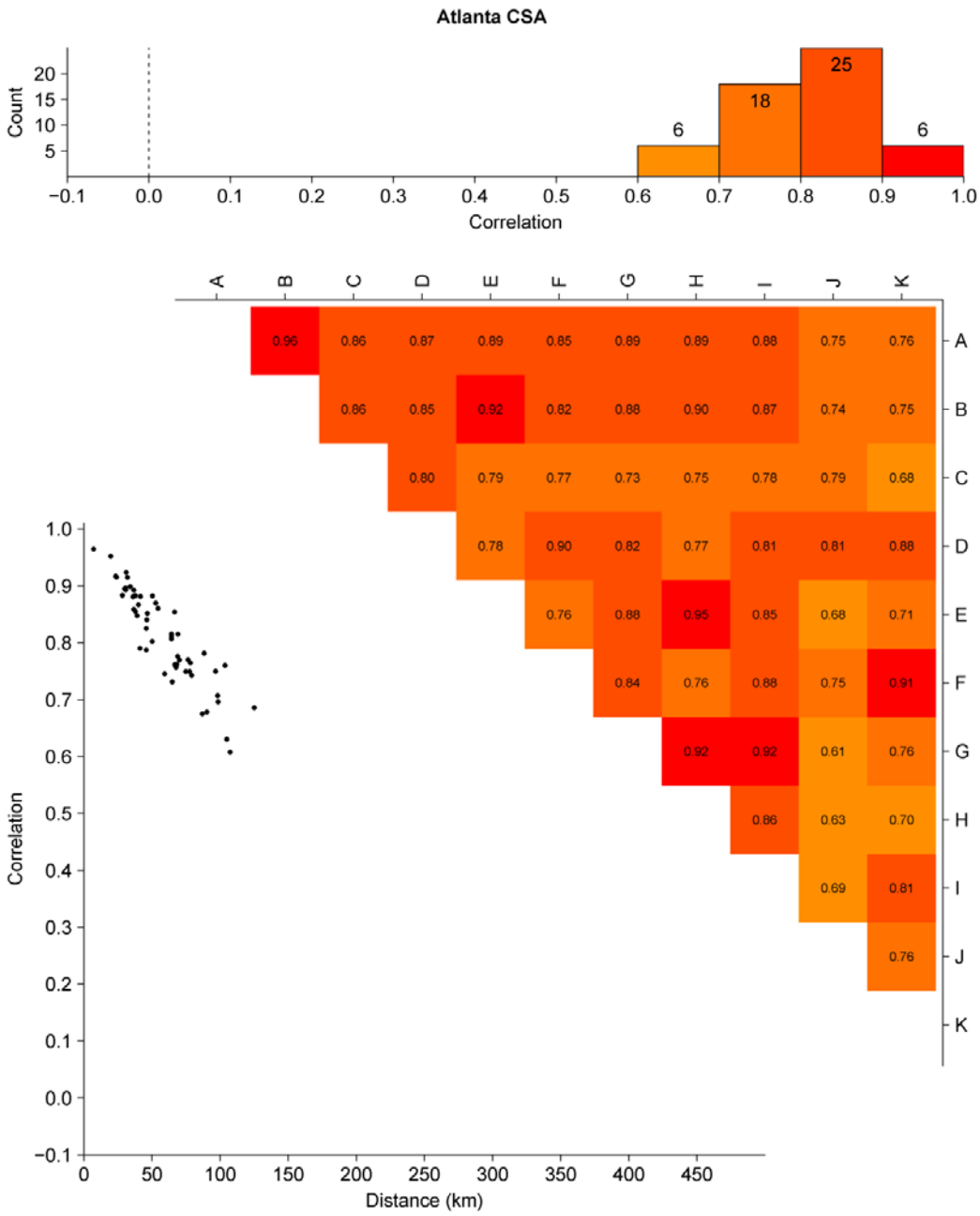
CSA/CBSAs using the 8-h daily max O_3 data. The correlation provides an indication of temporal linear dependence across sites while the COD provides an indication of the variability in absolute concentrations across sites. The COD is defined as follows:

$$COD_{jk} = \sqrt{\frac{1}{p}\sum_{i=1}^{p}\left(\frac{X_{ij} - X_{ik}}{X_{ij} + X_{ik}}\right)^2}$$

Equation 3-1

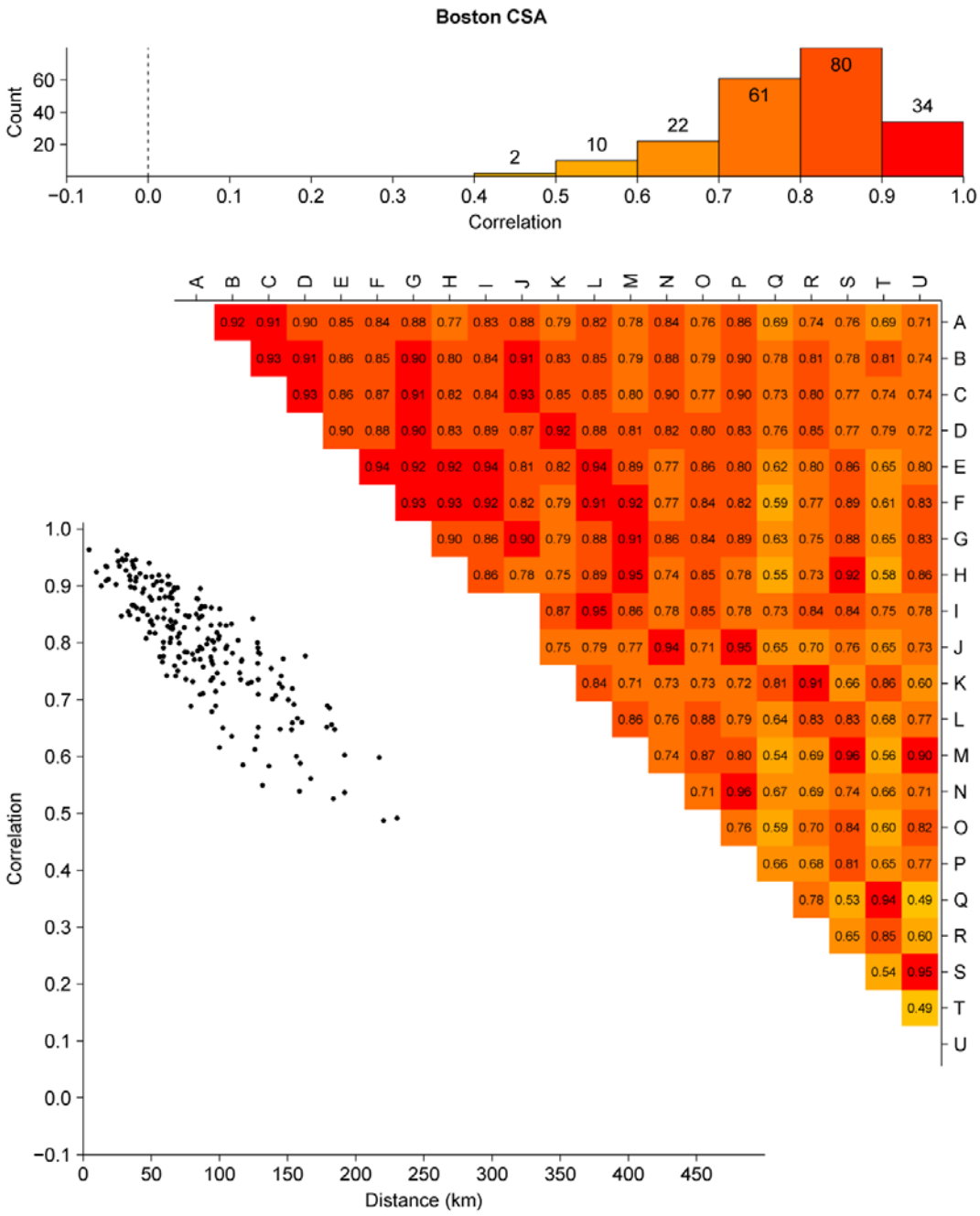
where X_{ij} and X_{ik} represent observed concentrations averaged over some measurement averaging period i (hourly, daily, etc.) at sites j and k, and p is the number of paired observations. A COD of 0 indicates there are no differences between concentrations at paired sites (spatial homogeneity), while a COD approaching 1 indicates extreme spatial heterogeneity. These methods for analysis of spatial variability follow those used in previous ISAs for CO, PM, SO_X and NO_X as well as those used in Pinto et al. (2004) for $PM_{2.5}$.

Histograms and contour matrices of the Pearson correlation coefficient between 8-h daily max O_3 concentrations from each monitor pair are included as supplemental material in Section 3.10.3, Figure 3-101 through Figure 3-120; examples for Atlanta, Boston and Los Angeles are shown in Figure 3-31 through Figure 3-33. Likewise, histograms, contour matrices, and scatter plots of the COD between 8-h daily max O_3 concentrations from each monitor pair are included as supplemental material in Section 3.10.3, Figure 3-121 through Figure 3-140; examples for Atlanta, Boston and Los Angeles are shown in Figure 3-34 through Figure 3-36. These figures also contain scatter plots of correlation and COD as a function of straight-line distance between monitor pairs.



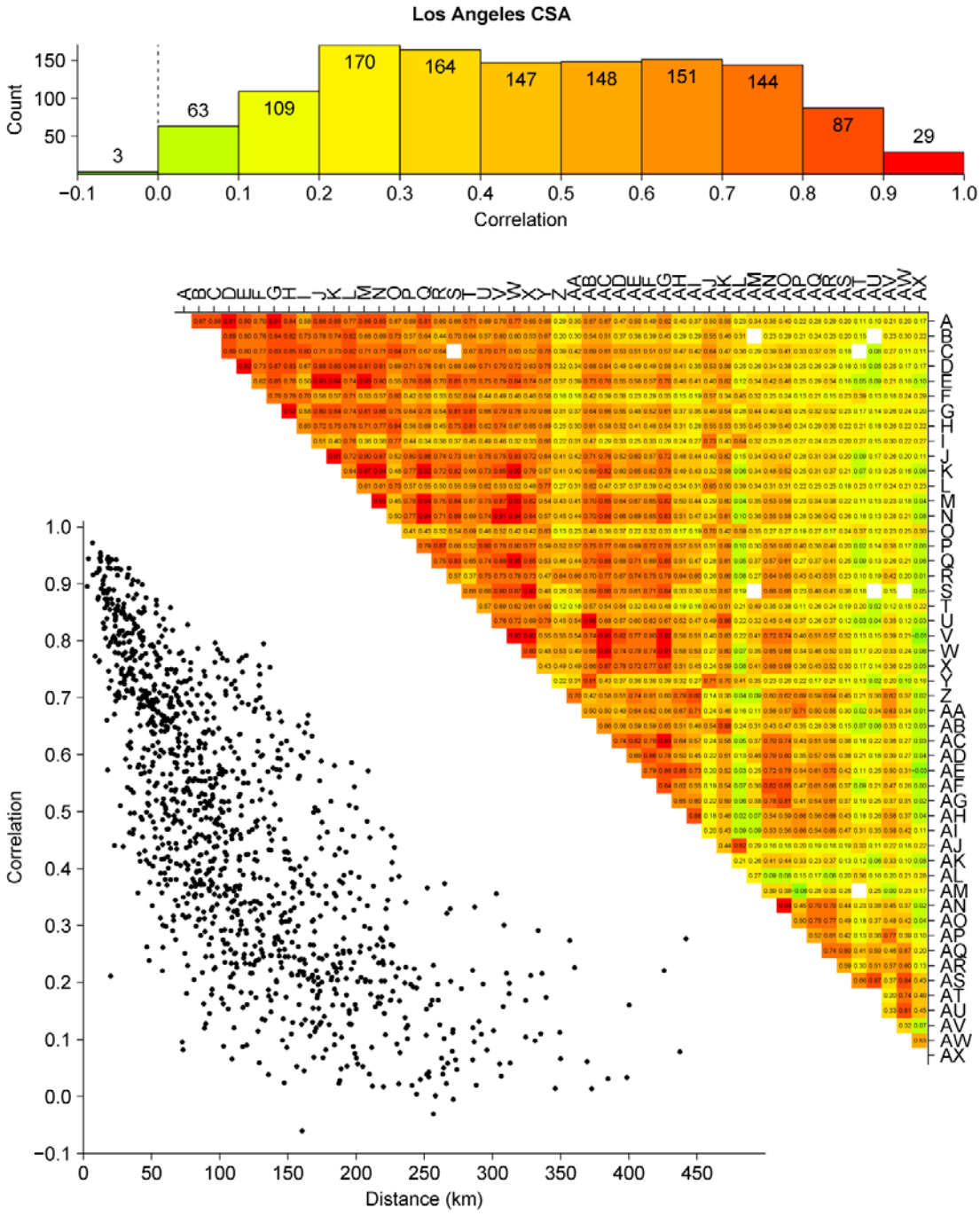
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.

Figure 3-31 Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Atlanta CSA.



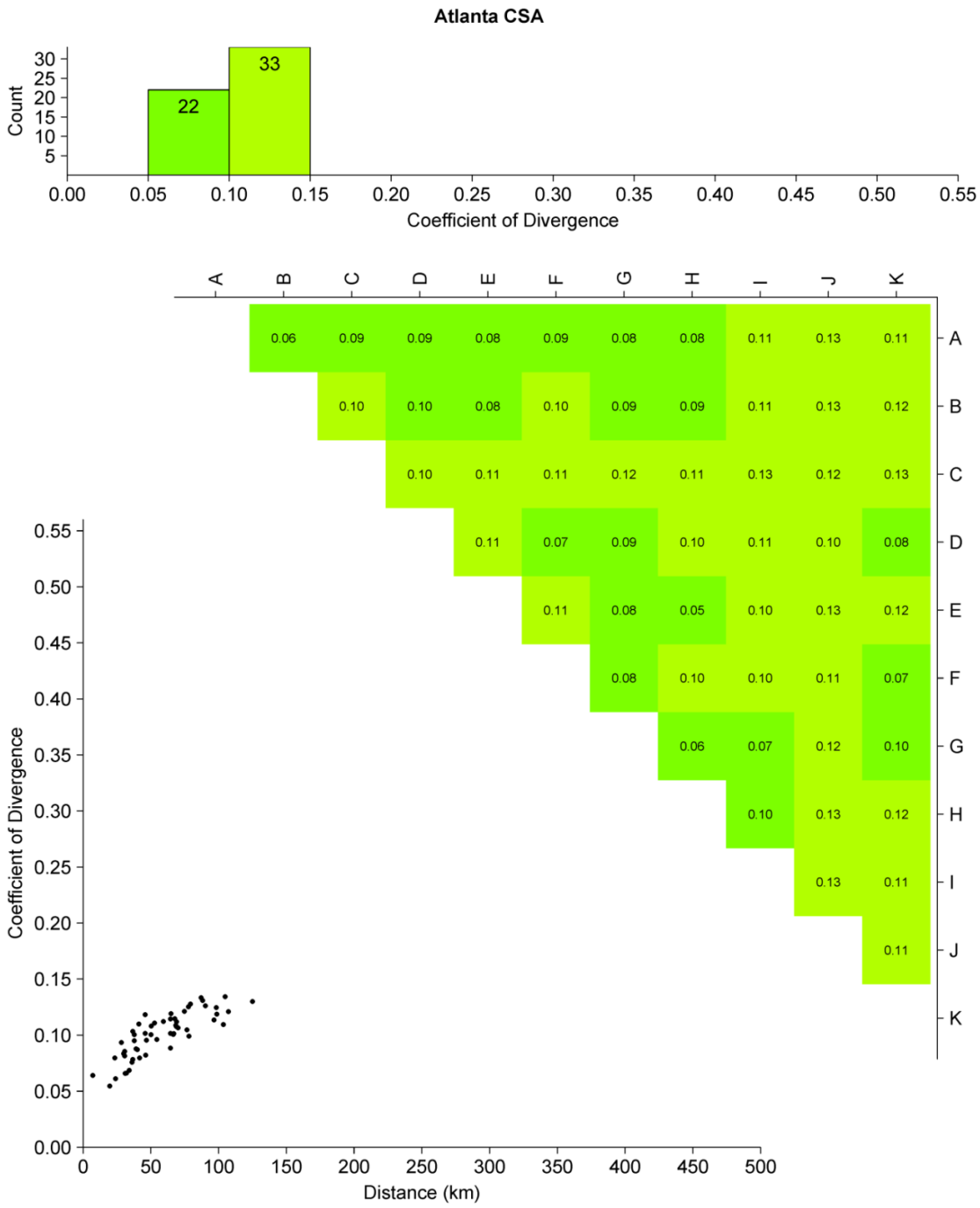
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.

Figure 3-32 Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Boston CSA.



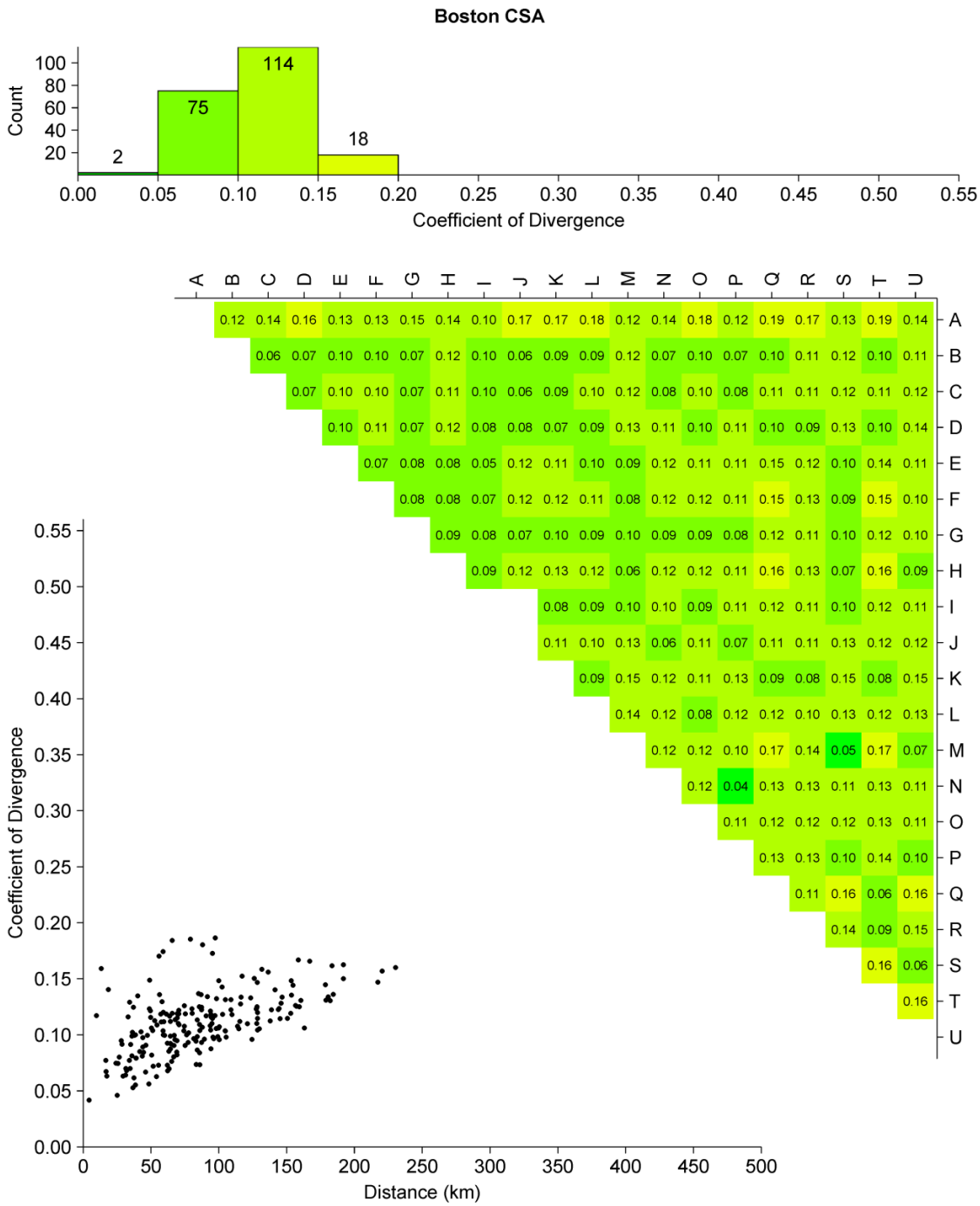
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.

Figure 3-33 Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Los Angeles CSA.



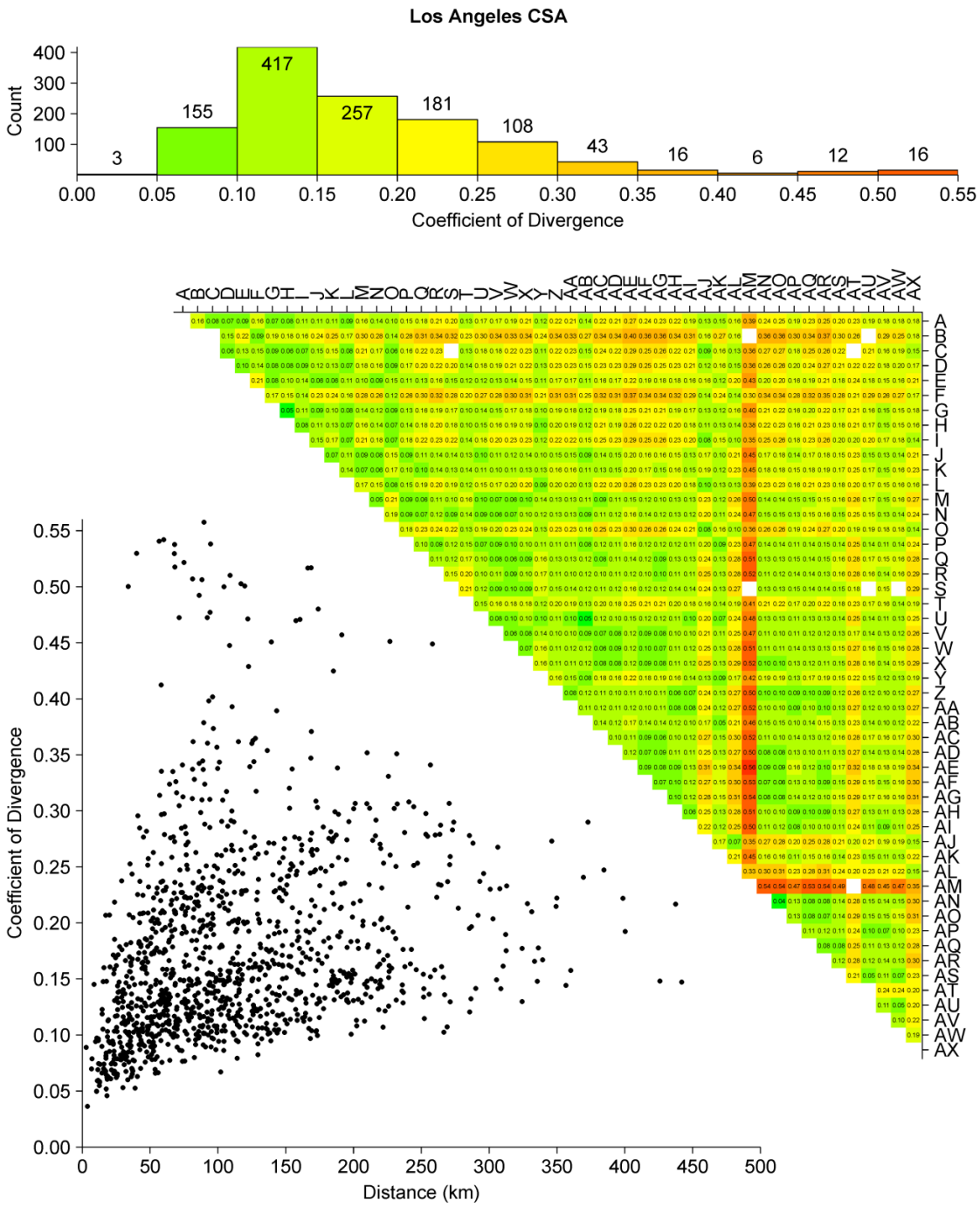
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.

Figure 3-34 Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Atlanta CSA.



The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.

Figure 3-35 Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Boston CSA.



The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.

Figure 3-36 Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Los Angeles CSA.

The monitor pairs within the Atlanta CSA (Figure 3-31) were generally well correlated with correlations between 8-h daily max O_3 concentrations ranging from 0.61 to 0.96. The correlations shown in the scatter plot were highest for close monitor pairs and dropped off with distance in a near-linear form. At a monitor separation distance of 50 km or less, the correlations ranged from 0.79 to 0.96. The monitor pairs within the Boston CSA (Figure 3-32) were also generally well correlated with correlations ranging from 0.49 to 0.96. Again, the correlations shown in the scatter plot were highest for close monitor pairs, but there was slightly more scatter in correlation as a function of distance in the Boston CSA compared with the Atlanta CSA. At a monitor separation distance of 50 km or less, the correlations ranged from 0.81 to 0.96. The monitor pairs within the Los Angeles CSA (Figure 3-33) showed a much broader range in correlations, extending from -0.06 to 0.97. At a monitor separation distance of 50 km or less, the correlations shown in the scatter plot ranged from 0.21 to 0.97. The negative and near-zero correlations were between monitors with a relatively large separation distance (>150 km), but even some of the closer monitor pairs were not very highly correlated. For example, Site AL located at Emma Wood State Beach in Ventura and Site AK situated in an agricultural valley surrounded by mountains 20 km inland (see map in Figure 3-37) had a correlation coefficient of only 0.21 over the 2007-2009 warm-season time period. This was slightly lower than the correlation between Site AL and Site AX on the Arizona border, 441 km away (R = 0.28). San Francisco and Seattle (Figure 3-118 and Figure 3-119 in Section 3.10.3) also showed a broad range in pair-wise correlations, likely resulting from their similar geography where background air coming in from the Pacific Ocean rapidly mixes with urban pollutants such as NO_X and VOCs from coastal cities and is transported downwind into diversified terrain to create spatially and temporally varying O_3 concentrations.

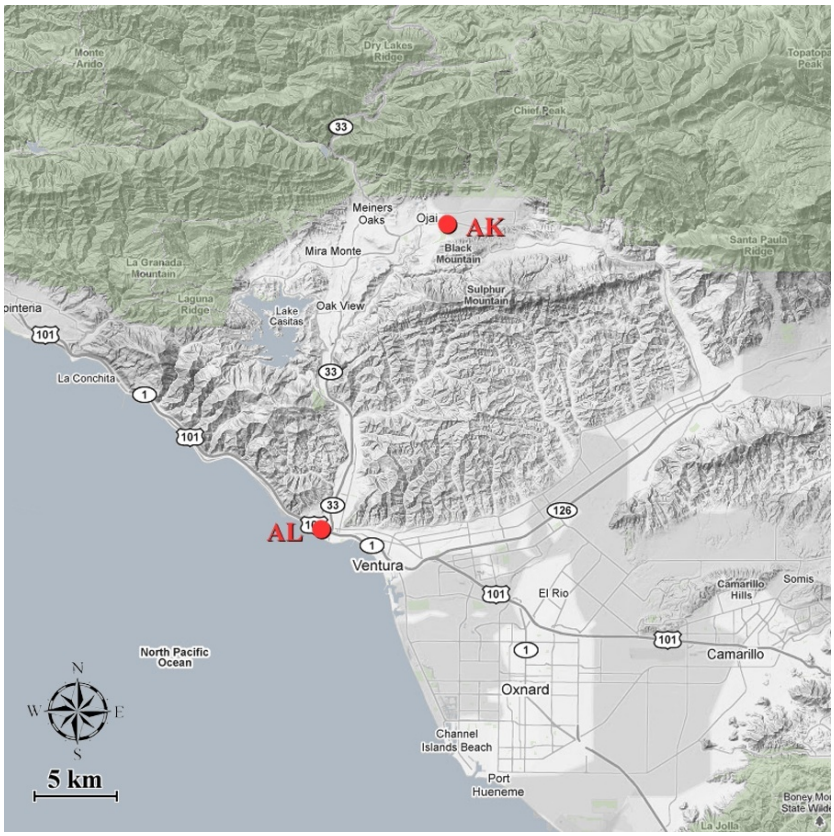


Figure 3-37 Terrain map showing the location of two nearby AQS ozone monitoring sites (red dots) along the western edge of the Los Angeles CSA. Site AL is near shore, 3 m above sea level, while Site AK is in an agricultural valley surrounded by mountains, 262 m above sea level.

The COD between 8-h daily max O_3 measured at paired monitors in all CSAs/CBSAs (Figure 3-121 through Figure 3-140 in Section 3.10.3) were generally low, with values similar to those shown in Figure 3-34 and Figure 3-35 for Atlanta and Boston. This suggests a generally uniform distribution in the 8-h daily max O_3 concentration across monitors within these cities and is consistent with the uniformity observed in the box plots (e.g., Figure 3-28, Figure 3-29, and Figure 3-81 through Figure 3-100 in Section 3.10.2). Los Angeles (Figure 3-30) and San Francisco (Figure 3-138 in Section 3.10.3), however, had several monitor pairs with COD >0.30 indicating greater spatial heterogeneity. This is consistent with the variability observed in the box plots for these two CSAs (Figure 3-30 and Figure 3-98 in Section 3.10.2). In particular, Site AM in the Los Angeles CSA had consistently lower concentrations (median = 20 ppb, IQR = 17-25 ppb) relative to other sites in the CSA (Figure 3-27), resulting in high CODs with other monitors as shown in Figure 3-36. The O_3 monitor at Site AM is located on the

Pechanga Tribal Government Building in Temecula, CA, and began collecting data on June 9, 2008. It is located in a suburban setting and is classified as a general background monitor. Another close by site (site ID = 060731201) located in the Pala Reservation, 9.5 km south of this one (just outside the boundary of the Los Angeles CSA) reported similarly low 2009 8-h daily max O_3 concentrations (median = 28 ppb, IQR = 23-32 ppb) between May-June, 2009 (the only warm-season months with available data from this site between 2007 and 2009).

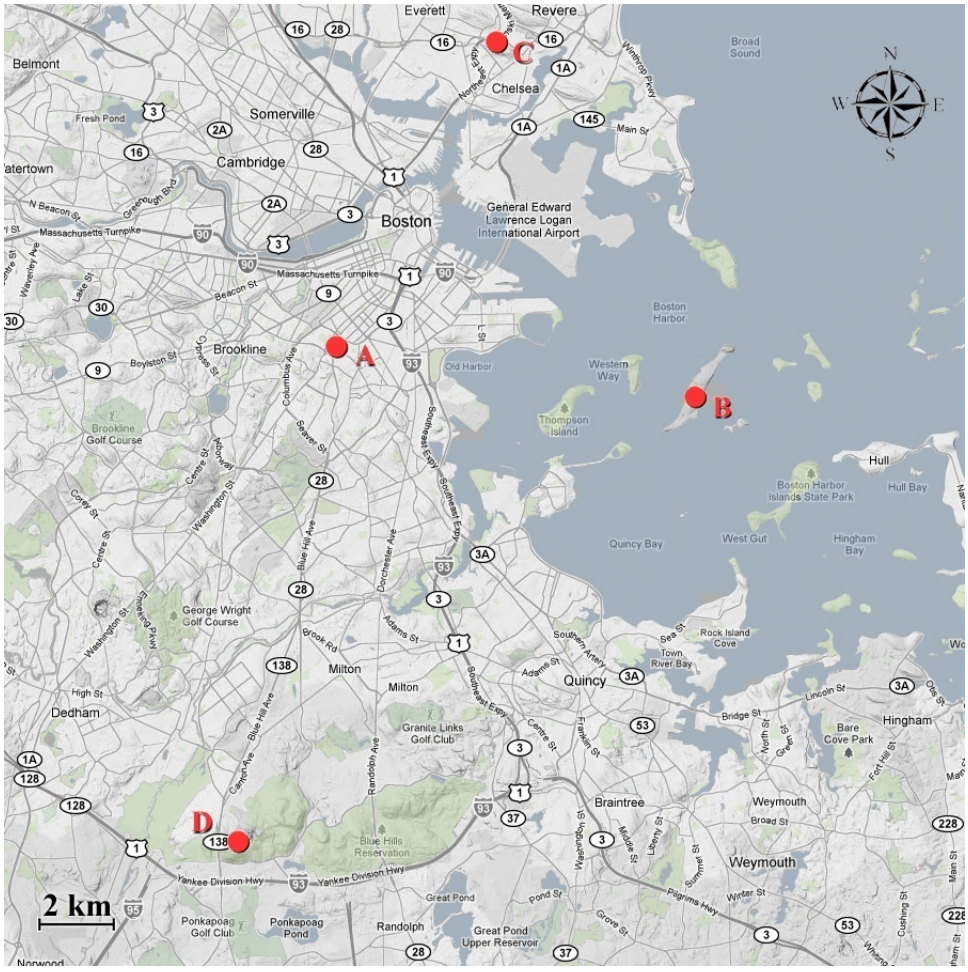


Figure 3-38 Terrain map showing the location of four AQS ozone monitoring sites (red dots) located in or near the city limits in the center of the Boston CSA. Site characteristics range from Site A near downtown at 6 m above sea level to Site D in a forested area on Blue Hill at 192 m above sea level.

There are instances where sites in an urban area may exhibit substantial differences in median concentrations, but still be moderately well correlated in time. For example, Sites A and D in Boston (see terrain map in Figure 3-38) have an 11 ppb difference in median 8-h daily max O_3 concentration (COD = 0.16), but a high correlation (R = 0.90). In this example, Site A is located in the Boston city limits at an elevation of 6 m while Site D is located 13 km to the south in a forested area on Blue Hill, the highest point in Norfolk County (elevation = 192 m). The difference in median O_3 concentration at these two sites can be attributed to differing degrees of NO_X titration between the neighborhood scale site (Site A) and the regional scale site (Site D) and to the influence of local topography.

Comparison of monitoring data within the selected focus cities has demonstrated considerable variability between cities in the behavior of the O_3 concentration fields. Median O_3 concentrations vary more within certain urban areas than others. Likewise, pair-wise monitor statistics (R and COD) are dependent on the urban area under investigation. These conclusions are consistent with those drawn in the 2006 O_3 AQCD where a subset of these focus cities were investigated using similar statistics. As a result, caution should be observed in using data from a sparse network of ambient O_3 monitors to approximate community-scale exposures.

Neighborhood-Scale Variability and the Near-Road Environment

Ozone is a secondary pollutant formed in the atmosphere from precursor emissions and therefore is generally more regionally homogeneous than primary pollutants emitted from stationary or mobile point sources. However, O_3 titration from primary NO emissions does result in substantial localized O_3 gradients. This is evident in the near-road environment where fresh NO emissions from motor vehicles titrate O_3 present in the urban background air, resulting in an O_3 gradient down-wind from the roadway. Ozone titration occurring in street canyons where NO emissions are continuously being generated is more efficient because of inhibited transport away from the source of NO.

Several studies have reported O_3 concentrations that increase with increasing distance from the roadway, both upwind and downwind of the road. Beckerman et al. (2008) measured O_3 profiles in the vicinity of heavily traveled roadways with Annual Average Daily Traffic (AADT) >340,000 vehicles in Toronto, Canada. Ozone was observed to increase with increasing distance from the roadway, both upwind and downwind of the road. This is consistent with scavenging of O_3 in the near-road environment by reaction with NO to form NO_2. Upwind of the road, concentrations were >75% of the maximum observed value at >100 m from the road; downwind, concentrations were approximately 60% of the maximum within 200-400 m of the road. The O_3 concentration adjacent to the road on the upwind side was approximately 40% of the maximum value observed at the

site. Concentrations measured with Ogawa passive samplers over a 1-week period ranged from 7.3-19.4 ppb with the mean at the two sites ranging from 13.0-14.7 ppb. In a study of patrol cars during trooper work shifts, Riediker et al. (2003) made simultaneous 9-h O_3 measurements inside patrol cars, at the roadside, and at a centrally-located ambient monitoring site. The roadside concentrations were approximately 81% of the ambient values (mean of 22.8 ppb versus 28.3 ppb). Wind direction relative to the roadway was not reported.

Johnson (1995) measured O_3, NO, and CO concentrations at upwind and downwind locations near a variety of roadways in Cincinnati, OH. The effects of O_3 scavenging by NO were apparent in the O_3 reduction in the interval between 9 m upwind and 82 m downwind of the road. A similar effect was observed by Rodes and Holland (1981) during an earlier study in which outdoor O_3 concentrations were monitored downwind of a freeway in Los Angeles, CA. In this study, O_3 concentrations measured near the roadway were approximately 20% of the concentrations measured simultaneously at more distant locations judged to be unaffected by the roadway. Minimal separation distances of the samplers from the roadway to eliminate measurable influence were estimated to be approximately 400-500 m for NO, NO_2, and O_3. Similar results have been observed outside the U.S., e.g., in the city of Daegu, Korea, where the yearly roadside concentrations of CO and SO_2 showed a well-defined decreasing trend with distance from the roadway, whereas concentrations of NO_2 and O_3 exhibited the reverse trend (Jo and Park, 2005). During the peak O_3 month of May, O_3 concentrations in a residential neighborhood were approximately 40% higher than concentrations at roadside monitors located 1 m from the edge of multiple-lane freeways.

3.6.2.2 Rural-Focused Variability and Ground-Level Vertical Gradients

AQS O_3 data for monitors located at several rural monitoring sites (e.g., national parks, national forests, state parks, etc.) were used to investigate rural-focused O_3 concentration variability in contrast with the urban-focused variability discussed in Section 3.6.2.1. These rural monitoring sites tend to be less directly affected by dire t anthropogenic pollution sources than urban sites. However, they can be regularly affected by transport of O_3 or O_3 precursors from upwind urban areas, or by local anthropogenic sources within the rural areas such as emissions from motor vehicles, power generation, biomass combustion, or oil and gas operations. As a result, monitoring data from these rural locations are not unaffected by anthropogenic emissions.

Six rural focus areas were selected for their geographic distribution across the U.S. as well as their unique topography and relevance to the ecological assessment in Chapter 9. Table 3-9 lists the rural focus areas and provides some cursory site information along with the number of available AQS monitors reporting year-round and only during the warm-season. Accompanying box plots depicting the distribution of 2007-2009 warm-season 8-h daily max O_3 data from each individual monitor in the six rural focus areas are included in Figure 3-39. This analysis was restricted to AQS monitors meeting the same data completeness criteria outlined in Table 3-3 for a direct comparison with the 20 urban focus areas investigated in Section 3.6.2.1. Given the population-center emphasis of the AQS network, limited monitoring sites (between one and five) were available for each rural focus area. Expanded analyses of O_3 concentrations measured using the more rural-focused CASTNET monitoring network are included in Chapter 9.

Table 3-9 Rural focus areas

Focus Area	Short Name	Year-Round O_3 Monitoring Sites[a]	Warm-Season O_3 Monitoring Sites[b]	Monitor Elevation (m)	Site Descriptions
Adirondack State Park, NY	ADSP	1	0	1,483	One site on the summit of Whiteface Mountain in the Adirondack Mountains
Mount Mitchell State Park, NC	MMSP	0	1	1,982	One site near the summit of Mount Mitchell (highest point in the eastern U.S.) in the Appalachian Mountains
Great Smoky Mountain National Park, NC-TN	SMNP	2	3	564-2,021	Five different locations within Great Smoky Mountain National Park in the Appalachian Mountains
Rocky Mountain National Park, CO	RMNP	1	0	2,743	One site in a valley at the foot of Longs Peak in the Rocky Mountains
San Bernardino National Forest, CA	SBNFc	1	0	1,384	One site in Lake Gregory Regional Park (near Crestline, CA) in the San Bernardino Mountains
Sequoia National Park, CA	SENP	2	0	560-1,890	Two contrasting sites at different elevations within Sequoia NP in the Sierra Nevada Mountains

[a]Number of AQS monitors meeting the year-round data set inclusion criteria; the year-round data set is limited to these monitors.
[b]Number of AQS monitors meeting the warm-season data set inclusion criteria; the warm-season data set includes May-September data from both the warm-season and year-round monitors.
[c]Same AQS site as Site AE in the Los Angeles CSA shown in Figure 3-27.

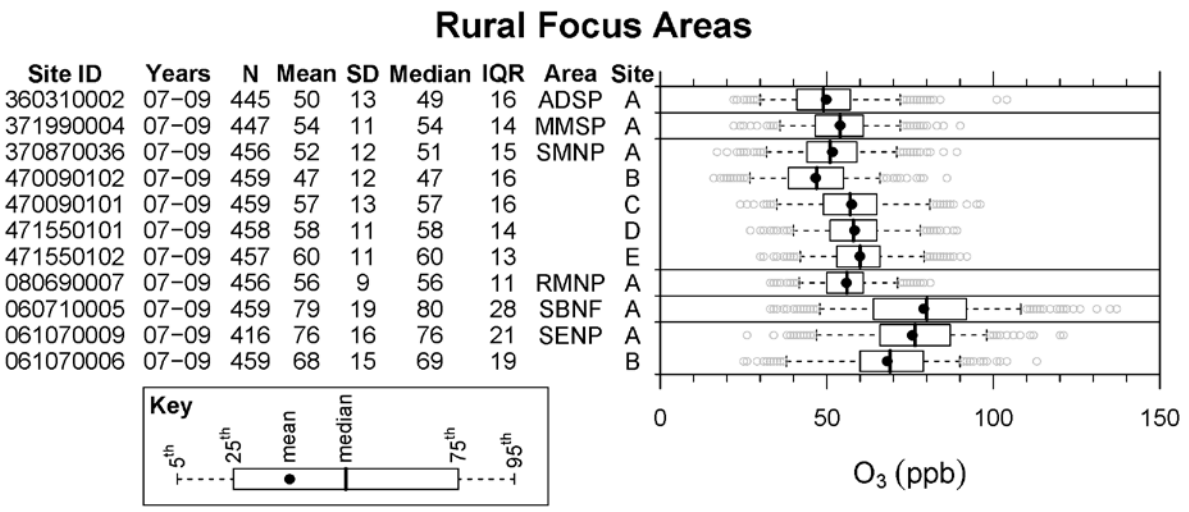
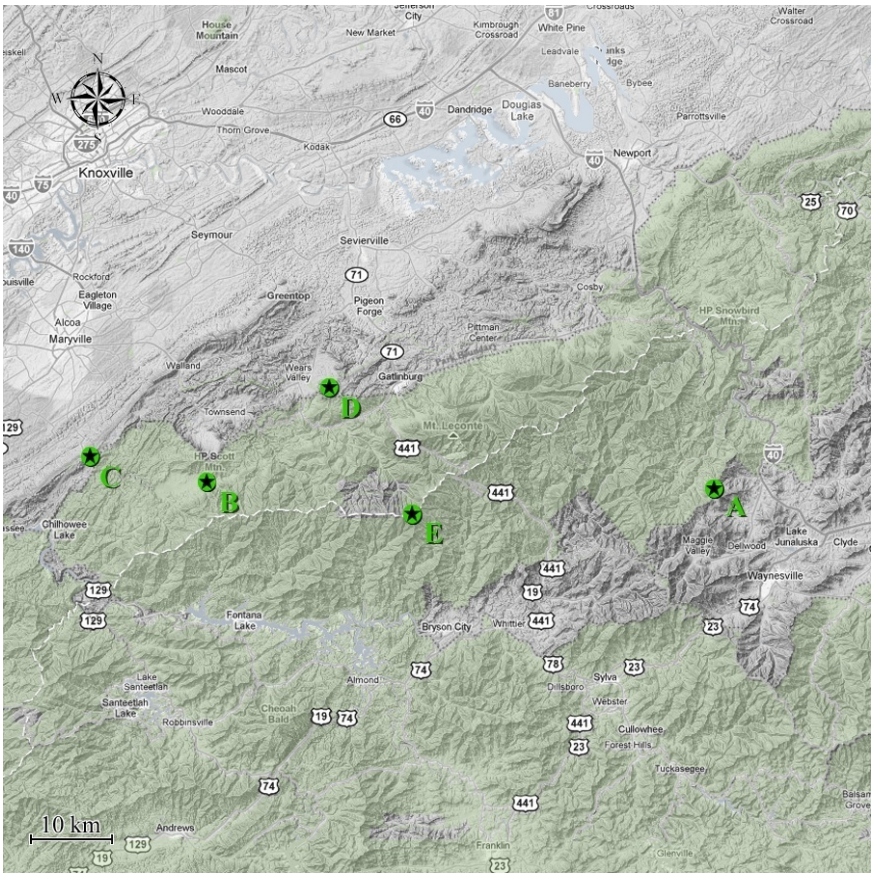


Figure 3-39 Rural focus area site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the rural focus areas. Includes: Adirondack State Park, NY (ADSP); Mount Mitchell State Park, NC (MMSP); Great Smoky Mountain National Park, NC-TN (SMNP); Rocky Mountain National Park, CO (RMNP); San Bernardino National Forest, CA (SBNF); and Sequoia National Park, CA (SENP).

Eastern Rural Focus Areas

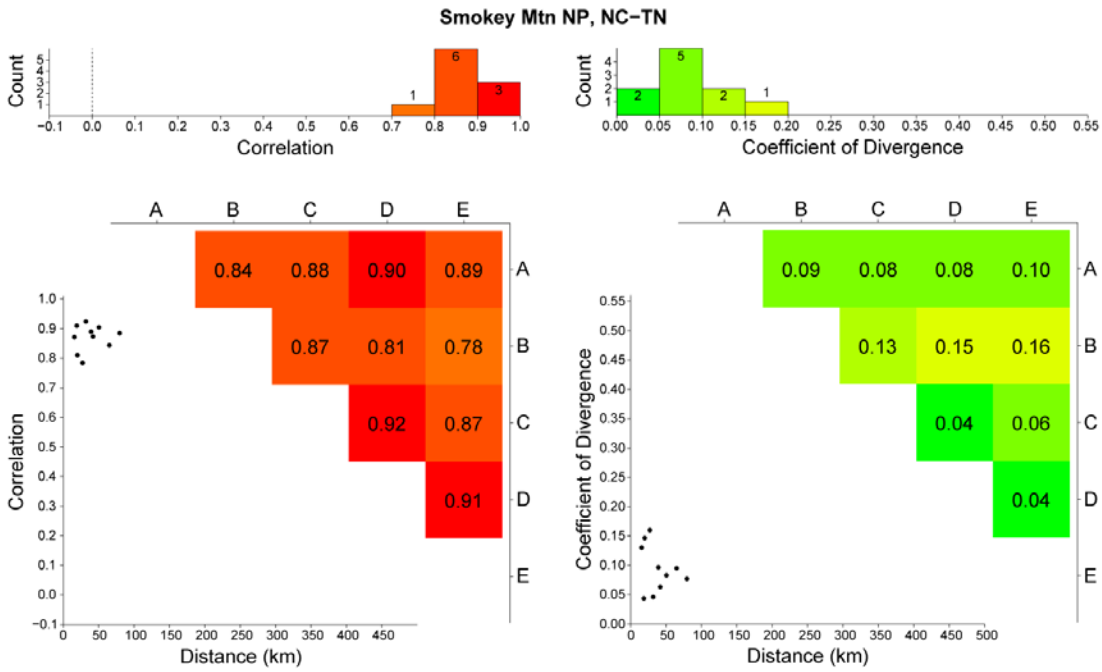
In the East, the distribution in warm-season 8-h daily max O_3 concentrations from the Adirondack State Park (ADSP) site on Whiteface Mountain in Upstate NY (median = 49 ppb) (Figure 3-39) was among the lowest of the rural focus monitors investigated, but was still higher than concentration distributions measured in the Boston CSA (medians ranging from 33 to 46 ppb) (Figure 3-30) located 320 km to the southeast. The ADSP AQS site was included in an analysis for the 2006 O_3 AQCD and had the lowest year-round median hourly O_3 concentration of the rural forested sites investigated (including Yellowstone NP, the Great Smoky Mountains NP, and Shenandoah NP). For the Appalachian Mountain monitors in Mount Mitchell State Park, NC (MMSP) and Great Smoky Mountain National Park, NC-TN (SMNP), there was a fair amount of variability in concentration distribution. Within SMNP, the median warm-season 8-h daily max O_3 concentration ranged from 47 ppb at the lowest elevation site (elevation = 564 m; site ID = 470090102) to 60 ppb at the highest elevation site (elevation = 2,021 m; site ID = 471550102); these sites are shown on the terrain map in Figure 3-40. The warm-season median 8-h daily max O_3 concentration gradient between these two sites located 26.2 km apart in SMNP was 0.9 ppb per 100 m elevation gain.

Data from the five sites within SMNP allowed for further investigation of spatial variability within the park; Figure 3-41 contains histograms, contour plots and scatter plots as a function of distance for the pair-wise correlation and COD (defined in Equation 3-1) for SMNP. The correlations between the five sites ranged from 0.78 to 0.92 and the CODs ranged from 0.04 to 0.16. The plots of correlation and COD as a function of distance between SMNP monitor pairs in Figure 3-41 show a large degree of spatial variability between monitors over relatively short distances. A host of factors may contribute to these variations, including proximity to local O_3 precursor emissions, variations in boundary-layer influences, meteorology and stratospheric intrusion as a function of elevation, and differences in wind patterns and transport behavior due to local topography.



The lowest elevation site (Site B) is 564 m above sea level, while the highest elevation site (Site E) is 2,021 m above sea level.

Figure 3-40 Terrain map showing the location of five AQS ozone monitoring sites (green/black stars) in Great Smoky Mountain National Park, NC-TN (SMNP).



The colors in the histogram bins correspond to the levels of the contour matrix. The histograms includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations and CODs.

Figure 3-41 Pair-wise monitor correlations (left) and coefficients of divergence (COD, right) expressed as a histogram (top), contour matrix (middle) and scatter plot vs. distance between monitors (bottom) for Great Smoky Mountain National Park, NC-TN (SMNP).

Western Rural Focus Areas

The Rocky Mountain National Park (RMNP) site in Colorado at 2,743 m in elevation had a warm-season 8-h daily max O_3 concentration distribution (median = 56 ppb, IQR = 11 ppb) (Figure 3-39) that is comparable to the distributions at sites in the Denver CSA located 75 km southeast at elevations around 1,600 m (medians ranging from 41 to 59 ppb, IQRs ranging from 10 to 16 ppb; see Figure 3-72 in Section 3.10.1). In nearby Boulder County, CO, a 1-year time-series (Sep 2007 - Aug 2008) of ambient surface-level O_3 measurements was collected by Brodin et al. (2010) along an elevation gradient ranging from 1,608 m to 3,528 m. The 7 sites used in this study are shown in Figure 3-42 along with the RMNP site and the 15 Denver CSA sites. In fall, winter, and spring, they observed a clear monotonic increase in O_3 concentration with elevation, with a rate of increase in the mean O_3 concentration of 1.5 ppb per 100 m elevation gain during winter. In summer, the O_3 gradient was similar in magnitude over the seven-site transect (1.3 ppb per 100 m), but much less monotonic; the majority of the vertical gradient occurred between the lowest two sites (4.5 ppb per 100 m) and between the highest two sites

(5.5 ppb per 100 m), with the middle five sites all having approximately equal median O_3 concentrations. Ozone concentrations at the lowest site in Boulder were influenced by NO titration as evidenced by traffic-related diel cycles in O_3 concentrations, but the remaining six sites were located at elevation in more rural/remote settings and illustrate a positive surface-level O_3 elevation gradient similar to that seen in SMNP and typical of areas under less direct influence of boundary layer pollution.

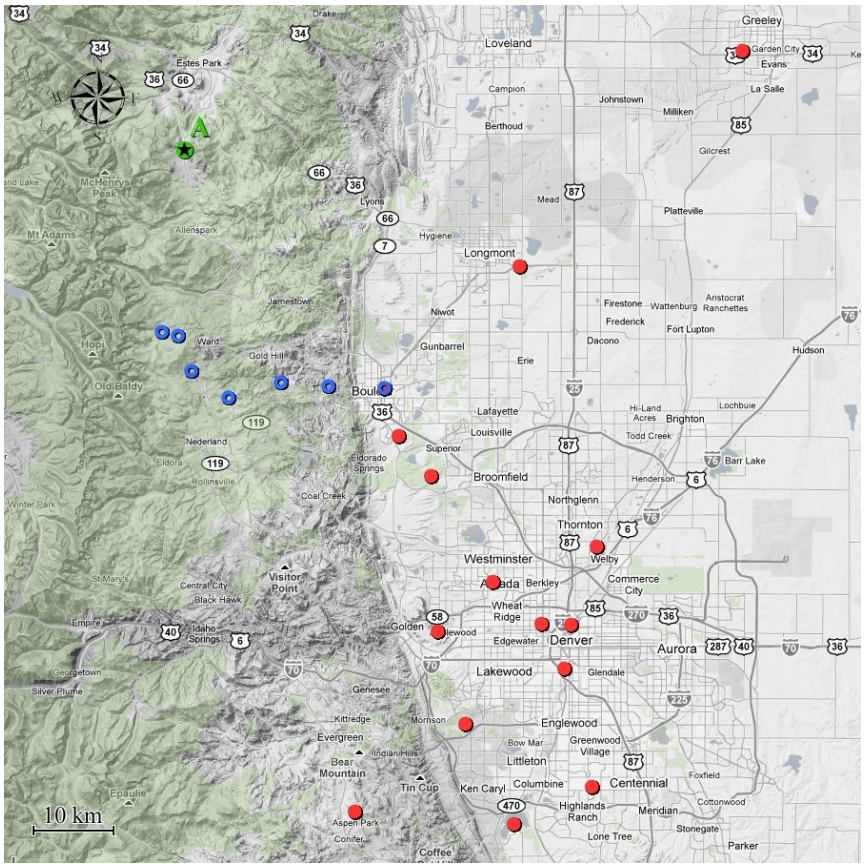


Figure 3-42 Terrain map showing the location of the AQS ozone monitoring site in Rocky Mountain National Park, CO (black/green star) and the Denver CSA (red dots) along with ozone monitoring sites used in the Brodin et al. (2010) study (blue circles). Elevations range from approximately 1,600 m above sea level in Denver and Boulder to 3,528 m above sea level at the highest mountainous site.

The three sites in California–one in San Bernardino National Forest (SBNF) and two in Sequoia National Park (SENP)–had the highest distribution of 8-h daily max O_3 concentrations of the selected rural focus area monitors included in Figure 3-39. The

SBNF site had a warm-season 8-h daily max O_3 concentration mean of 80 ppb and a maximum of 137 ppb measured on July 1, 2007. This site is located in Crestline, CA, 90 km down-wind of Los Angeles in the San Bernardino Mountains. This site was included in the Los Angeles CSA shown in Figure 3-27 (Site AE) and had the highest median 8-h daily max O_3 concentration of any AQS site in the Los Angeles CSA during this time period (Figure 3-30). This site was also included in an analysis performed for the 2006 O_3 AQCD where similarly high O_3 concentrations were observed using 2004 year-round hourly observations.

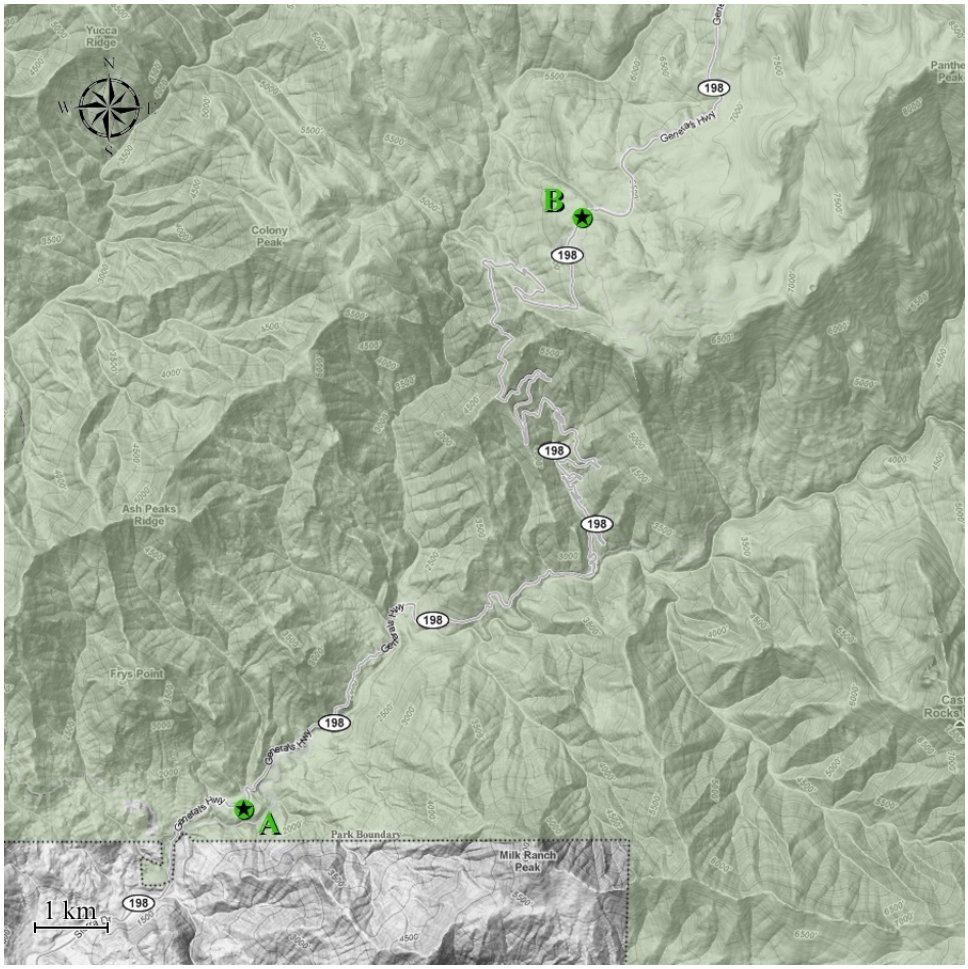


Figure 3-43 Terrain map showing the location of two AQS ozone monitoring sites (black/green stars) in Sequoia National Park, CA. The lower site (site ID = 061070009) is 560 m above sea level and the higher site (site ID = 061070006) is 1,890 m above sea level.

The two sites in SENP are located 9.7 km apart at contrasting elevations as is illustrated in the terrain map in Figure 3-43. The correlation in 8-h daily max O_3 between these two sites was 0.86 and the COD was 0.09, which are within the range in correlations and CODs for SMNP (Figure 3-41). The distribution of 8-h daily max O_3 concentrations at the lower elevation site (elevation = 560 m; site ID = 061070009) is shifted slightly higher with a median of 76 ppb compared to the higher elevation site (elevation = 1,890 m; site ID = 061070006) with a median of 69 ppb. The lower elevation site is located at the entrance to the park and is at a low enough elevation to be influenced by boundary layer pollution coming upwind from Fresno and the San Joaquin Valley. The higher elevation site is in the free troposphere above the planetary boundary layer and is less influenced by such pollution. This gives rise to a negative average surface-level elevation gradient of -0.5 ppb per 100 m elevation gain in SENP, illustrating the location-specific complexities inherent to high-altitude surface-level O_3 concentrations.

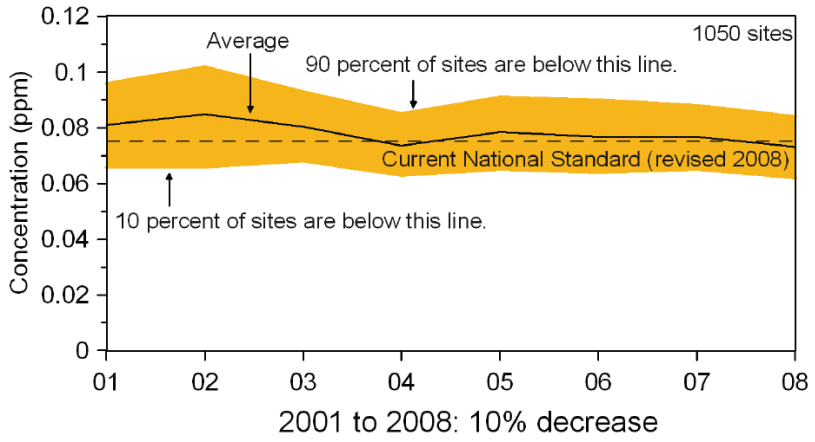
Since O_3 produced from emissions in urban areas is transported to more rural downwind locations, elevated O_3 concentrations can occur at considerable distances from urban centers. In addition, major sources of O_3 precursors such as highways, power plants, biomass combustion, and oil and gas operations are commonly found in rural areas, adding to the O_3 in these areas. Due to lower chemical scavenging in nonurban areas, O_3 tends to persist longer in rural than in urban areas which tends to lead to higher cumulative exposures in rural areas influenced by anthropogenic precursor emissions. The persistently high O_3 concentrations observed at many of these rural sites investigated here indicate that cumulative exposures for humans and vegetation in rural areas can be substantial and often higher than cumulative exposures in urban areas.

3.6.3 Temporal Variability

3.6.3.1 Multiyear Trends

Nationally, O_3 concentrations have declined over the last decade, as shown in Figure 3-44 from the 2010 National Air Quality Status and Trends report (U.S. EPA, 2010e). The majority of this decline occurred before 2004 with national average concentrations remaining relatively flat between 2004 and 2008. The large decreases in 2003 and 2004 coincides with NO_X emissions reductions resulting from implementation of the NO_X State Implementation Plan (SIP) Call rule, which began in 2003 and was fully implemented in 2004. This rule was designed to reduce NO_X emissions from power plants and other large combustion sources in the eastern U.S. The reduction in NO_X and

O_3 during the 2003-2004 timeframe is particularly evident in the eastern U.S. where the NO_X SIP Call was focused (U.S. EPA, 2010e).



Source: U.S. EPA (2010e)

Figure 3-44 National 8-h ozone trends, 2001-2008 (average of the annual fourth highest 8-h daily max concentrations in ppm).

Weather can have a strong influence on O_3 and O_3 trends as well. The number of hot, dry days can significantly alter the number of high-O_3 days in any given year, even if O_3-forming emissions do not change. To better evaluate the progress and effectiveness of emissions reduction programs, EPA uses a statistical model to estimate the influence of atypical weather on O_3 formation (U.S. EPA, 2010e). After adjusting for the influence of weather, the downward trend in national 8 hours O_3 concentrations between 2001 and 2008 increases slightly from an 8% reduction to an 11% reduction. These trends are region-specific, with lower reductions (3%) in California and higher reductions (15%) in eastern states over this same time period (U.S. EPA, 2010e).

Sites that showed the greatest reduction in O_3 over this period were in or near the following metropolitan areas: Anderson, IN; Chambersburg, PA; Chicago, IL; Cleveland, OH; Houston, TX; Michigan City, IN; Milwaukee, WI; New York, NY; Racine, WI; Watertown, NY; and parts of Los Angeles, CA. Sites that showed an increase in O_3 over this time period and had measured concentrations above the 2008 O_3 standard[9] during the 2006-2008 time period were located in or near the following metropolitan areas: Atlanta,

[9] On September 16, 2009, EPA announced it would reconsider the 2008 O3 NAAQS, which, at the time, included primary and secondary standards of 0.075 ppm (8-h daily max).

GA; Baton Rouge, LA; Birmingham, AL; Denver, CO; El Centro, CA; San Diego, CA; Seattle, WA; and parts of Los Angeles, CA.

As noted in the 2006 O_3 AQCD, trends in national parks and rural areas are similar to nearby urban areas, reflecting the regional nature of O_3 pollution. Therefore, 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 regional pollution (see Section 3.4 for a discussion of background O_3 concentrations and international transport). Trends in tropospheric O_3 on a global scale have been monitored around the world using ozonesondes, remote surface monitors, mountain top monitors, and satellites. Positive trends in O_3 measurements in the free troposphere above western North America at altitudes of 3-8 km (above sea level) during April and May of 1995 to 2008 were reported by Cooper et al. (2010) and discussed in Section 3.4.1 as they relate to intercontinental transport. Note, however, that these results relate to O_3 trends above ground level and not to surface O_3. Other observations of global trends in the burden of tropospheric O_3 as they relate to climate change are discussed in Chapter 10, Section 10.2.3.1.

3.6.3.2 Hourly Variations

Ozone concentrations frequently possess a strong degree of diel variability resulting from daily patterns in temperature, sunlight, and precursor emissions. Other 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 also play a role in daily O_3 patterns. The 2006 O_3 AQCD looked at composite urban diel variations from April to October 2000 to 2004 and found 1-h maxima to occur in mid-afternoon and 1-h minima to occur in early morning. On a national basis, however, there was a high degree of spread in these times and caution was raised in extrapolating results from one city to another in determining the time of day for O_3 maxima and minima.

Urban diel variability in O_3 concentrations was investigated for the 20 focus cities listed in Table 3-7 using 1-h avg O_3 data from AQS. The year-round data set described in Table 3-3 was used to compare diel patterns during cold months (October - April) and warm months (May - September) between 2007 and 2009. The warm-season data set, also described in Table 3-3, was used to compare weekday and weekend diel patterns. Figure 3-141 through Figure 3-145 in the supplemental material in Section 3.10.4 show these patterns for each of the 20 cities; examples for Atlanta, Boston and Los Angeles are shown in Figure 3-45.

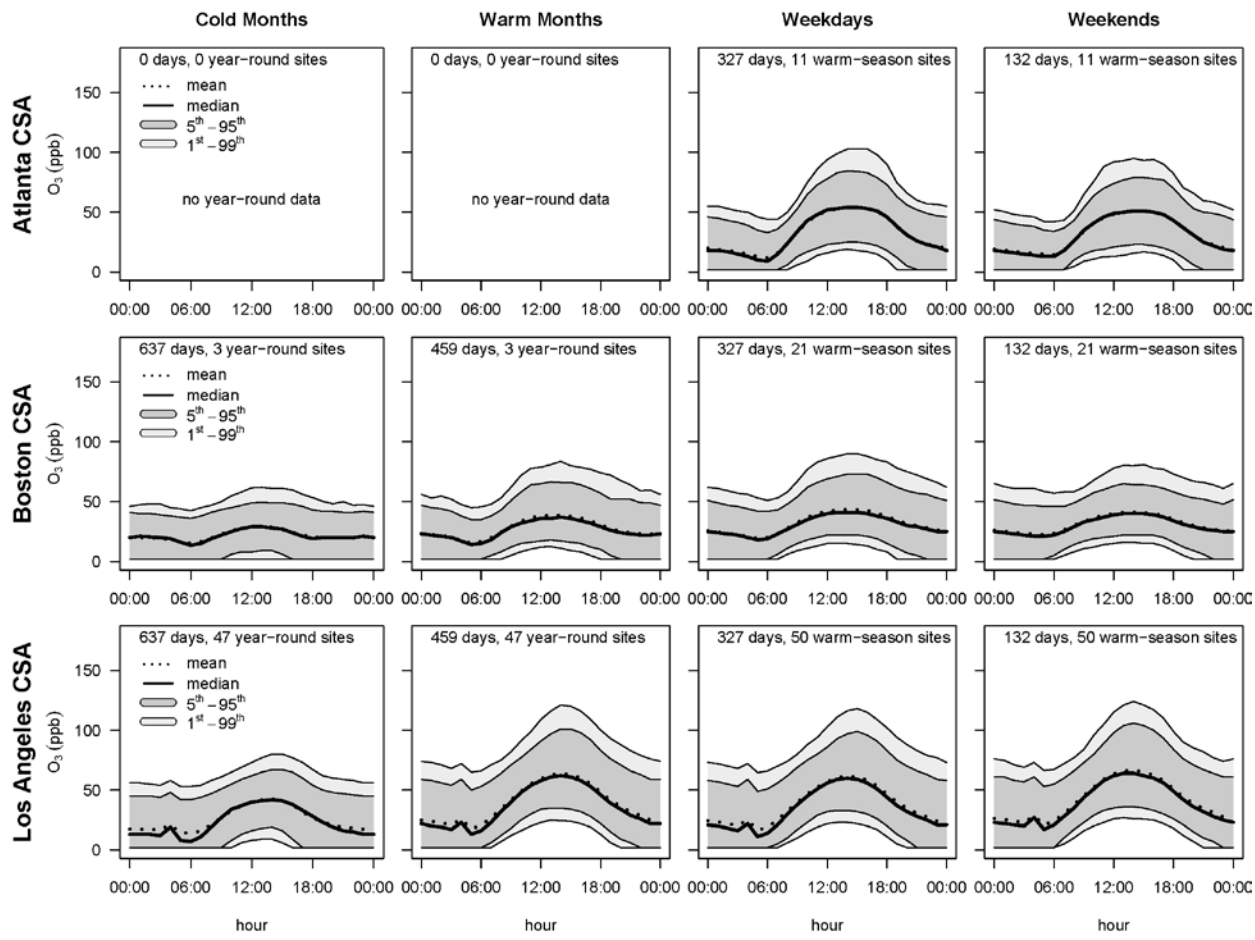


Figure 3-45 Diel patterns in 1-h avg ozone for Atlanta, Boston and Los Angeles between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half). Atlanta had no year-round monitors available for the cold month/warm month comparison.

In general, all the urban areas showed 1-h daily max concentrations occurring typically in the early afternoon. In all cities, these afternoon peaks were more pronounced in the warm months than in the cold months. However, a small peak was still present during the cold months. During warm months, the difference between the median daily extrema varied considerably by city. For example, in Los Angeles, the median 1-h daily min (10 ppb) at ~5:00 a.m. was 50 ppb less than the median 1-h daily max (60 ppb) at ~2:00 p.m. By contrast, in Boston, the median 1-h daily min (13 ppb) occurred at the same time, but was only 25 ppb less than the median 1-h daily max (38 ppb). Cities with large daily swings (>40 ppb) in median 1-h O_3 concentrations included Atlanta, Birmingham, Los Angeles, Phoenix, Pittsburgh, and Salt Lake City (Figure 3-141 through Figure 3-145

in Section 3.10.4). Cities with small daily swings (<25 ppb) in median 1-h O_3 concentrations included Boston, Minneapolis, San Francisco and Seattle (Figure 3-141 through Figure 3-145 in Section 3.10.4). These results are very similar to those found in the 2006 O_3 AQCD where many of these same urban areas were investigated. This supports the conclusions drawn in the AQCD that diel patterns in O_3 have remained stable over the last 20 years, with times of occurrence of the daily maxima varying by no more than an hour from year to year.

Using the warm-season data, there was very little difference in the median diel profiles for weekdays compared with weekends across all urban areas. This result stresses the complexity of O_3 formation and the importance of meteorology, entrainment, biogenic precursor emissions, and transport in addition to anthropogenic precursor emissions. There was, however, a subtle deviation between weekdays and weekends in the lower percentiles (1st and 5th) of the distribution. The lower end of the distribution tended to be lower on weekdays relative to weekends. This is consistent with analyses in the 2006 O_3 AQCD and is a result of lower traffic volumes on weekends relative to weekdays, leading to less NO emissions and O_3 titration on the weekends.

Seasonal and site-to-site variations in diel patterns within a subset of the urban focus areas presented here were investigated in the 2006 O_3 AQCD. In northern cities, there was substantial seasonal variability in the diel patterns with higher extreme values in the O_3 distribution during the warm season than during the cold season. In southern cities, the seasonal differences in extreme O_3 concentrations were much smaller, and some of the highest O_3 concentrations in the Houston CSA were found outside of summer. The general pattern that emerged from investigating site-to-site variability within the urban areas was that peaks in 1-h avg O_3 concentrations are higher and tend to occur later in the day at downwind sites relative to sites located in the urban core. Differences between sites were not only related to the distance between them, but also depend on the presence or absence of nearby O_3 sources or sinks.

Rural diel variability in O_3 concentrations was investigated for the six rural focus areas listed in Table 3-9 using 1-h avg O_3 data from AQS. As with the urban analysis, the year-round data set described in Table 3-3 was used to compare diel patterns during cold months (October - April) and warm months (May - September) between 2007 and 2009. The warm-season data set, also described in Table 3-3, was used to compare weekday and weekend diel patterns. Figure 3-46 shows the diel patterns for each of the rural areas investigated.

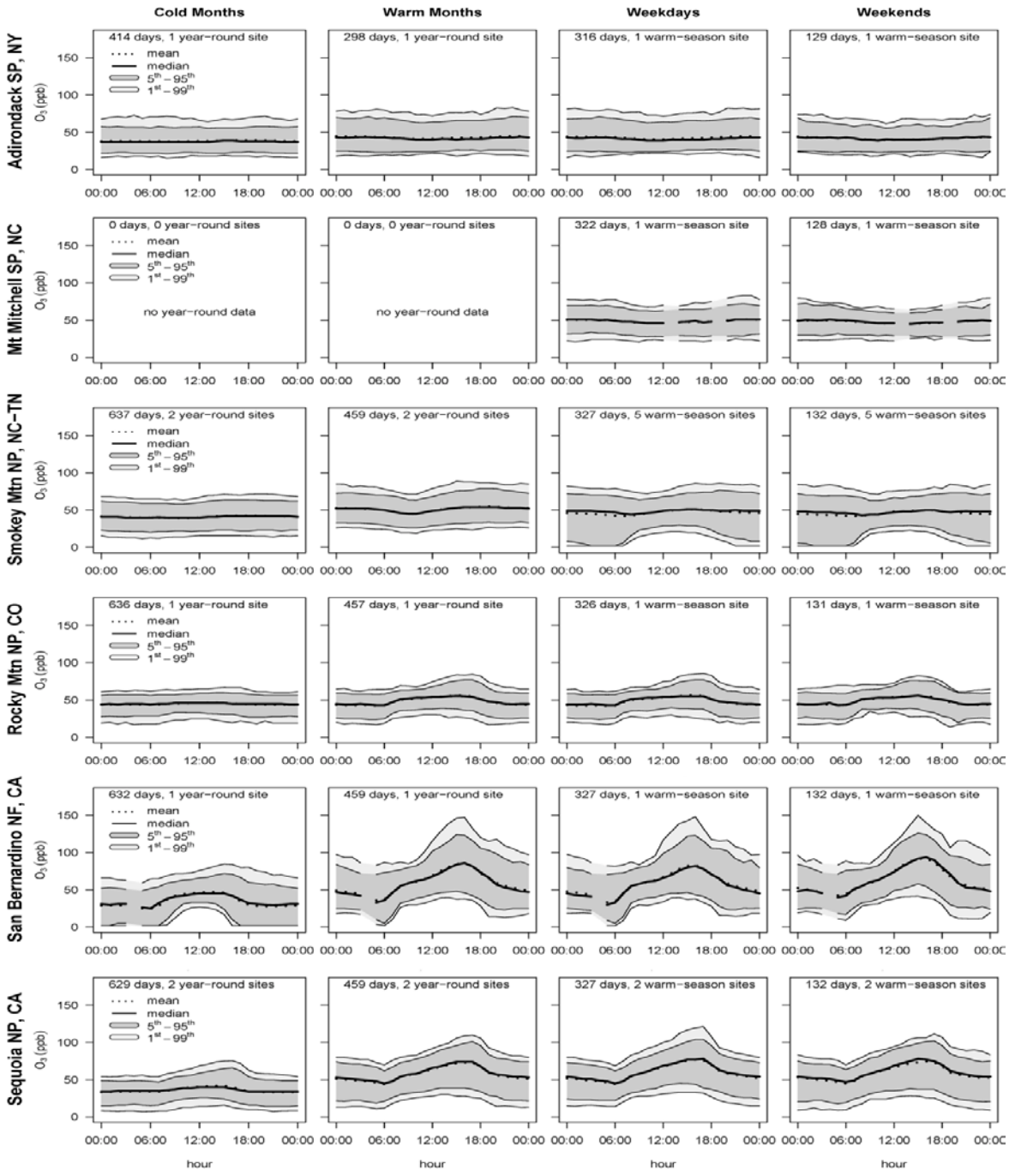


Figure 3-46 Diel patterns in 1-h avg ozone for six rural focus areas between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half). Mt. Mitchell SP, NC had no year-round monitors available for the cold month/warm month comparison.

There was considerable variability in the diel patterns observed in the six rural focus areas. The eastern sites in ADSP, MMSP, and SMNP all exhibited a generally flat profile with very little hourly variability in the median concentration and the upper percentiles. In SMNP, there was some diel variability in the lower percentiles, with higher values during the daylight hours in the warm season data. This behavior was not present in the data coming from the two year-round monitors located at lower elevation sites (Sites C and Site D; see map in Figure 3-40), however, possibly resulting from differing impacts from local sources within SMNP. For the western rural areas, there was a clear diel pattern to the hourly O_3 data with a peak in concentration in the afternoon similar to those seen in the urban areas in Figure 3-45 and Figure 3-141 through Figure 3-145 in Section 3.10.4. This was especially obvious at the SBNF site which sits 90 km east of Los Angeles in the San Bernardino Mountains at an elevation of 1,384 m. This site was located here to monitor O_3 transported downwind from major urban areas in the South Coast Air Basin. It had the highest 2007-2009 median 8-h daily max O_3 concentration of any AQS site in the Los Angeles CSA (see Figure 3-30), and is clearly impacted by the upwind urban plume which has sufficient time and sunlight to form O_3 from precursor emissions and concentrate the O_3 in the shallow boundary layer present at this elevation.

As with the urban analysis, there was very little difference observed in the weekday and weekend diel profiles using the warm-season data, even down at the lower percentiles in the distribution. This is consistent with the regional nature of tropospheric O_3. Using the year-round data, there was an upward shift in the distribution going from the cold months to the warm months, and in some instances the general shape of the distribution changed considerably as was seen in several urban sites.

3.6.4 Associations with Co-pollutants

Correlations between O_3 and other criteria pollutants are discussed in this section. Since O_3 is a secondary pollutant formed in the atmosphere from precursor emissions, it is not expected to be highly correlated with primary pollutants such as CO and NO_X. Furthermore, O_3 formation is strongly influenced by meteorology, entrainment, and transport of both O_3 and O_3 precursors, resulting in a broad range in correlations with other pollutants which can vary substantially with season.

To investigate correlations with co-pollutants, 8-h daily max O_3 from the year-round and warm-season data sets (Table 3-4 and Table 3-5) were compared with co-located 24-h avg CO, SO_2, NO_2, $PM_{2.5}$ and PM_{10} obtained from AQS for 2007-2009. Figure 3-47 and Figure 3-48 contain copollutant box plots of the correlation between co-located monitors for the year-round data set and the warm-season data set, respectively.

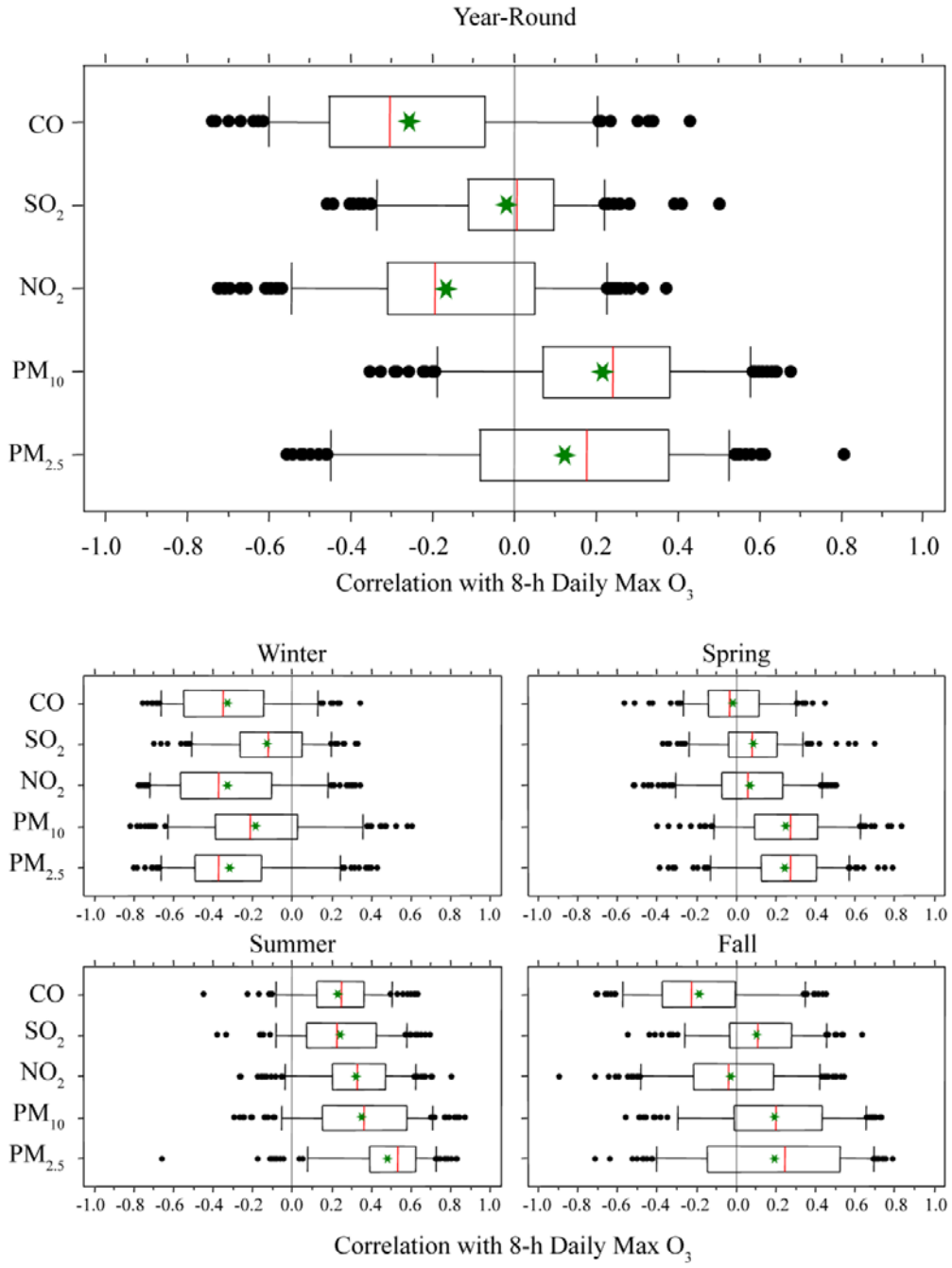


Figure 3-47 Distribution of Pearson correlation coefficients for comparison of 8-h daily max ozone from the year-round data set with co-located 24-h avg CO, SO_2, NO_2, PM_{10} and $PM_{2.5}$ from AQS, 2007-2009 (top figure) with seasonal stratification (bottom four figures). Shown are the median (red line), mean (green star), inner-quartile range (box), 5th and 95th percentiles (whiskers) and extremes (black circles).

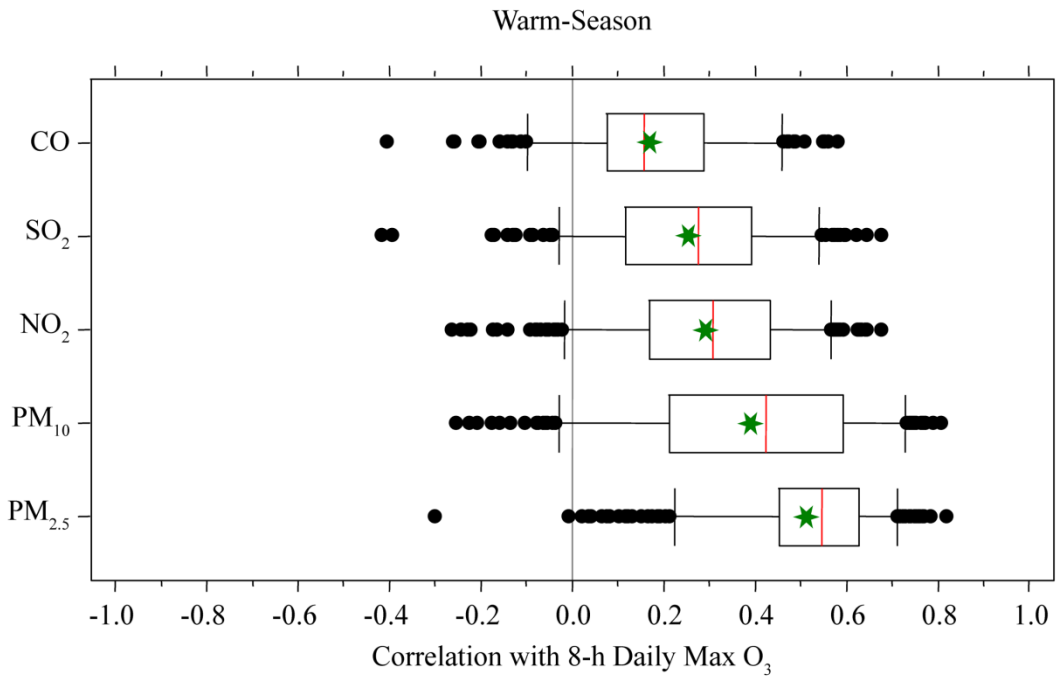


Figure 3-48 Distribution of Pearson correlation coefficients for comparison of 8-h daily max ozone from the warm-season (May-Sept) data set with co-located 24-h avg CO, SO_2, NO_2, PM_{10} and $PM_{2.5}$ from AQS, 2007-2009. Shown are the median (red line), mean (green star), inner-quartile range (box), 5th and 95th percentiles (whiskers), and extremes (black circles).

The year-round 8-h daily max O_3 data (Figure 3-47) had a very wide range in correlations with all the 24-h avg co-pollutants. A clearer pattern emerged when the data were stratified by season (bottom four plots in Figure 3-47) with mostly negative correlations in the winter and mostly positive correlations in the summer for all co-pollutants. In summer, the IQR in correlations is positive for all co-pollutants. However, the median seasonal correlations are still modest at best with the highest positive correlation at 0.52 for $PM_{2.5}$ in the summer and the highest negative correlation at -0.38 for $PM_{2.5}$ in the winter. Spring and fall lie in between with spring having a slightly narrower distribution than fall for all co-pollutants. The warm-season 8-h daily max O_3 data (Figure 3-48) shows a very similar distribution to the summer stratification of the year-round data due to their overlap in time periods (May-Sept and Jun-Aug, respectively).

The seasonal fluctuations in correlations present in Figure 3-47 result in part from the mixture of primary and secondary sources for the co-pollutants. For example, O_3 is a secondary pollutant whereas $PM_{2.5}$ has both primary and secondary origins and these two pollutants show the largest summertime/wintertime swing in correlation distributions.

This situation arises because the secondary component to $PM_{2.5}$ is larger during the summer and is formed in conditions conducive to secondary O_3 formation. This results in positive correlations between O_3 and $PM_{2.5}$ during the summer. During the winter, photochemical production of O_3 is much smaller than during summer and O_3 comes mainly from aloft, i.e., the free troposphere (see Section 3.4 for further details). In addition, concentrations of $PM_{2.5}$ are much lower aloft. On relatively clean days, this can lead to high concentrations of O_3 and lower concentrations of primary pollutants such as $PM_{2.5}$ or NO. On relatively dirty days with elevated NO and $PM_{2.5}$, the intruding O_3 is readily titrated by NO in the boundary layer. These processes result in negative correlations between O_3 and $PM_{2.5}$ during the winter.

3.7 Chapter Summary

This section contains a summary of the major topics included in this chapter on the atmospheric chemistry and ambient concentrations of tropospheric O_3 and other related photochemical oxidants. This chapter has built upon information previously reported in the 2006 O_3 AQCD and includes updated material on: (1) physical and chemical processes of O_3 formation and removal; (2) atmospheric modeling; (3) policy relevant background concentrations; (4) monitoring techniques and networks; and (5) ambient concentrations.

3.7.1 Physical and Chemical Processes

Ozone in the troposphere is a secondary pollutant; it is formed by photochemical reactions of precursor gases and is not directly emitted from specific sources. Ozone and other oxidants, such as peroxyacetyl nitrate and hydrogen peroxide form in polluted areas by atmospheric reactions involving two main classes of precursor pollutants: VOCs and NO_X. Carbon monoxide is also important for O_3 formation in polluted areas and in the remote troposphere. The formation of O_3, other oxidants, and oxidation products from these precursors is a complex, nonlinear function of many factors including: (1) the intensity and spectral distribution of sunlight; (2) atmospheric mixing; (3) concentrations of precursors in the ambient air and the rates of chemical reactions of these precursors; and (4) processing on cloud and aerosol particles.

Ozone is present not only in polluted urban atmospheres but throughout the troposphere, even in remote areas of the globe. The same basic processes involving sunlight-driven reactions of NO_X, VOCs and CO contribute to O_3 formation throughout the troposphere. These processes also lead to the formation of other photochemical products, such as

PAN, nitric acid, and sulfuric acid, and to other compounds, such as formaldehyde and other carbonyl compounds. In urban areas, NO_X, VOCs and CO are all important for O_3 formation. In nonurban vegetated areas, biogenic VOCs emitted from vegetation tend to be the most important precursor to O_3 formation. In the remote troposphere, methane – structurally the simplest VOC – and CO are the main carbon-containing precursors to O_3 formation. In the troposphere, O_3 is subsequently lost through a number of gas phase reactions as well as deposition to surfaces.

Convective processes and small scale turbulence transport O_3 and other pollutants both upward and downward throughout the planetary boundary layer and the free troposphere. In many areas of the U.S., O_3 and its precursors can be transported over long distances, aided by vertical mixing. The transport of pollutants downwind of major urban centers is characterized by the development of urban plumes. Meteorological conditions, small-scale circulation patterns, localized chemistry, and mountain barriers can influence mixing on a smaller scale, resulting in frequent heterogeneous O_3 concentrations across an individual urban area.

Emissions of O_3 precursor compounds (NO_X, VOCs, and CO) can be divided into anthropogenic and natural source categories. Natural sources can be further divided into biogenic from vegetation, microbes, and animals, and abiotic from biomass burning, lightning, and geogenic sources. However, the distinction between natural sources and anthropogenic sources is often difficult to make in practice, as human activities affect directly or indirectly emissions from what would have been considered natural sources during the preindustrial era. The magnitudes of O_3 precursor sources are strongly location- and time-dependent and so average emission estimates should not be used to apportion sources of exposure.

3.7.2 Atmospheric Modeling

CTMs have been widely used to compute the interactions among atmospheric pollutants and their transformation products, and the transport and deposition of pollutants. They have also been widely used to improve our basic understanding of atmospheric chemical processes and to develop control strategies. The domains of CTMs extend from a few hundred kilometers on a side to the entire globe.

Most major regional (i.e., sub-continental) scale air-related modeling efforts at EPA rely on the CMAQ modeling system. CMAQ's horizontal domain typically extends over North America with efforts underway to extend it over the entire Northern Hemisphere. The upper boundary for CMAQ is typically set at 100 hPa, which is located on average at about 16-km altitude. CMAQ is most often driven by the MM5 mesoscale meteorological

model, though it may be driven by other meteorological models including the WRF model and the RAMS. Other major air quality systems used for regional scale applications include CAMx and WRF/Chem.

Fine scale resolution is necessary to resolve features which can affect pollutant concentrations such as urban heat island circulation; sea breezes; mountain and valley breezes; and the nocturnal low-level jet. Horizontal domains are typically modeled by nesting a finer grid model within a larger domain model of coarser resolution. Caution must be exercised in using nested models because certain parameterizations like those for convection might be valid on a relatively coarse grid scale but may not be valid on finer scales and because incompatibilities can occur at the model boundaries. The use of finer resolution in CTMs will require advanced parameterizations of meteorological processes such as boundary layer fluxes, deep convection, and clouds, and necessitate finer-scale inventories of land use, source locations, and emission inventories.

Because of the large number of chemical species and reactions that are involved in the oxidation of realistic mixtures of anthropogenic and biogenic hydrocarbons, condensed mechanisms must be used to simplify atmospheric models. These mechanisms can be tested by comparison with smog chamber data. However, the existing chemical mechanisms often neglect many important processes such as the formation and subsequent reactions of long-lived carbonyl compounds, the incorporation of the most recent information about intermediate compounds, and heterogeneous reactions involving cloud droplets and aerosol particles. As a result, models such as CMAQ have had difficulties with capturing the regional nature of O_3 episodes, in part because of uncertainty in the chemical pathways converting NO_X to HNO_3 and recycling of NO_X.

The largest errors in photochemical modeling are still thought to arise from the meteorological and emissions inputs to the model. Algorithms must be used for simulating meteorological processes that occur on spatial scales smaller than the model's grid spacing and for calculating the dependence of emissions on meteorology and time. Significant errors in emissions can occur if inappropriate assumptions are used in these parameterizations.

The performance of CTMs must be evaluated by comparison with field data as part of a cycle of model evaluations and subsequent improvements. Discrepancies between model predictions and observations can be used to point out gaps in current understanding of atmospheric chemistry and to spur improvements in parameterizations of atmospheric chemical and physical processes.

3.7.3 Background Concentrations

Because the mean tropospheric lifetime of O_3 is 30-35 days, O_3 can be transported from continent to continent and around the globe in the Northern Hemisphere. The degree of influence from intercontinental transport varies greatly by location and time. High elevation sites are most susceptible to the intercontinental transport of pollution, particularly during spring. However, the chemistry involving O_3 formation is nonlinear, thereby complicating the task of isolating the influence of intercontinental transport of O_3 and O_3 precursors on U.S. air quality. Careful consideration of fine-scale spatial and temporal variation is necessary to appropriately characterize the impact of intercontinental transport on tropospheric O_3.

Since North American background (i.e., O_3 concentrations that would exist in the absence of anthropogenic emissions from the U.S. Canada and Mexico) is a construct that cannot be directly measured, the range of background O_3 concentrations are estimated using chemistry transport models (CTMs). The 2006 O_3 AQCD (U.S. EPA, 2006b) provided regional estimates of North American background O_3 concentrations based on a coarse resolution (2°×2.5°, or ~200 km×200 km) GEOS-Chem model. For the current assessment, updated results from a finer resolution (0.5°×0.667°, or ~50 km×50 km) GEOS-Chem model were used. In general, the GEOS-Chem predictions tend to show smaller disagreement with observations at the high-altitude sites than at the low-altitude sites. Overall agreement between model results for the base case and measurements is within a few ppb for spring-summer means in the Northeast and the Southeast, except in and around Florida where the base case over predicts O_3 by 10 ppb at one site, at least. In the Upper Midwest, the model predictions are within 5 ppb of measurements, the same is true for sites in the intermountain West and at lower elevations sites in the West including California. However, the model under predicts O_3 by 10 ppb at the Yosemite site. These results suggest that the model is capable of calculating March to August mean O_3 to within ~ 5 ppb at most (26 out of 28) sites chosen. Currently, there are no simulations of North American background concentrations available in the literature apart from those using GEOS-Chem alone. However, as noted in , the 2006 O_3 AQCD, an ensemble approach as is done in many other applications of atmospheric models is to be preferred.

The GEOS-Chem calculations presented here represent the latest results documented in the literature. However, all models undergo continuous updating of inputs, parameterizations of physical and chemical processes, and inputs and improvements in model resolution. Inputs that might be considered most relevant include emissions inventories, chemical reactions and meteorological fields. This leads to uncertainty in model predictions in part because there is typically a lag between updated information for these above inputs. Examples might include updated emissions for year specific shipping,

wildfires and updates to the 2005 NEI; updates to the chemistry of isoprene and multi-phase processes, including those affecting the abundance of halogens; and updates to species such as methane. To the extent that results from an updated model become available, they will be presented and used to help inform NAAQS setting.

3.7.4 Monitoring

The FRM for O_3 measurement is the CLM and is based on the detection of chemiluminescence resulting from the reaction of O_3 with ethylene gas. Almost all of the SLAMS that reported data to AQS from 2005 to 2009 used UV absorption photometer FEMs and greater than 96% of O_3 monitors met precision and bias goals during this period.

State and local monitoring agencies operate O_3 monitors at various locations depending on the area size and typical peak concentrations (expressed in percentages below, or near the O_3 NAAQS). SLAMS make up the ambient air quality monitoring sites that are primarily needed for NAAQS comparisons and include PAMS, NCore, and all other State or locally-operated stations except for the monitors designated as SPMs.

In 2010, there were 1250 SLAMS O_3 monitors reporting values to the EPA AQS database. Since O_3 levels decrease significantly in the colder parts of the year in many areas, O_3 is required to be monitored at SLAMS monitoring sites only during the "ozone season" which varies by state. PAMS provides more comprehensive data on O_3 in areas classified as serious, severe, or extreme nonattainment for O_3. There were a total of 119 PAMS reporting values to the EPA AQS database in 2009. NCore is a new multi-pollutant monitoring network currently being implemented to meet multiple monitoring objectives. Each state is required to operate at least one NCore site and the network will consist of about 60 urban and 20 rural sites nationwide.

CASTNET is a regional monitoring network established to assess trends in acidic deposition and also provides concentration measurements of O_3. CASTNET O_3 monitors operate year round and are primarily located in rural areas. At the beginning of 2010, there were 80 CASTNET sites located in, or near, rural areas. The NPS also operates a POMS network. The POMS couples the small, low-power O_3 monitor with a data logger, meteorological measurements, and solar power in a self contained system for monitoring in remote locations. Twenty NPS POMS reported O_3 data to AQS in 2010. A map of the current and proposed rural NCore sites, along with the CASTNET, and the NPS POMS sites was shown in Figure 3-18.

Satellite observations for O_3 are growing as a resource for many purposes, including model evaluation, assessing emissions reductions, pollutant transport, and air quality management. Satellite remote sensing instruments do not directly measure the composition of the atmosphere. Satellite retrievals are conducted using the solar backscatter or thermal infrared emission spectra and a variety of algorithms. Most satellite measurement systems have been developed for stratospheric measurement of the total O_3 column. Mathematical techniques have been developed and must be applied to derive information from these systems about tropospheric O_3.

3.7.5 Ambient Concentrations

Ozone is the only photochemical oxidant other than NO_2 that is routinely monitored and for which a comprehensive database exists. Other photochemical oxidants are typically only measured during special field studies. Therefore, the concentration analyses contained in this chapter have been limited to widely available O_3 data obtained directly from AQS for the period from 2007 to 2009.

Most continuous O_3 monitors report hourly average concentrations to AQS. This data can be used as reported (1-h avg), or reported as a daily metric such as: (1) the average of the hourly observations over a 24-h period (24-h avg); (2) the maximum 8-h running average of the hourly observations occurring in a 24-h period (8-h daily max), or (3) the maximum hourly observation occurring in a 24-h period (1-h daily max). The median 24-h avg, 8-h daily max, and 1-h daily max O_3 concentrations across all U.S. sites reporting data to AQS between 2007 and 2009 were 29, 40, and 44 ppb, respectively. Representing the upper end of the distribution, the 99th percentiles of these same metrics across all sites were 60, 80, and 94 ppb, respectively. Correlations between these different averaging time metrics generated from the same hourly observations in the 3-year nation-wide data set were shown in Figure 3-19. The 8-h daily max and 1-h daily max metrics were highly correlated (median R = 0.97, IQR = 0.96-0.98) while comparisons with the 24-h avg metric were lower (e.g., median R = 0.83, IQR = 0.78-0.88 for comparison between the 24-h avg and the 1-h daily max). The ratio and correlation between these metrics, however, can be very site-specific.

To investigate urban-scale O_3 variability, 20 focus cities were selected for closer analysis; these cities were selected based on their importance in O_3 epidemiologic studies and on their geographic distribution across the U.S. Several of these cities had relatively little spatial variability in 8-h daily max O_3 concentrations (e.g., inter-monitor correlations ranging from 0.61 to 0.96 in Atlanta) while other cities exhibited considerably more variability in O_3 concentrations (e.g., inter-monitor correlations

ranging from -0.06 to 0.97 for Los Angeles). The negative and near-zero correlations in Los Angeles were between monitors with a relatively large separation distance (>150 km), but even some of the closer monitor pairs were not very highly correlated. Similar to the correlation, the coefficient of divergence was found to be highly dependent on the urban area under investigation. As a result, caution should be observed in using data from a sparse network of ambient O_3 monitors to approximate community-scale exposures.

To investigate rural-focused O_3 variability using AQS data, all monitors located within six rural monitoring areas were examined. These rural monitoring sites are impacted by transport of O_3 or O_3 precursors from upwind urban areas, and by local anthropogenic emissions within the rural areas such as emissions from motor vehicles, power generation, biomass combustion, or oil and gas operations. As a result, monitoring data from these rural locations are not unaffected by anthropogenic emissions. The rural area investigated with the largest number of available AQS monitors was Great Smoky Mountain National Park in NC and TN where the median warm-season 8-h daily max O_3 concentration ranged from 47 ppb at the lowest elevation site (elevation = 564 m; site ID = 470090102) to 60 ppb at the highest elevation site (elevation = 2,021 m; site ID = 471550102), with correlations between the 5 sites ranging from 0.78 to 0.92 and CODs ranging from 0.04 to 0.16. A host of factors may contribute to variations observed at these rural sites, including proximity to local O_3 precursor emissions, variations in boundary-layer influences, meteorology and stratospheric intrusion as a function of elevation, and differences in wind patterns and transport behavior due to local topography. Expanded analyses of O_3 concentrations measured using the more rural-focused CASTNET monitoring network are included in Chapter 9.

Since O_3 produced from emissions in urban areas is transported to more rural downwind locations, elevated O_3 concentrations can occur at considerable distances from urban centers. In addition, major sources of O_3 precursors such as highways, power plants, biomass combustion, and oil and gas operations are commonly found in rural areas, adding to the O_3 in these areas. Due to lower chemical scavenging in nonurban areas, O_3 tends to persist longer in rural than in urban areas which tends to lead to higher cumulative exposures in rural areas influenced by anthropogenic precursor emissions. The persistently high O_3 concentrations observed at many of these rural sites investigated here indicate that cumulative exposures for humans and vegetation in rural areas can be substantial and often higher than cumulative exposures in urban areas.

According to the 2010 National Air Quality Status and Trends report (U.S. EPA, 2010e), O_3 concentrations have declined steadily over the last decade; with the majority of this decline occurring before 2004. A noticeable decrease in O_3 between 2003 and 2004 coincides with NO_X emissions reductions resulting from implementation of the NO_X SIP

Call rule, which began in 2003 and was fully implemented in 2004. This rule was designed to reduce NO_X emissions from power plants and other large combustion sources in the eastern U.S. As noted in the 2006 O_3 AQCD, trends in national parks and rural areas are similar to nearby urban areas, reflecting the regional nature of O_3 pollution. However, 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 regional pollution. Global scale observations have, indeed, indicated a general rise in O_3 by a factor of 2 or more as discussed in Chapter 10, Section 10.2.3.1.

Urban O_3 concentrations show a strong degree of diel variability resulting from daily patterns in temperature, sunlight, and precursor emissions. Other 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 also play a role in daily O_3 patterns. Urban diel variations investigated in this assessment show no substantial change in patterns since the 2006 O_3 AQCD. The 1-h max concentrations tend to occur in mid-afternoon and 1-h min concentrations tend to occur in early morning, with more pronounced peaks in the warm months relative to the cold months. There is city-to-city variability in these times, however, and caution is raised in extrapolating results from one city to another in determining the time of day for O_3 maxima and minima.

Rural O_3 concentrations show a varying degree of diel variability depending on their location relative to larger urban areas. Three rural areas investigated in the east showed relatively little diel variability, reflecting the regional nature of O_3 in the east. In contrast, three rural areas investigated in the west did display diel variability resulting from their proximity to fresh urban emissions. These six areas investigated were selected as illustrative examples and do not represent all rural areas in the U.S.

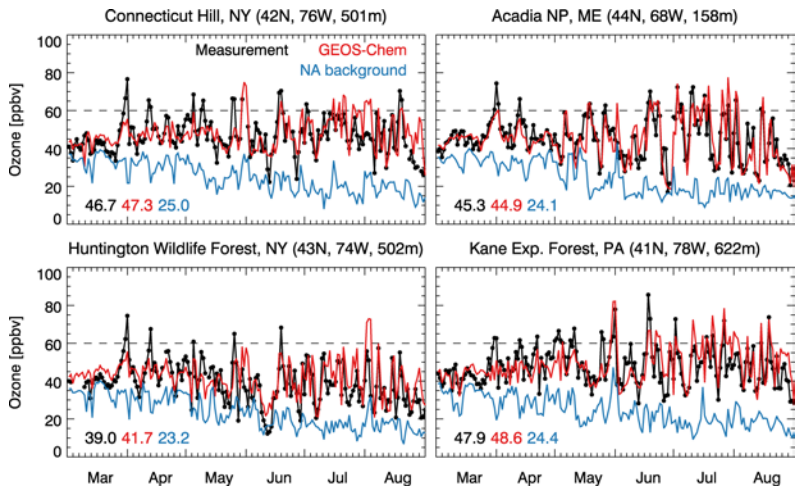
Since O_3 is a secondary pollutant formed in the atmosphere from precursor emissions, it is not expected to be highly correlated with primary pollutants such as CO and NO_X. Furthermore, O_3 formation is strongly influenced by meteorology, entrainment, and transport of both O_3 and O_3 precursors, resulting in a broad range in correlations with other pollutants which can vary substantially with season. In the copollutant analyses shown in Figure 3-45, the year-round 8-h daily max O_3 data exhibited a very wide range in correlations with all the 24-h avg co-pollutants. A clearer pattern emerged when the data are stratified by season with mostly negative correlations in the winter and mostly positive correlations in the summer for all co-pollutants. The median seasonal correlations are modest at best with the highest positive correlation at 0.52 for $PM_{2.5}$ in the summer and the highest negative correlation at -0.38 for $PM_{2.5}$ in the winter.

Therefore, statistical analyses that may be sensitive to correlations between co-pollutants need to take seasonality into consideration, particularly when O_3 is being investigated.

3.8 Supplemental Ozone Model Predictions from the Literature

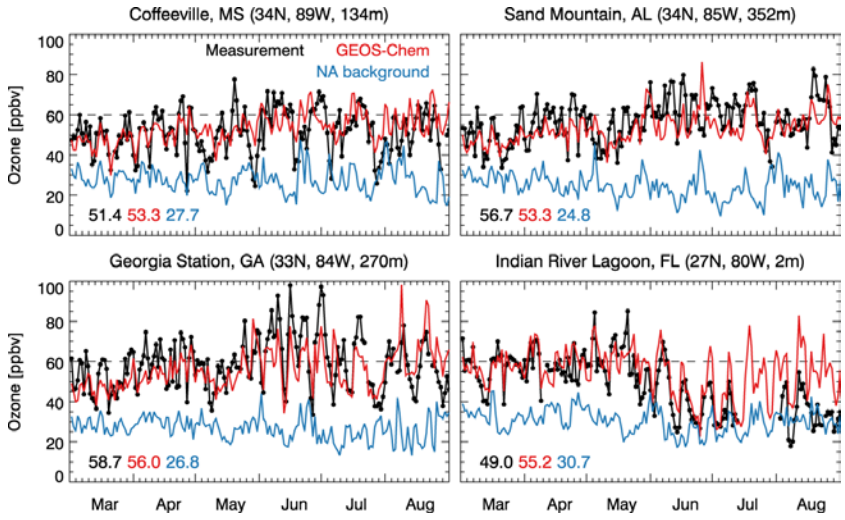
3.8.1 Time Series of GEOS-Chem Model Predictions and Observations at Selected CASTNET Sites

This section contains comparisons between GEOS-Chem predictions of 8-h daily max O_3 concentrations with observations for 2006 from Zhang et al. (In Press). Further details on these predictions can be found in Section 3.4.3. Figures 3-49 through 3-55 show GEOS-Chem predictions for the base model (i.e., model including all anthropogenic and natural sources; labeled as GEOS-Chem in the figure) and the North American background model (i.e., model including natural sources everywhere in the world and anthropogenic sources outside the U.S., Canada, and Mexico; labeled as NA background in the figure) along with measurements obtained from selected CASTNET sites (labeled as Measurement in the figure). Figures 3-56 a-b show a comparison of GEOS-Chem output with measurements at Mt. Bachelor, OR from March-August, 2006. Figure 3-57 shows a comparison of vertical profiles (mean ± 1 standard deviation) calculated by GEOS-Chem with ozonesondes launched at Trinidad Head and Boulder, CO.



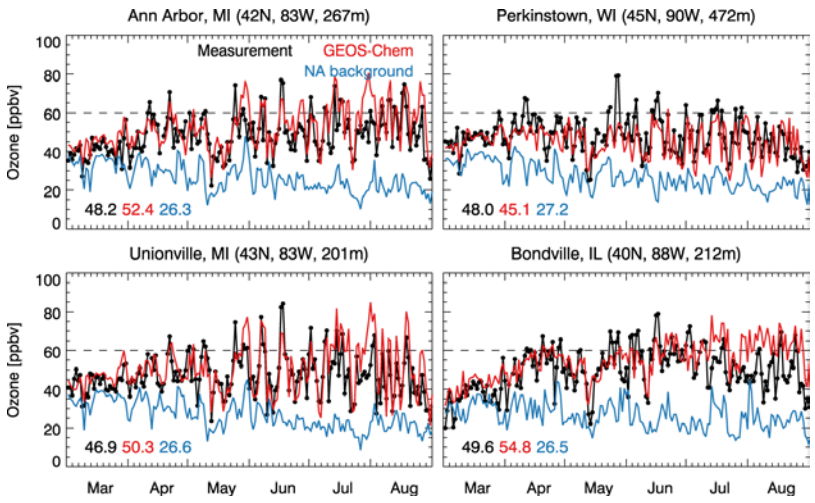
Source: Zhang et al. (In Press).

Figure 3-49 Comparison of time series of measurements of daily maximum 8-hour average ozone concentrations at four CASTNET sites in the Northeast with GEOS-Chem predictions for the base case and for the North American background case in 2006.



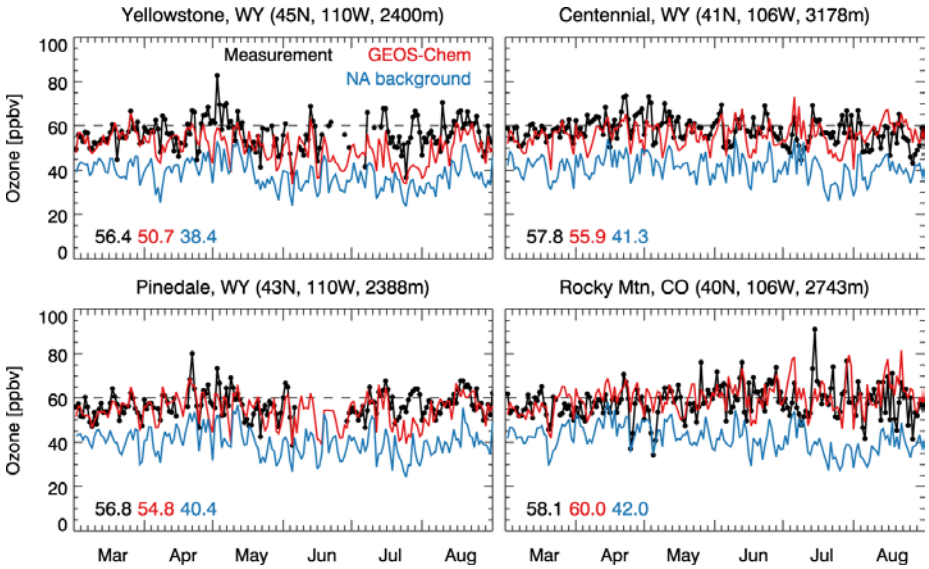
Source: Zhang et al. (In Press).

Figure 3-50 Comparison of time series of measurements of daily maximum 8-hour average ozone concentrations at four CASTNET sites in the Southeast with GEOS-Chem predictions for the base case and for the North American background case in 2006.



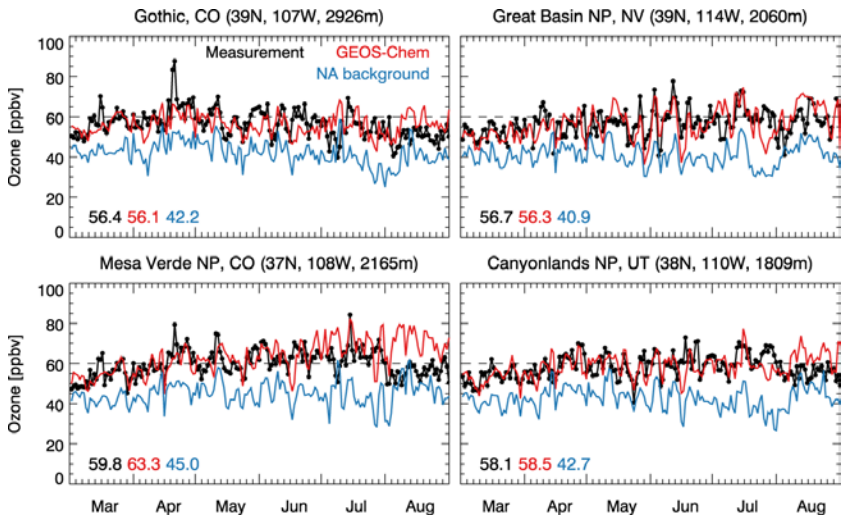
Source: Zhang et al. (In Press).

Figure 3-51 Comparison of time series of measurements of daily maximum 8-hour average ozone concentrations at four CASTNET sites in the Upper Midwest with GEOS-Chem predictions for the base case and for the North American background case in 2006.



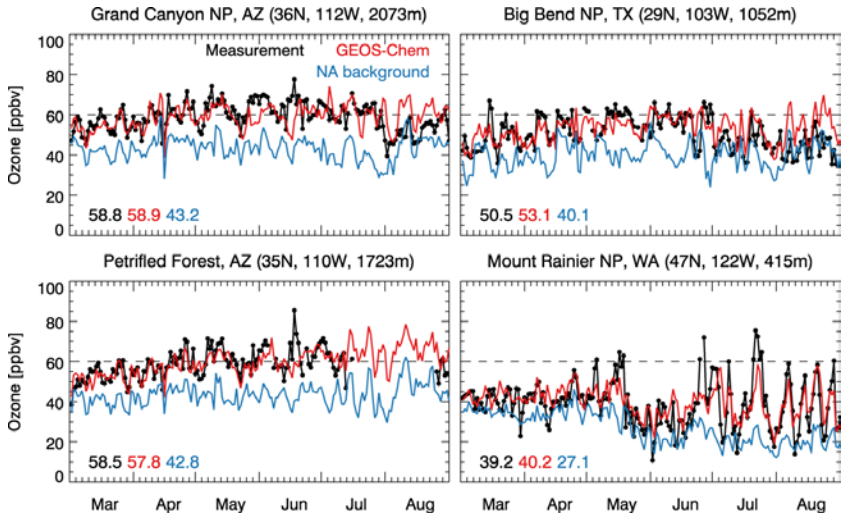
Source: Zhang et al. (In Press).

Figure 3-52 Comparison of time series of measurements of daily maximum 8-hour average ozone concentrations at CASTNET sites in the Intermountain West with GEOS-Chem predictions for the base case and the North American background case in 2006.



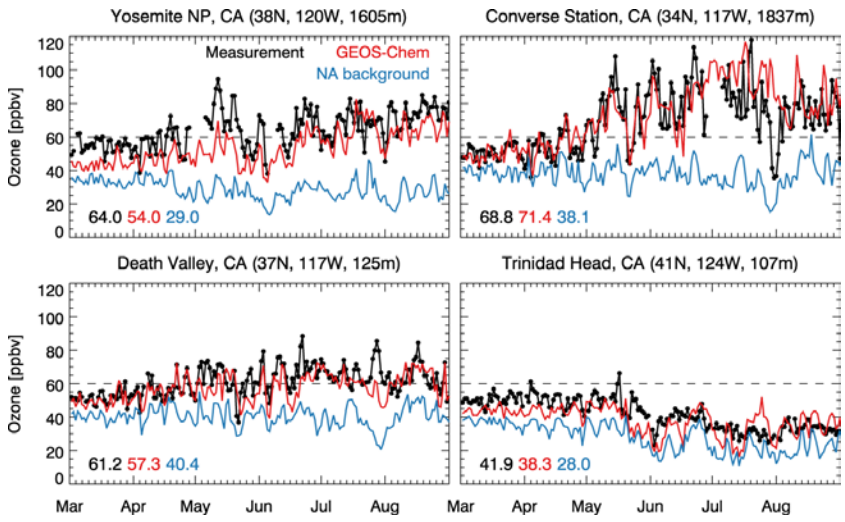
Source: Zhang et al. (In Press).

Figure 3-53 Comparison of time series of measurements of daily maximum 8-hour average ozone concentrations at CASTNET sites in the Intermountain West with GEOS-Chem predictions for the base case and the North American background case in 2006.



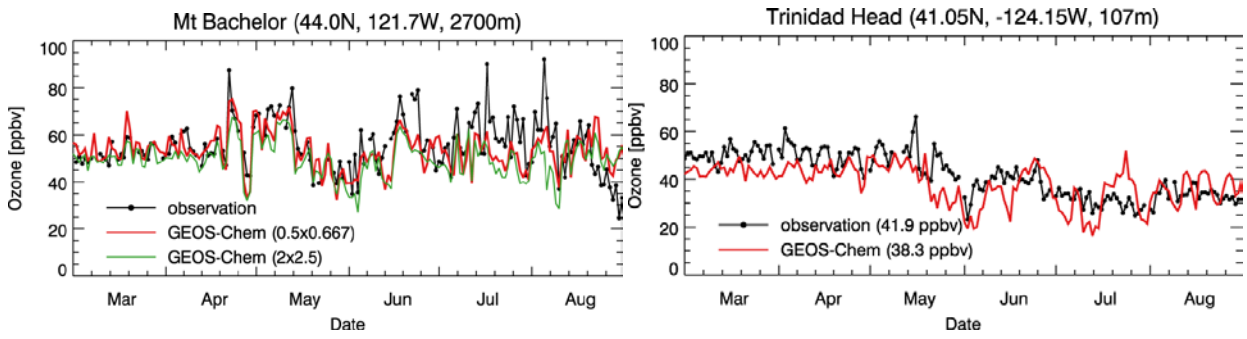
Source: Zhang et al. (In Press).

Figure 3-54 Comparison of time series of measurements of daily maximum 8-hour average ozone concentrations at CASTNET sites in the West with GEOS-Chem predictions for the base case and the North American background case in 2006.



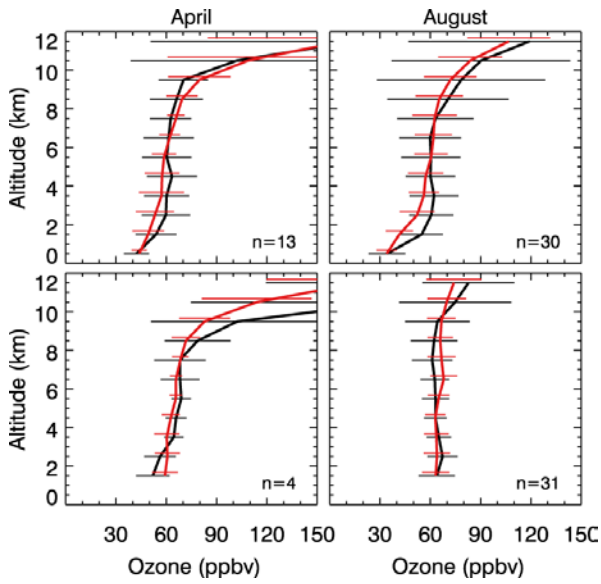
Source: Zhang et al. (In Press).

Figure 3-55 Comparison of time series of measurements of daily maximum 8-hour average ozone concentrations at monitoring sites in Californiawith GEOS-Chem predictions for the base case and the North American background case in 2006.



Source: Zhang et al. (In Press).

Figure 3-56 Comparison of daily maximum 8-h average ozone predicted using GEOS-Chem at 0.5°×0.67° and 2°×2.5° (left figure only) resolution with measurements at Mount Bachelor, OR (left) and Trinidad Head, CA (right) from March to August 2006.



Source: Zhang et al. (In Press).

The letter 'n' refers to the number of ozonesonde profiles, and the model was sampled on the same days as the ozonesonde launches. As can be seen from the figure, variability in both model and measurements increases with altitude, but variability in the model results is much smaller at both sites, at high altitudes than seen in the observations.

Figure 3-57 Comparison of monthly mean ± 1 standard deviation ozone calculated GEOS-Chem (in red) with ozonesondes (in black) at Trinidad Head and Boulder, CO during April and August 2006.

3.9 Supplemental Ozone Model Predictions Using the Latest Release of GEOS-Chem

3.9.1 Introduction

This section summarizes work that is currently underway on O_3 modeling over the U.S. using the latest release of GEOS-Chem (v9-01-01). This release includes several changes to the emissions inputs supplied to the model. Two of the updates that are likely to affect the simulated O_3 concentrations are 1) a correction for the yield of isoprene nitrates that increases the lifetime of NO_X and may result in greater ozone production, and 2) a correction for lightning NO_X emissions which may also increase O_3. A full list of updates is provided in the release notes for the current version of the model (Harvard University, 2011b). For the current analysis, GEOS-Chem was applied using nested grids with anthropogenic emissions updated for each model year from the 2005 NEI inventory. Zhang et al. (In Press) recently completed a similar study for North America, using the same grid configuration, but an earlier version of the GEOS-Chem model with 2005 emissions inputs.

This summary includes an overview of the GEOS-Chem model application and evaluation methods, an assessment of model performance for the base case simulations, modeling results for several background O_3 simulations, and a discussion of the attributes and limitations of the modeling methods and results. The full report is available online (U.S. EPA, 2011c).

3.9.2 GEOS-Chem Model Application

For the current analysis, GEOS-Chem is being applied using nested grids with 2°×2.5° horizontal resolution at the global scale and 0.5°×0.667° horizontal resolution over North America (140°-40°W, 10°-70°N). In addition, a coarser resolution grid (4°×5°) is also being used for the start-up simulation period—an annual simulation period run to spin up the model and to ensure a reasonable representation of long-range (global) transport. The modeling domain includes 47 vertical layers that increase in thickness with height above ground; the top of the modeling domain is at approximately 80 km. The GEOS-Chem model is being applied for the years 2006, 2007 and 2008 with a one-year spin-up period (2005).

As noted in Section 3.3, the GEOS-Chem model is driven by assimilated meteorological observations from GEOS and is able to represent long-range transport as well as stratospheric-tropospheric exchange processes. For this analysis, meteorological inputs for the four simulation years were provided by the Harvard University Atmospheric Chemistry Modeling (ACM) Group (Harvard University, 2011c). The version of the model used for this study utilizes the GEOS-5 data product from NASA's Global Modeling and Assimilation Office (GMAO). Data used by GEOS-Chem include surface albedo, parameters defining properties at the surface including moisture content and land type, various precipitation measures, cloud fraction, heat and radiation fluxes, PBL thickness, air temperature, tropopause pressure, ground (skin) temperature, U and V wind components, friction velocity, specific humidity and others.

Emission inputs for 2005 were also provided by Harvard's ACM Group (Harvard University, 2011a). They include both anthropogenic and biogenic emissions, and account for fossil fuel combustion and usage, biomass burning, biofuel burning, and natural aerosol emissions. Examples of categories of emissions included are aircraft emissions, shipping emissions, and soil and fertilizer NO_X emissions. The emissions also include estimates for NO_X generated by lightning. Various sources of data provide global coverage with the more reliable and highly resolved emissions data sources taking precedence. For example, the 2005 NEI inventory is used in order to enhance the emissions estimates over the United States. Temporal resolution for emissions varies

depending on data source from annual to seasonal. Within the model, emissions are introduced at hourly intervals. Anthropogenic emissions were projected to each simulated year (2006, 2007, and 2008) using scale factors developed for each region of the world based on available information. More detailed information on the scale factors for anthropogenic emissions and links to additional documents can be found on the Harvard University ACM Group website (Harvard University, 2011d).

All other inputs for the application of GEOS-Chem were provided by Harvard's ACM Group, including Total Ozone Mapping Spectrometer (TOMS) data, surface UV albedo, dry deposition coefficients, and land use codes. Note that roughness lengths and terrain heights are included in the GEOS-5 data. Other files define the chemical mechanism and provide data for calculating photolysis rates. The leaf area index used for ozone dry deposition was based on data from the Moderate Resolution Imaging Spectroradiometer (MODIS). Use of MODIS data is expected to result in less ozone dry deposition and higher ozone concentrations compared to the use of Advanced Very High Resolution Radiometer (AVHRR) derived values. Additional operating parameters for GEOS-Chem are provided in the full report (U.S. EPA, 2011c).

3.9.3 Model Scenarios

Table 3-10 summarizes the different model scenarios considered for this analysis. In addition to the Base Case which modeled the existing atmosphere for 2006, 2007, and 2008 with all natural and anthropogenic emissions turned on, three background air quality scenarios were considered to explore different impacts on U.S. O_3 concentrations. They included 1) a U.S. Background scenario with all anthropogenic emissions in the U.S. turned off; 2) a North American Background scenario with all anthropogenic emissions in North America (U.S., Canada, and Mexico) turned off (equivalent to the previously used definition introduced in Section 3.4); and 3) a Natural Background scenario with all anthropogenic emissions across the globe turned off. Methane concentrations used in the GEOS-Chem model were adjusted to reflect the different emission scenarios with zonal average concentrations listed in Table 3-2 of the full report (U.S. EPA, 2011c).

Table 3-10 Summary of GEOS-Chem model scenarios

Model Scenario	Anthropogenic Emissions from the U.S.	Anthropogenic Emissions from Canada and Mexico	Anthropogenic Emissions from the Rest of the Globe	Natural Emissions Everywhere
Base Case	On	On	On	On
U.S. Background	Off	On	On	On
N.A. Background[a]	Off	Off	On	On
Natural Background	Off	Off	Off	On

[a]North American (N.A.) background is equivalent to the previously used definition

3.9.4 Model Performance Evaluation

Model evaluation was performed on the Base Case for the three simulation years. This evaluation focused primarily on the ability of the GEOS-Chem model to replicate observed O_3 and other pollutant concentrations for the entire U.S., selected subregions of the U.S., and at individual sites representing key areas in the U.S. that have been identified as important for characterizing background O_3 concentrations (In Press). The evaluation also included a qualitative assessment of how well the stratospheric-tropospheric exchange is being simulated and an examination of the effects of interannual variability in meteorology on the Base Case results. A wide range of statistical and graphical analyses relating to model performance are presented in the full report (U.S. EPA, 2011c). Key findings from the model performance evaluation include:

- Model performance for all species was consistent among the three modeled years (2006, 2007, and 2008)
- Ozone concentrations were overestimated by the GEOS-Chem model for all three years and nearly all regions and time periods considered in this analysis.
- Overestimation was greater for 24-h avg O_3 than for 8-h daily max O_3.
- Model performance for O_3 varied by season and by subregion.
- As expected, given the grid resolution, O_3 concentrations were better represented for the more rural CASTNET sites compared to the more urban AQS sites.
- Based on comparison with the CASTNET data, the bias and error statistics for 8-h daily max O_3 suggested reasonably good performance. Overestimation of

O_3 during the summer and autumn months was most prevalent in the eastern U.S. (Central States, Great Lakes, Southeast, and Northeast subregions). For the western subregions, there was less overestimation of O_3 and overall good agreement with the observations. The best agreement with the observations was achieved for the Intermountain West subregion.

- Site-specific model performance for 8-h daily max O_3 concentration (again for the CASTNET sites) indicated that for some sites, especially those in the west, the annual variation in O_3 concentration is very well replicated. For most of the subregions, model performance improves with site elevation.
- The spatial and temporal variability of NO_2, SO_2, CO data from the AQS network are not well characterized. NO_2 concentrations are underestimated for all subregions and time periods. SO_2 is underestimated in the Intermountain West, where observed values are low and overestimated elsewhere, including in the East where observed values are higher. Simulated CO is only weakly correlated with the observed concentrations, and concentrations are underestimated for all regions and time periods. The modeled values exhibit less seasonal variation than the observed values. These results are perhaps understandable, especially for NO_2 and CO, given the coarse grid resolution and the probable strong response of AQS monitors to local emissions.
- Model performance for 24-h avg $PM_{2.5}$ is mixed. For many of the regions and time periods, the bias and error statistics indicate good model performance. However, the seasonal variation in $PM_{2.5}$ that is characterized by higher concentrations during the summer months is not replicated by the model.
- Overall, model performance for dry deposition is quite good. Dry deposition of O_3 is underestimated by the model, which could contribute to overestimation of the O_3 concentrations.
- Comparison of simulated and observed O_3 profiles for five case-study periods (a total of 12 days) and several locations within the western U.S. gave mixed results. For some cases, the simulated vertical profiles showed poor agreement with the observations. For other cases the results were more promising in that although the detailed vertical structure of observed profiles was not well simulated, the model results showed layers of high O_3 in the middle troposphere, consistent with observations.

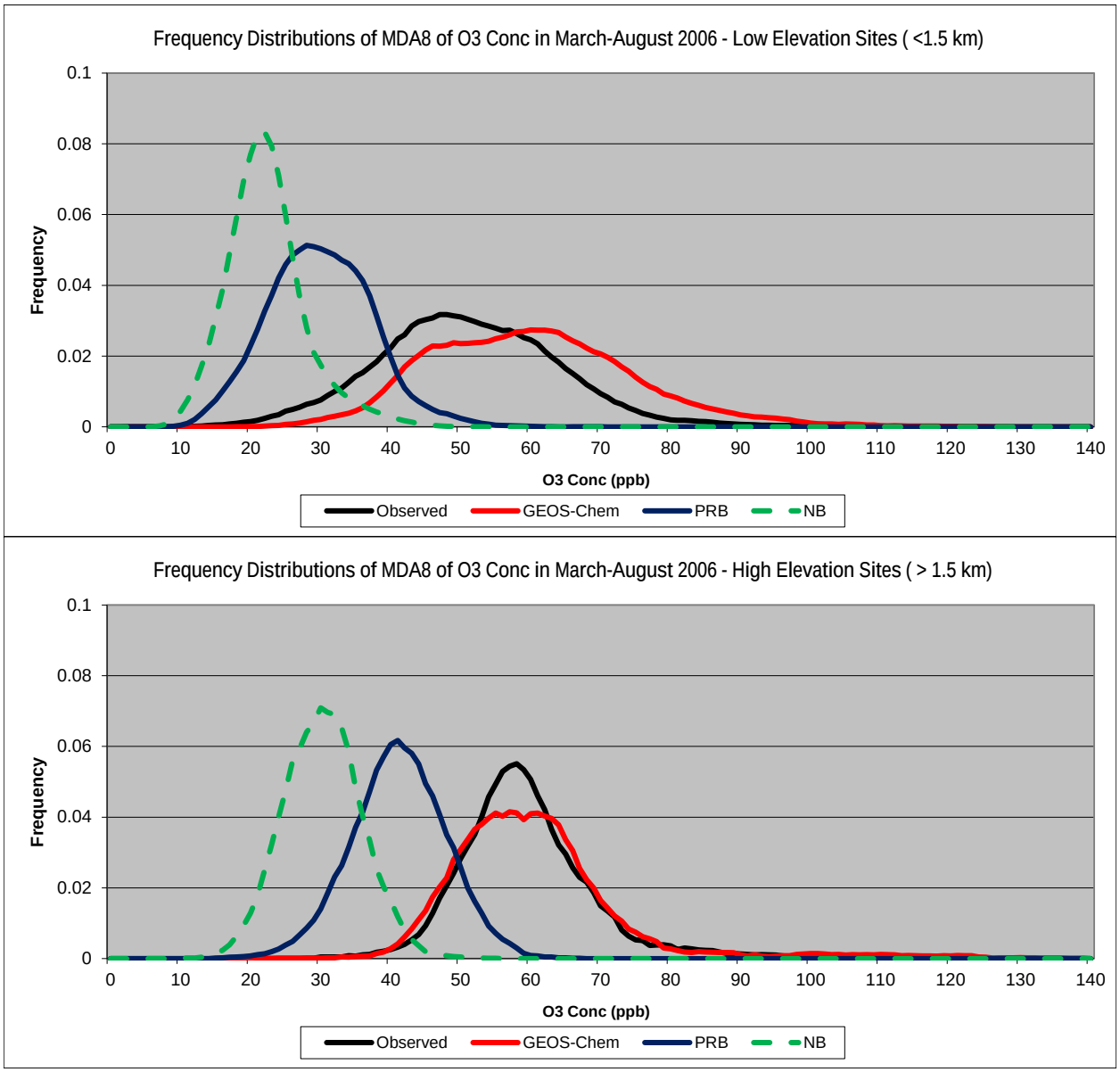


Figure 3-58 Frequency distributions of 8-hr daily max ozone concentration from March – August 2006 for low-elevation (<1.5 km; top panel) and high-elevation (>1.5 km; bottom panel) CASTNET sites. Observed values are in black; modeled Base Case values are in red (labeled GEOS-Chem), modeled North American Background values are in blue (labeled PRB), and modeled Natural Background values are in Green (labeled NB).

Figure 3-58 includes a comparison between the frequency distribution of observed 8-h daily max O_3 from March - August, 2006 at CASTNET sites with the Base Case model results (labeled GEOS-Chem in the figure) at corresponding sites and times. This figure illustrates the overestimation of the Base Case model relative to observations at low elevation (< 1.5 km) CASTNET sites, and the general agreement between the model and observations at high elevation CASTNET sites (> 1.5 km). Further details on the sites used in the model performance evaluation and additional model evaluation results including site-specific case studies are included in the full report (U.S. EPA, 2011c).

3.9.5 Model Results

Figure 3-59 displays the mean 8-hr daily max O_3 concentration for the Base Case (left panel) and North American Background scenario (right panel), based on all three simulation years. For the current atmosphere scenario, mean 8-hr daily max O_3 concentrations range from 21.3 to 82.6 ppb within the modeling grid. For the North American background scenario, mean 8-hr daily max O_3 concentration ranges from 17.4 to 42.9 ppb. The annual average North American background 8-hr daily max O_3 concentration for the entire U.S. is estimated to be 31.0 ppb. This value varies geographically; for the western U.S., the estimated range is 35.5–38.9 ppb and for the eastern U.S., the estimated range is 27.6–31.2 ppb. The highest estimated North American Background concentrations do not necessarily occur in the areas with the highest modeled Base Case concentrations.

The estimated North American Background 8-hr daily max O_3 concentrations vary by season, as illustrated in Figure 3-60. For most areas within the domain, the highest concentrations tend to occur during the spring (March–May). High values also occur during the summer (June-August) in the western U.S., especially over the more mountainous regions. For the spring months, the average North American Background 8-hr daily max O_3 concentration is estimated to be 33.2 ppb for the entire U.S.; it ranges from 37.8–41.7 ppb for the western U.S. and from 29.3–32.6 ppb for the eastern U.S. For the summer months, the average North American Background 8-hr daily max O_3 concentration is estimated to be 30.0 ppb for the entire U.S.; it ranges from 33.9–40.4 ppb for the western U.S. and from 22.9–34.2 ppb for the eastern U.S.

Figure 3-58 includes the frequency distribution of the 8-h daily max O_3 concentrations from March - August, 2006 at CASTNET sites modeled in the North American Background scenario and the Natural Background scenario for direct comparison with observations and the Base Case model results (labeled GEOS-Chem in the figure).

Additional analyses of the North American Background model results including case studies at selected CASTNET sites are included in the full report (U.S. EPA, 2011c).

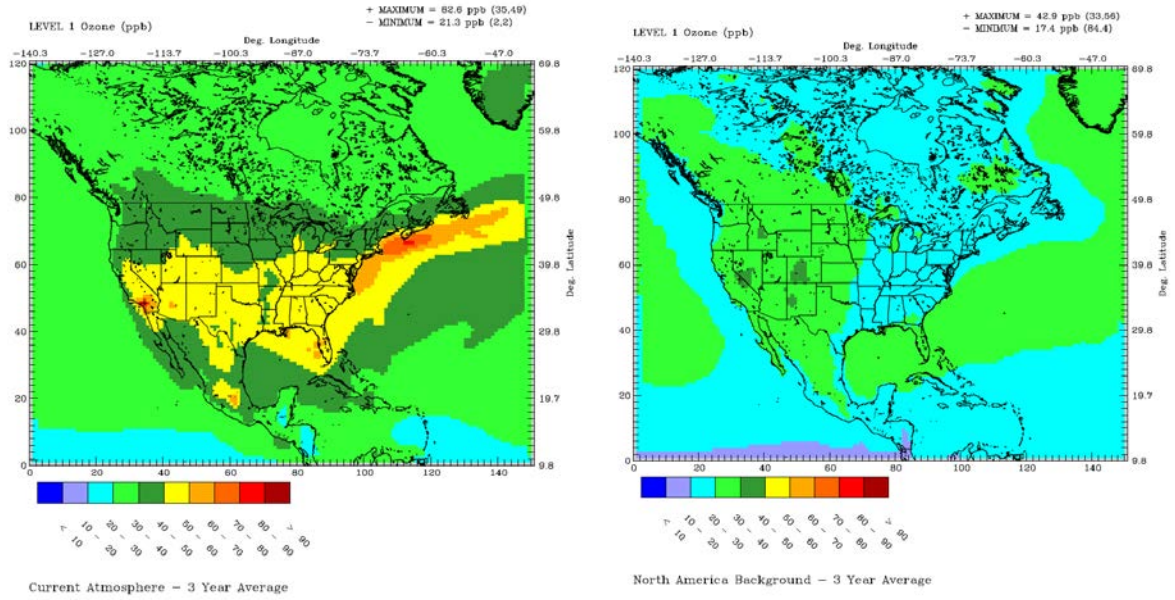


Figure 3-59 Mean 8-hr daily max O_3 concentration (ppb) for the Base Case (left panel) and North American Background scenario (right panel), based on the 2006, 2007 and 2008 simulation period.

All model scenarios showed considerable spatial and temporal variability across the U.S. and none can be represented by a single value. For the Base Case scenario, mean 8-h daily max O_3 concentrations ranged from 21.3 to 82.6 ppb within the modeling grid. For the North American Background scenario, 8-h daily max O_3 concentrations ranged from 17.4 to 42.9 ppb. For the U.S. Background scenario, 8-h daily max O_3 concentrations ranged from 19.9 to 73.4 ppb. Compared to the North American Background, the simulated U.S. Background values are higher throughout the domain including over the continental U.S. This increase is attributable to Canadian, Mexican and offshore emissions. For the Natural Background scenario, the concentrations are substantially lower with 8-h daily max O_3 concentrations from 12.8 to 30.7 ppb. Within the U.S., the simulated Natural Background concentrations were very low along the northeast corridor and the highest concentrations were found over Colorado. Additional model results including a seasonal and geographic analysis for the U.S. Background and Natural Background scenarios are included in the full report (U.S. EPA, 2011c).

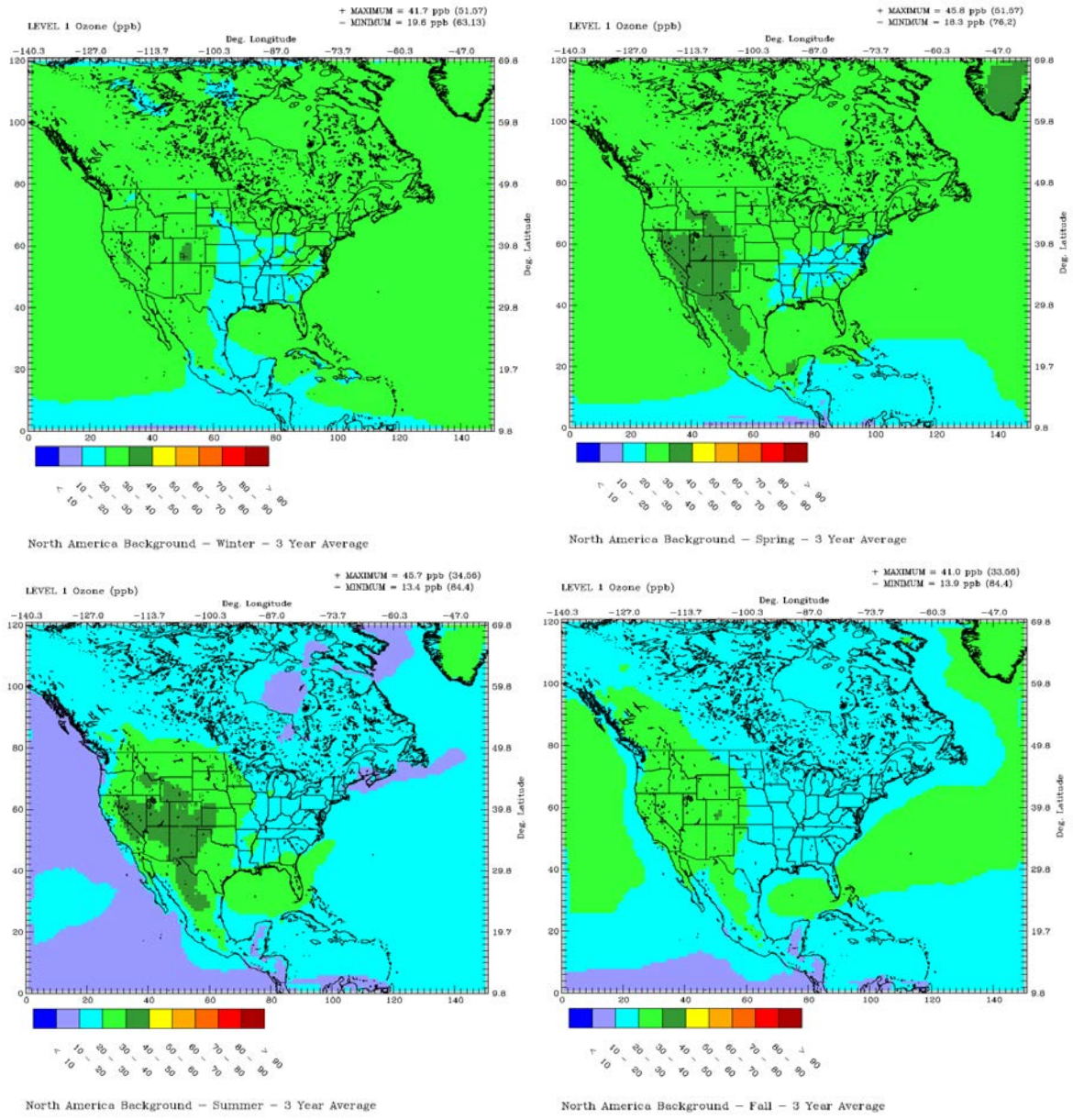


Figure 3-60 Mean 8-hr daily max O_3 concentration (ppb) for the North American Background scenario during winter (Dec-Feb, upper right panel), spring (Mar-May, upper right panel), summer (Jun-Aug, lower left panel), and fall (Sep-Nov, lower right panel), based on the 2006, 2007 and 2008 simulation period.

3.9.6 Model Attributes and Limitations

The GEOS-Chem tool allows the estimation of contributions to background O_3 concentrations from a variety of sources and source regions, and the non-linear effects associated with the removal of emissions from selected sources and source regions has been shown to be small. The following is a summary of the attributes and limitations of the GEOS-Chem results included here:

- The grid resolution required for a global simulation is not expected to resolve regional- and urban-scale O_3 production in the U.S. and elsewhere and thus may under- or over-estimate the anthropogenic contribution to long-range O_3 transport.
- The GEOS-Chem chemical mechanism includes a relatively detailed representation of the reactions and species involved in the production of O_3 in the atmosphere. Details of the mechanism are presented in Evans et al. (2003a). The mechanism includes hundreds of reactions and more than 80 species. In a comparison of chemical mechanisms, Emmerson (2009) noted that the GEOS-Chem mechanism (and the other mechanisms evaluated in their paper) should be able to represent the atmospheric chemistry in the troposphere. Nevertheless, all chemical mechanisms suffer from the necessity to limit the number of reactions and species to a finite set rather than the many thousands of reactions and species actually taking part in the chemistry of the troposphere. Perhaps even more important, limitations in grid resolution of the model can limit the model's ability to properly represent the relative proportions of species. This limitation could result in alterations in the estimates of O_3 production rates compared to what would be simulated with higher grid resolution. Good performance at monitors will not guarantee that alterations in the chemical mix (e.g., by removing a category of emissions) will produce the correct response in O_3 production. Hence, the chemical mechanism and the interaction of the chemical mechanism with grid resolution must be considered to be potential sources of uncertainty in the model results.
- Emissions estimates for GEOS-Chem are based on data available to the model developers. These data are more readily available for some parts of the world (e.g., the U.S. and Europe) than others (e.g., developing nations). The magnitude and distribution of emissions are therefore sources of uncertainty in the model runs, and this uncertainty may be difficult to quantify for many parts of the world. Although the chemical mechanism in GEOS-Chem includes a wide range of hydrocarbons, the number of emitted species

included in the model is much smaller. The speciation of emissions into constituent hydrocarbons is difficult even for domestic U.S. emissions, where relatively robust data are available for making these estimates. For parts of the world where data are lacking, even greater uncertainty is present. The use of a more limited set of emitted species is likely appropriate given that a more detailed speciation of hydrocarbons would necessarily involve some guess work. Uncertainties in the speciation of hydrocarbons introduce another uncertainty into the GEOS-Chem simulation results.

- Considering the scale and resolution of the modeling domain, parameterizations of small-scale processes, such as boundary layer ventilation and downward mixing of free tropospheric and surface air are key sources of uncertainty in any global model application, including this application of GEOS-Chem.
- Finally, it is difficult to fully evaluate model performance, given the grid resolution and the available data. In particular, it is difficult to confirm that the model reliably simulates the vertical distribution (and transport) of O_3 aloft as well as the various processes, such as vertical mixing within the troposphere and stratospheric O_3 intrusion, that influence background O_3 concentrations.

3.9.7 Summary of Modeling Results

The assessment of model performance for this analysis reveals consistent overestimation of O_3 concentrations throughout the U.S., but especially in the eastern U.S. In the western U.S. and at high elevations, the model performance was much better with Base Case model estimates matching well with observations from multiple CASTNET sites. Three different definitions of background were considered including North American Background, U.S. Background, and Natural Background. The Base Case and all three background scenarios showed considerable spatial and temporal variability across the U.S. The estimated 8-h daily max O_3 concentrations ranged from 17.4 to 42.9 ppb for the North American Background scenario, from 19.9 to 73.4 ppb for the U.S. Background scenario, and from 12.8 to 30.7 ppb for the Natural Background scenario.

3.10 Supplemental Figures of Observed Ambient Ozone Concentrations

3.10.1 Ozone Monitor Maps for the Urban Focus Cities

This section contains supplemental maps showing the location of O_3 monitors reporting to AQS for each of the 20 urban focus cities introduced in Section 3.6.2.1. The monitors are delineated in the maps as year-round or warm-season based on their inclusion in the year-round data set and the warm-season data set discussed in Section 3.6.2.1. The maps also include the CSA/CBSA boundary selected for monitor inclusion, the location of urban areas and water bodies, the major roadway network, as well as the population gravity center based on the entire CSA/CBSA and the individual focus city boundaries. Population gravity center is calculated from the average longitude and latitude values for the input census tract centroids and represents the mean center of the population in a given area. Census tract centroids are weighted by their population during this calculation.

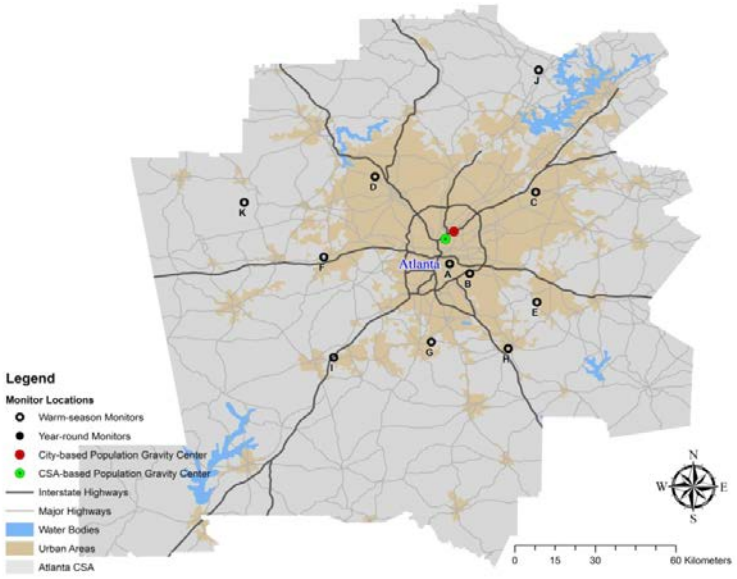


Figure 3-61 Map of the Atlanta CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

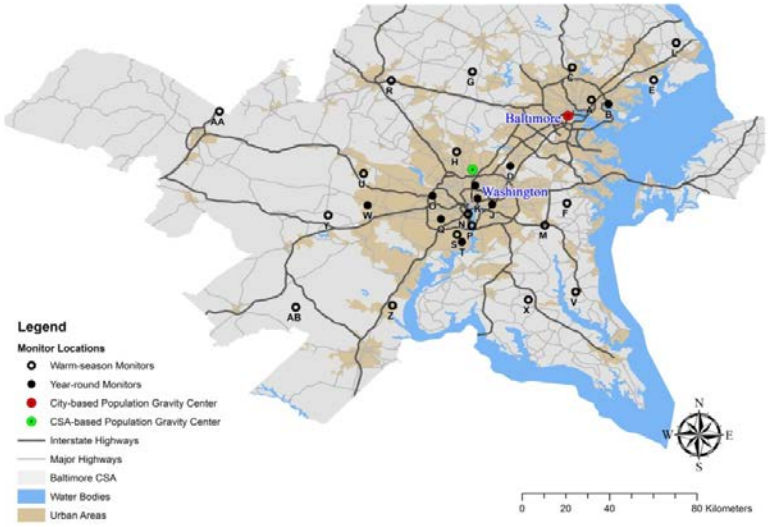


Figure 3-62 Map of the Baltimore CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

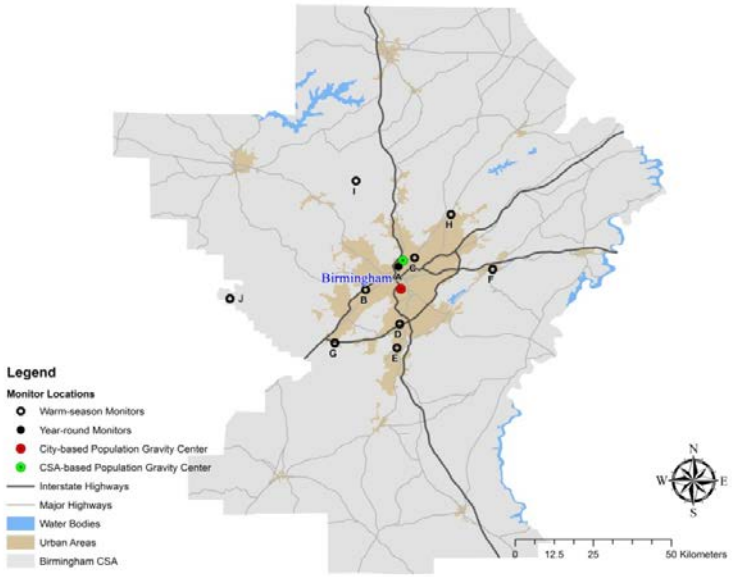


Figure 3-63 Map of the Birmingham CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

Figure 3-64 Map of the Boston CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

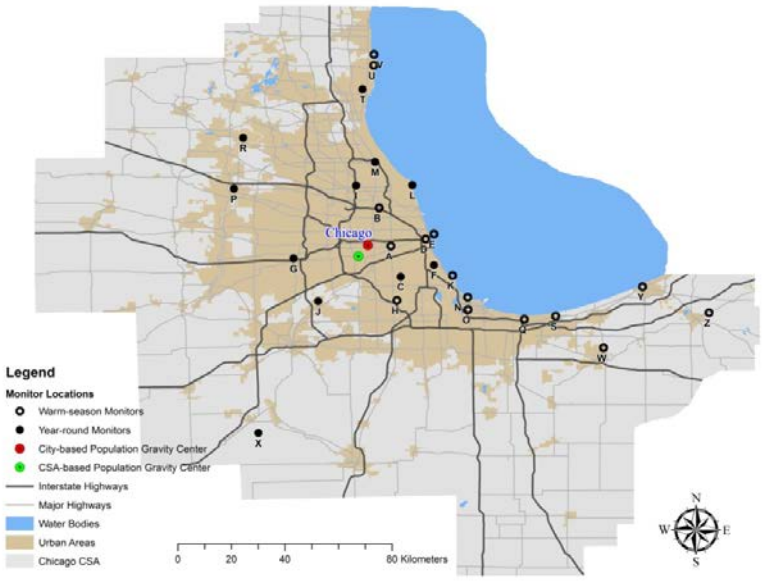


Figure 3-65 Map of the Chicago CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

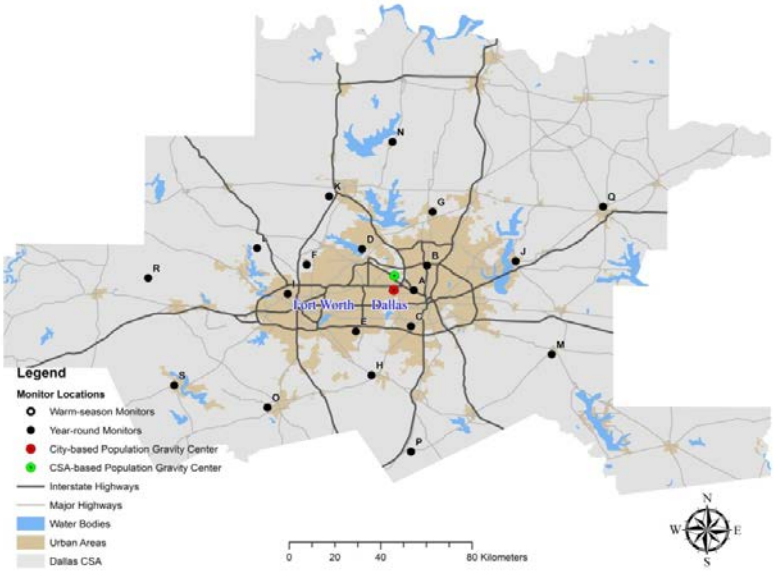


Figure 3-66 Map of the Dallas CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

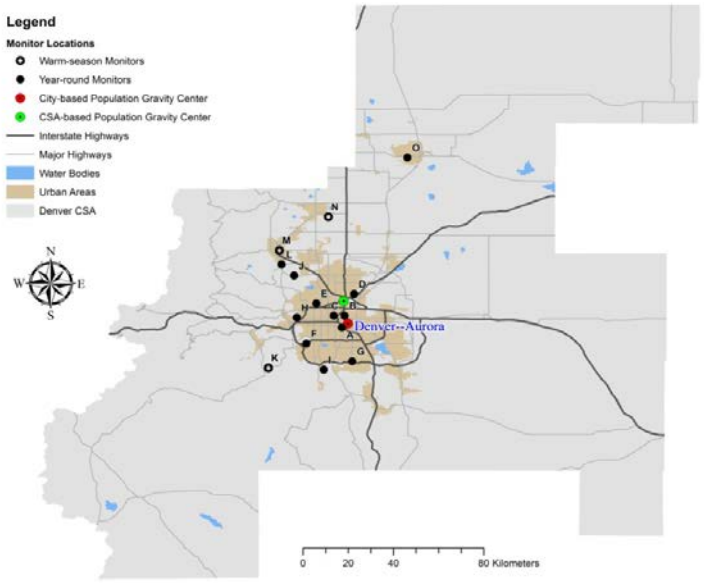


Figure 3-67 Map of the Denver CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

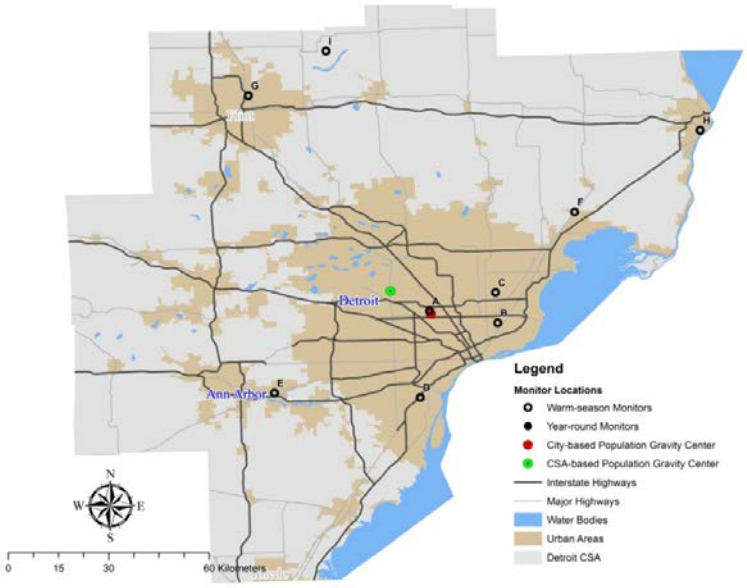


Figure 3-68 Map of the Detroit CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

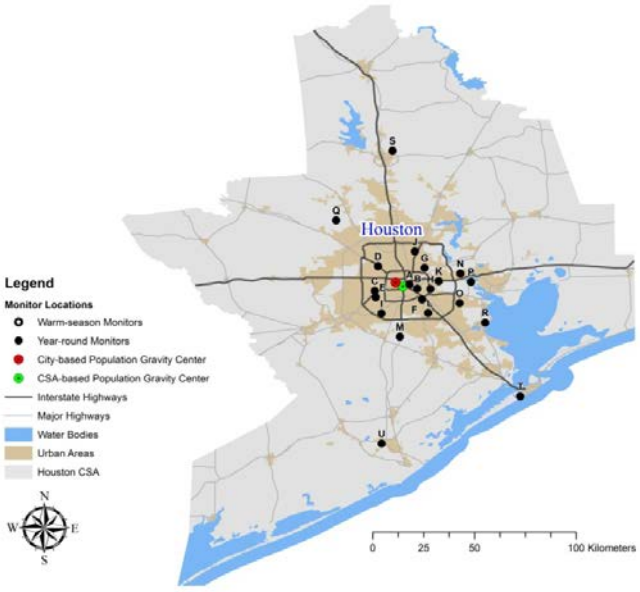


Figure 3-69 Map of the Houston CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

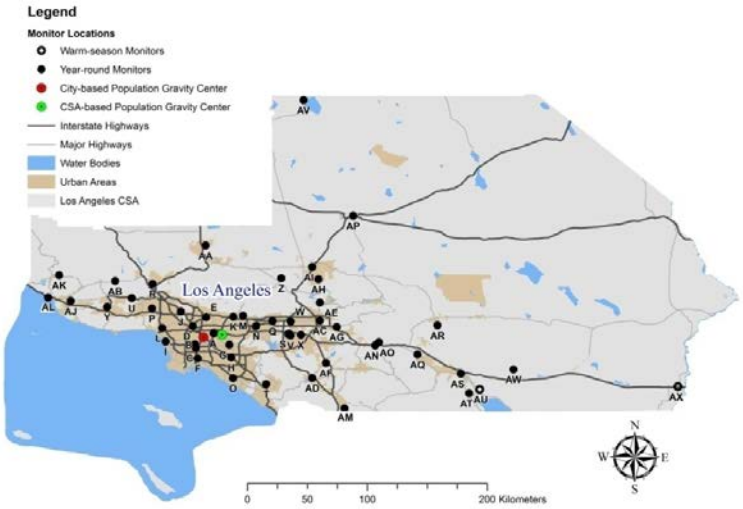


Figure 3-70 Map of the Los Angeles CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

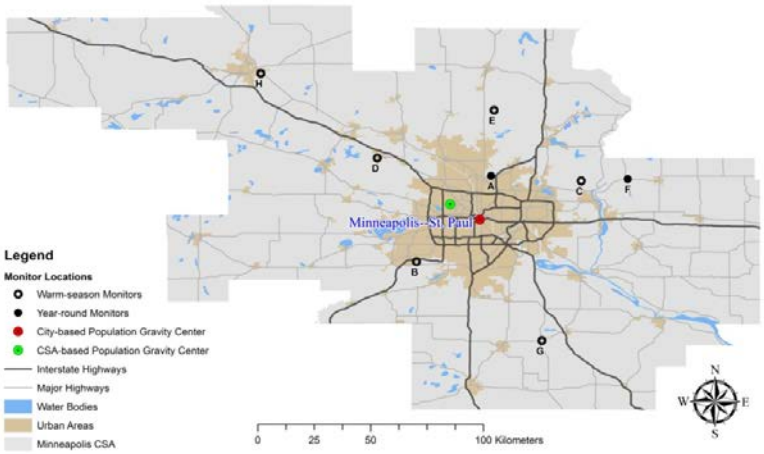


Figure 3-71 Map of the Minneapolis CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

Figure 3-72 Map of the New York CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

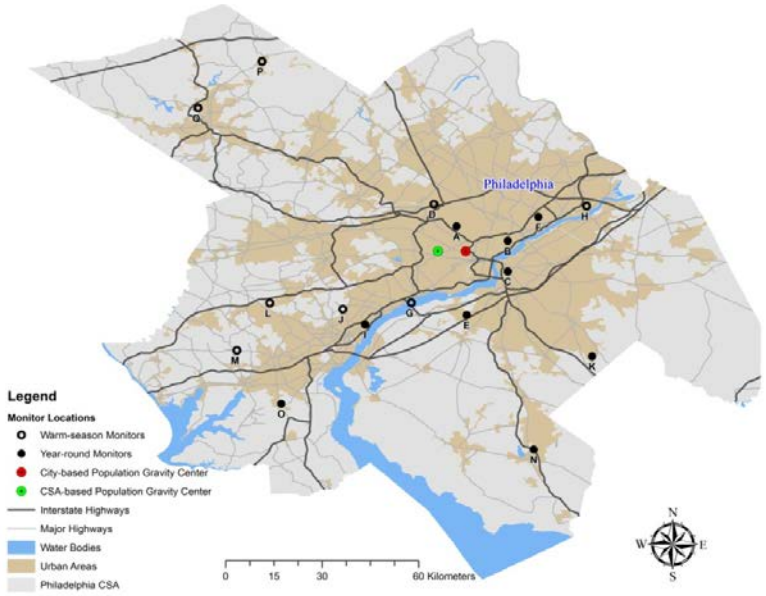


Figure 3-73 Map of the Philadelphia CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

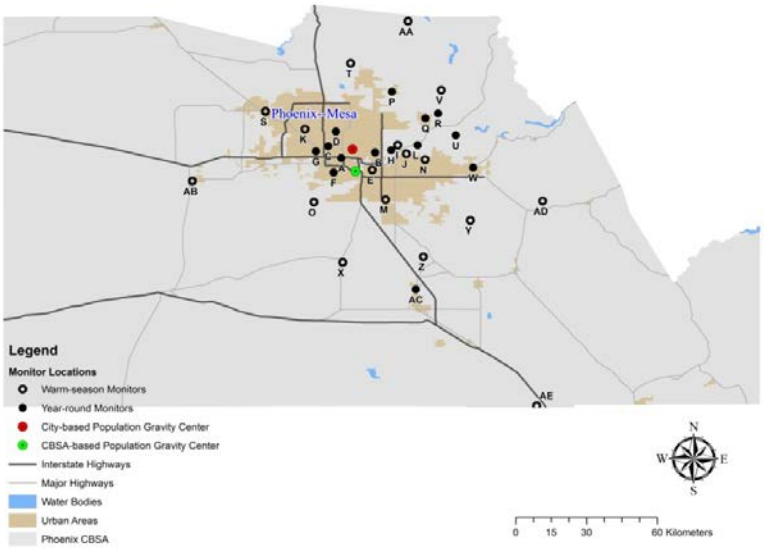


Figure 3-74 Map of the Phoenix CBSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

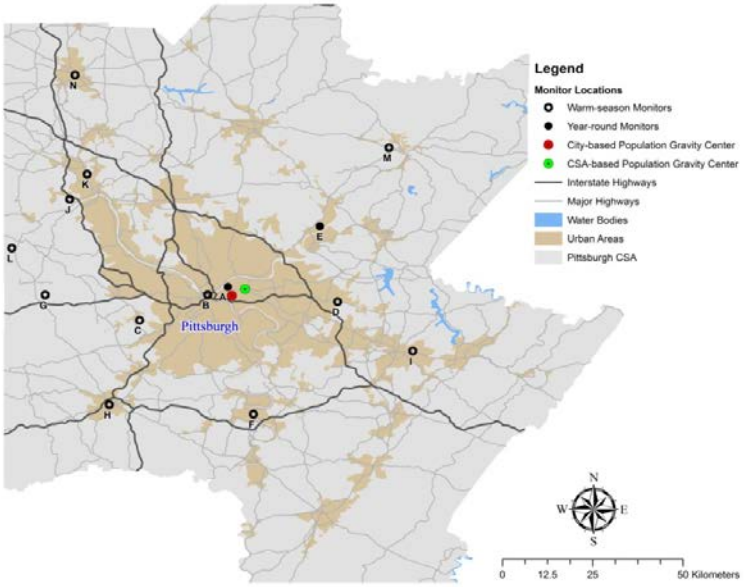


Figure 3-75 Map of the Pittsburgh CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

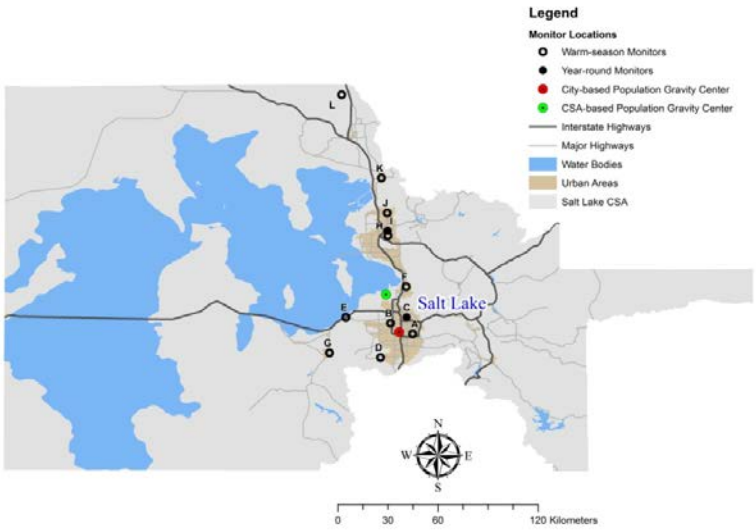


Figure 3-76 Map of the Salt Lake City CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

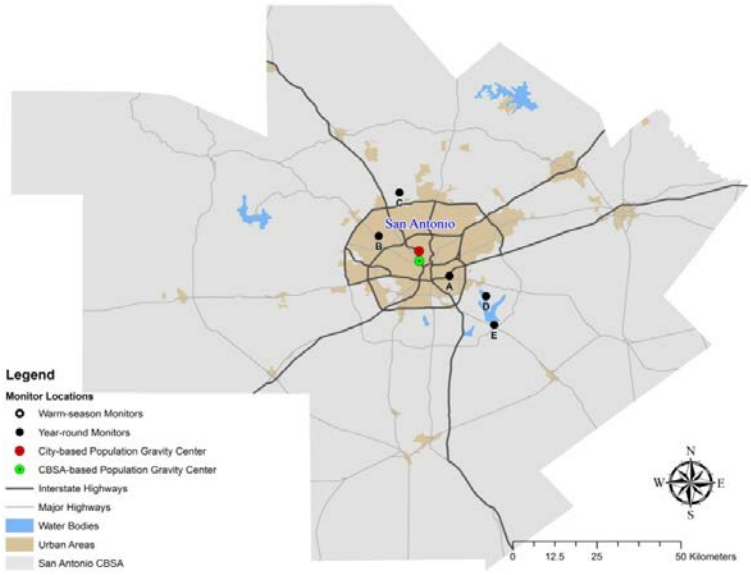


Figure 3-77 Map of the San Antonio CBSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

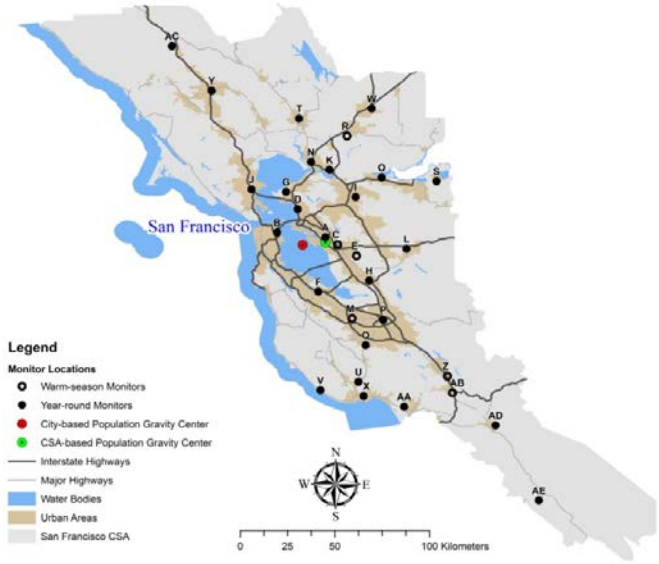


Figure 3-78 Map of the San Francisco CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

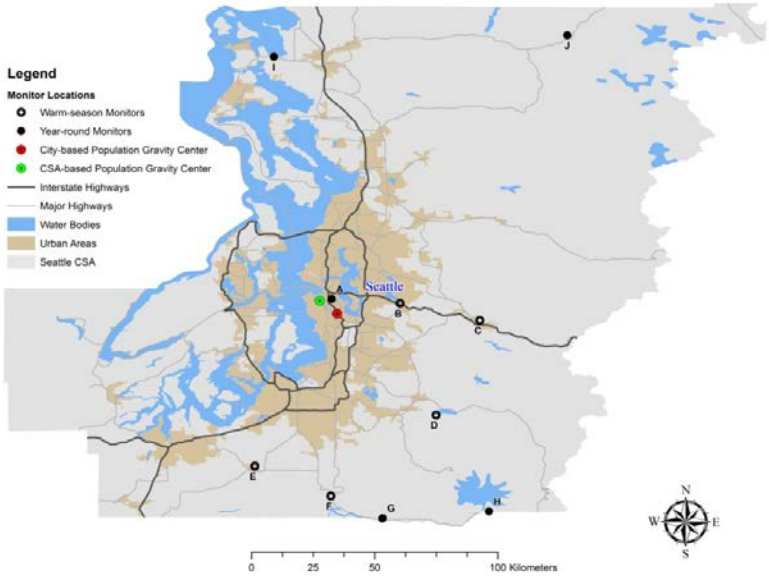


Figure 3-79 Map of the Seattle CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

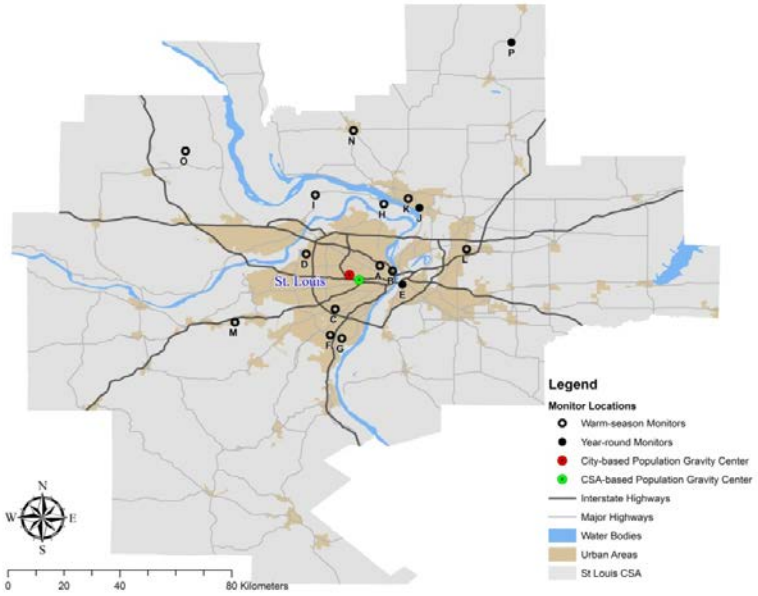


Figure 3-80 Map of the St. Louis CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

3.10.2 Ozone Concentration Box Plots for the Urban Focus Cities

This section contains box plots depicting the distribution of 2007-2009 warm-season 8-h daily max O_3 data from each individual monitor in the 20 urban focus cities introduced in Section 3.6.2.1. Monitor information including the AQS site id, the years containing qualifying data between 2007 and 2009, and the number of 8-h daily max O_3 observations included in the data set are listed next to the box plot. Statistics including the mean, standard deviation (SD), median and inner quartile range (IQR) are also shown for each monitor with the site letter corresponding to the sites listed in the figures above.

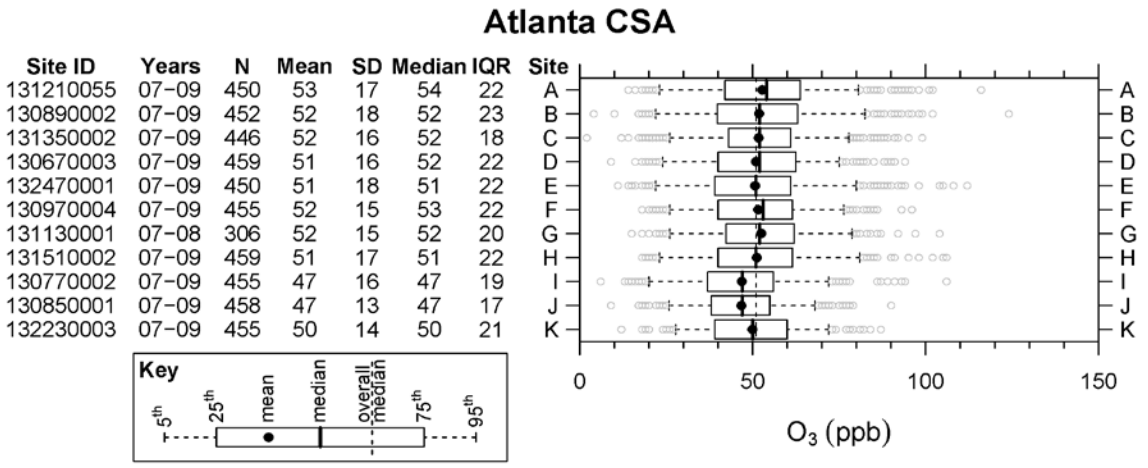


Figure 3-81 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Atlanta CSA.

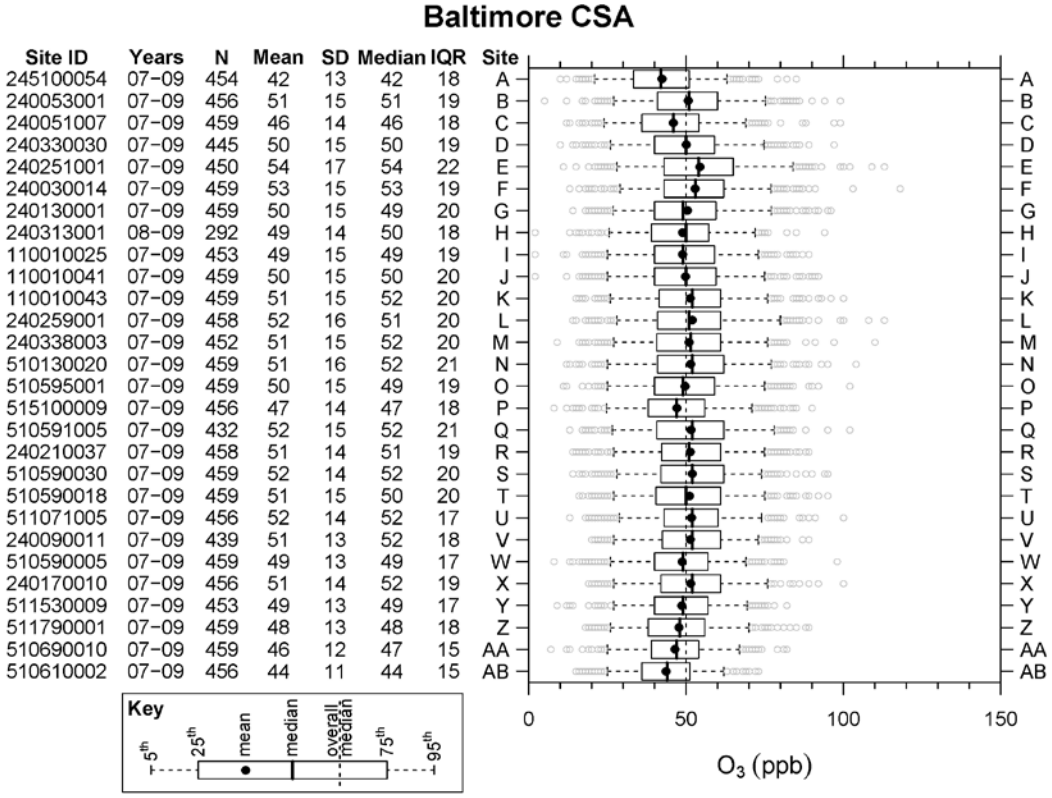


Figure 3-82 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Baltimore CSA.

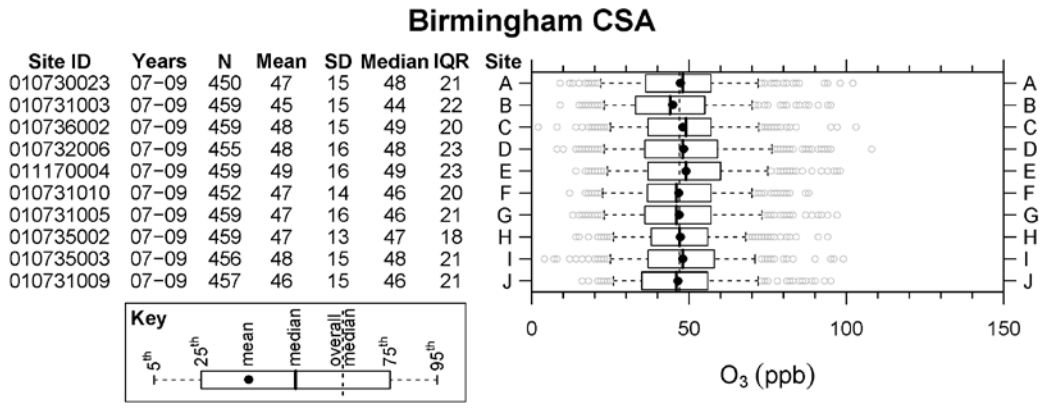


Figure 3-83 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Birmingham CSA.

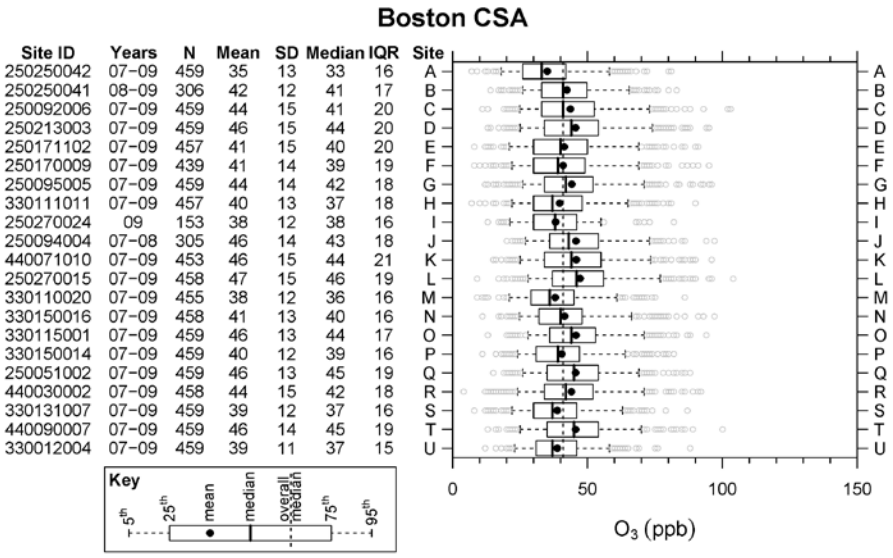


Figure 3-84 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Boston CSA.

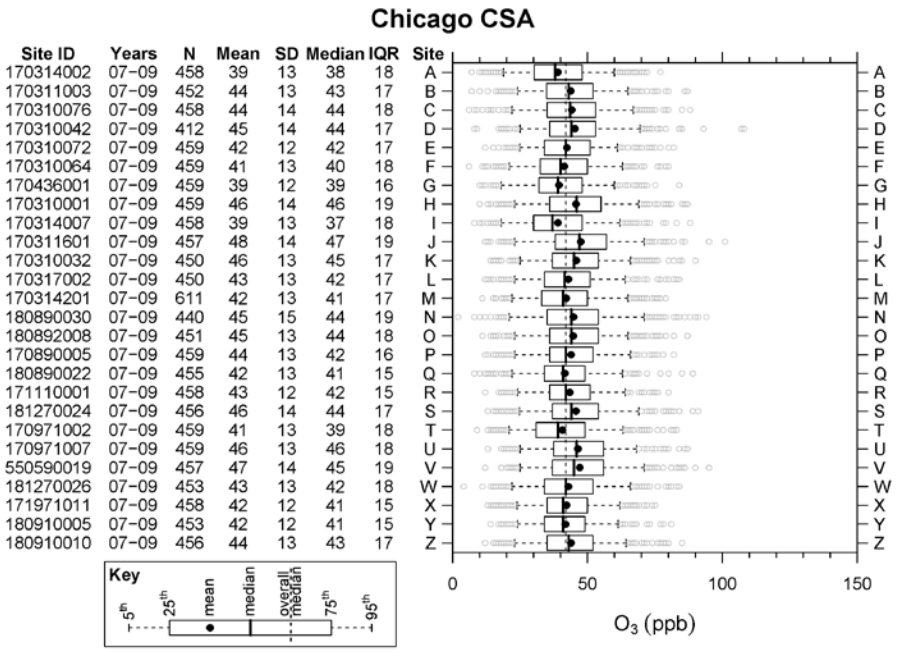


Figure 3-85 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Chicago CSA.

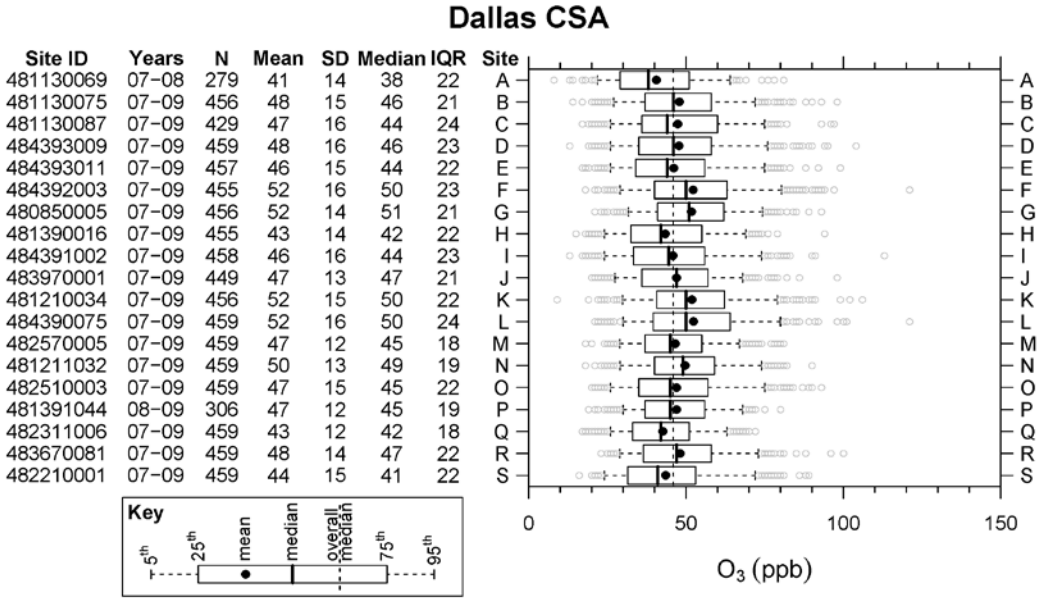


Figure 3-86 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Dallas CSA.

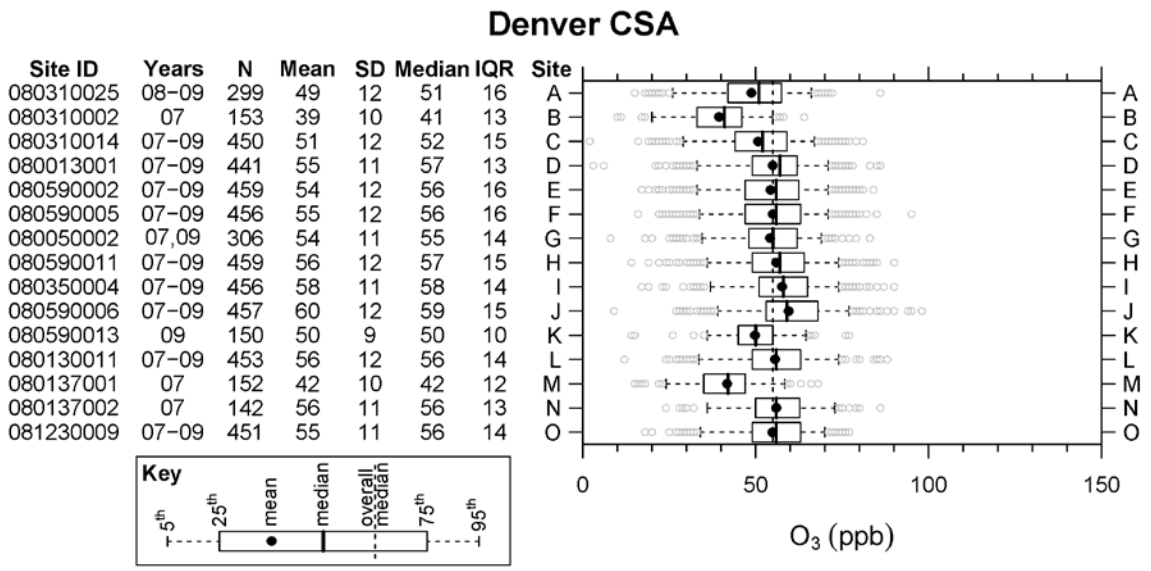


Figure 3-87 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Denver CSA.

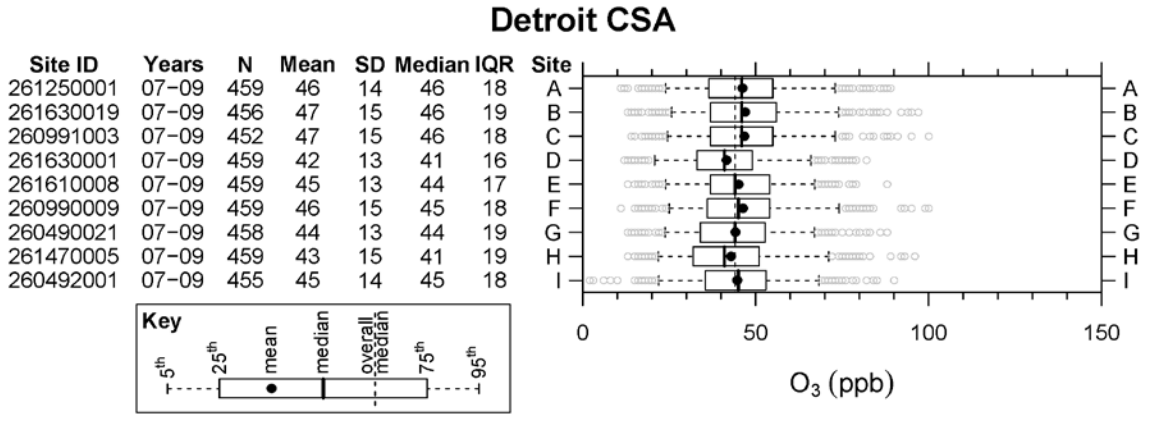


Figure 3-88 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Detroit CSA.

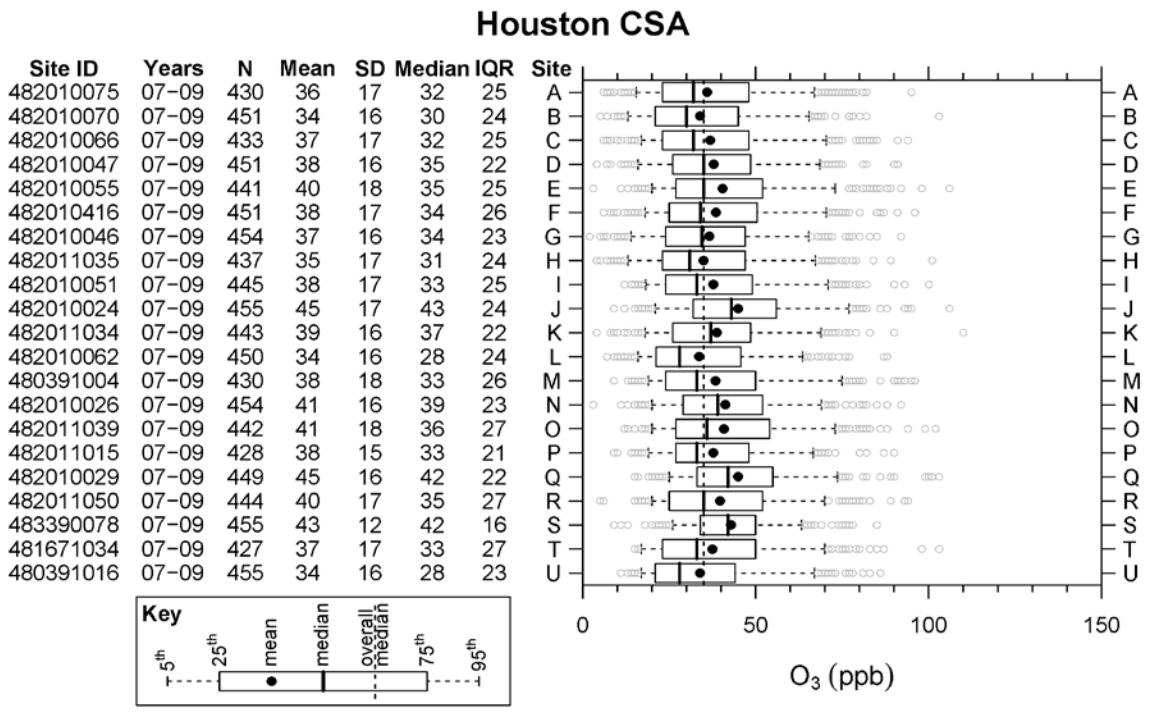


Figure 3-89 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Houston CSA.

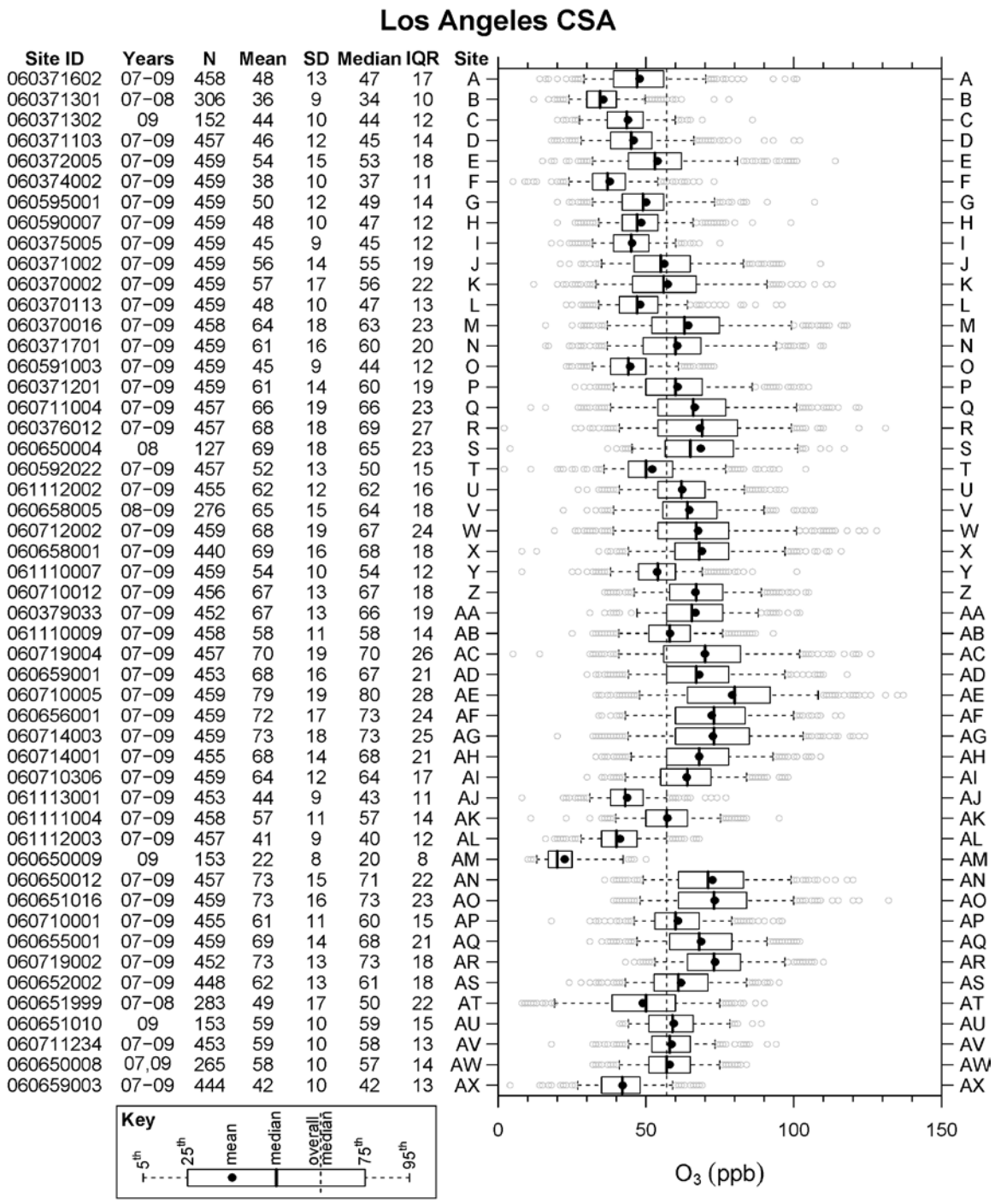


Figure 3-90 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Los Angeles CSA.

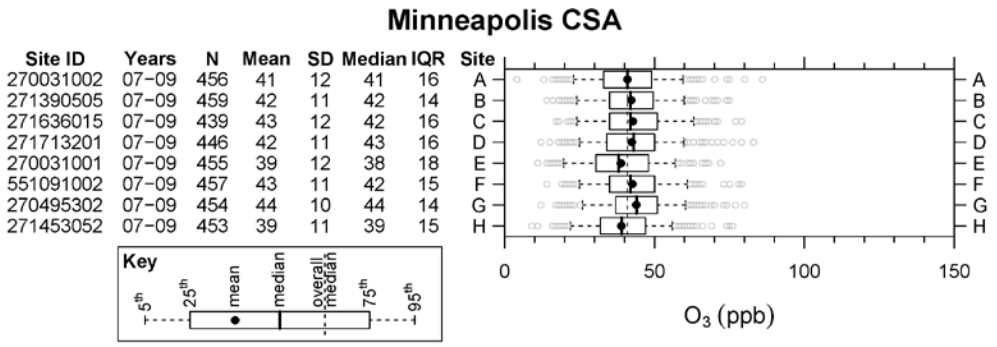


Figure 3-91 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Minneapolis CSA.

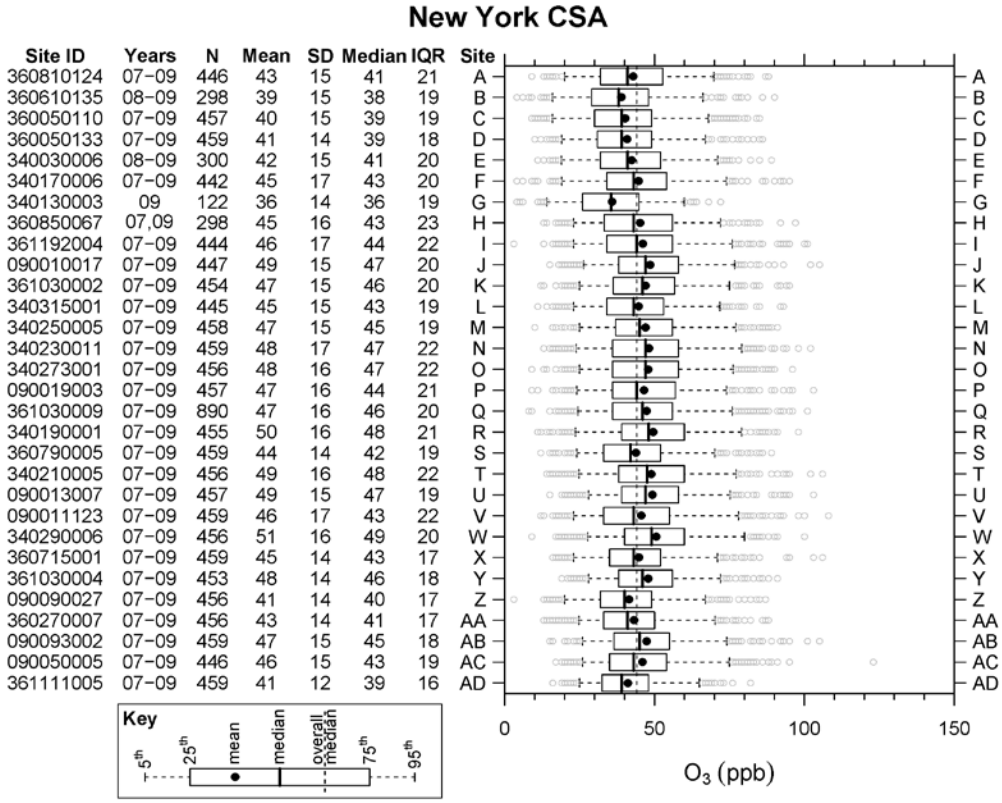


Figure 3-92 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the New York CSA.

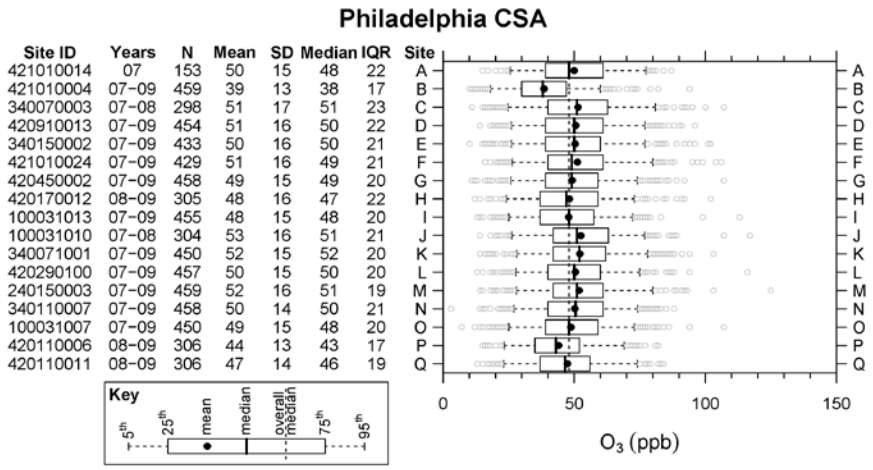


Figure 3-93 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Philadelphia CSA.

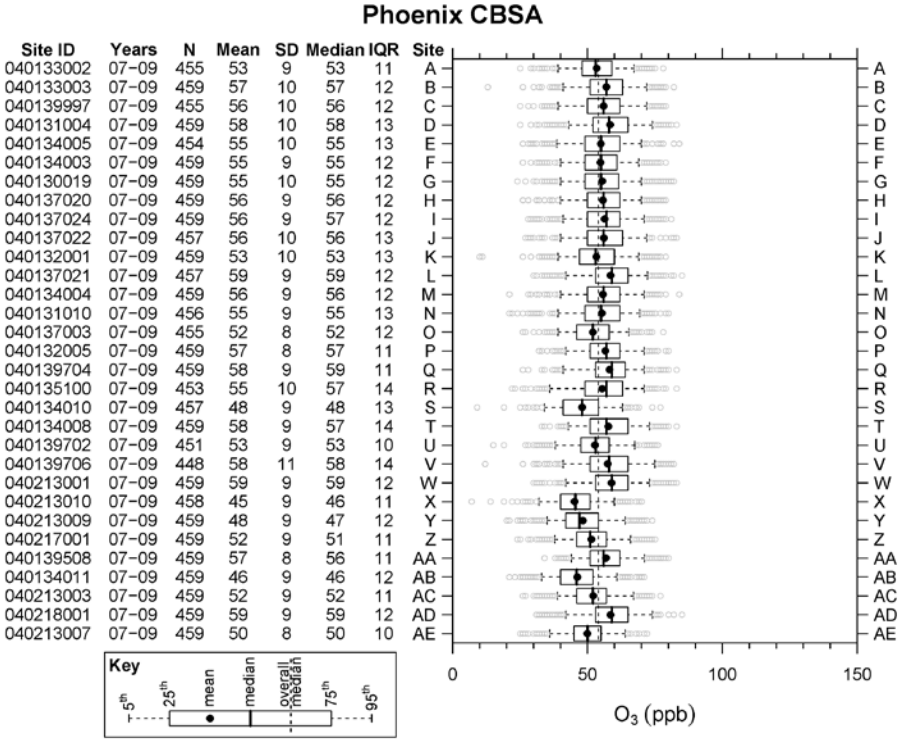


Figure 3-94 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Phoenix CBSA.

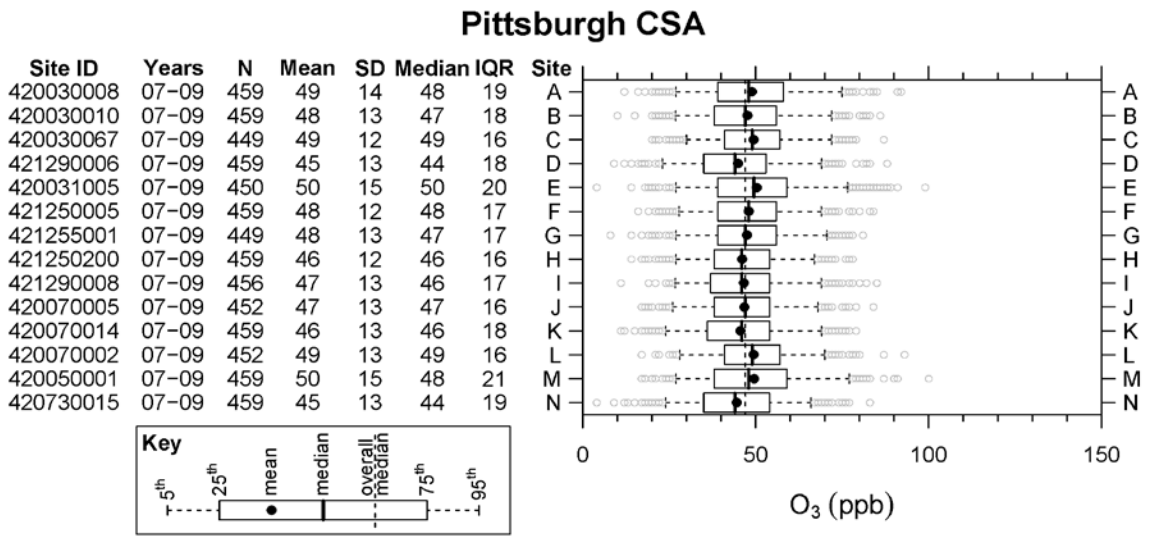


Figure 3-95 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Pittsburgh CSA.

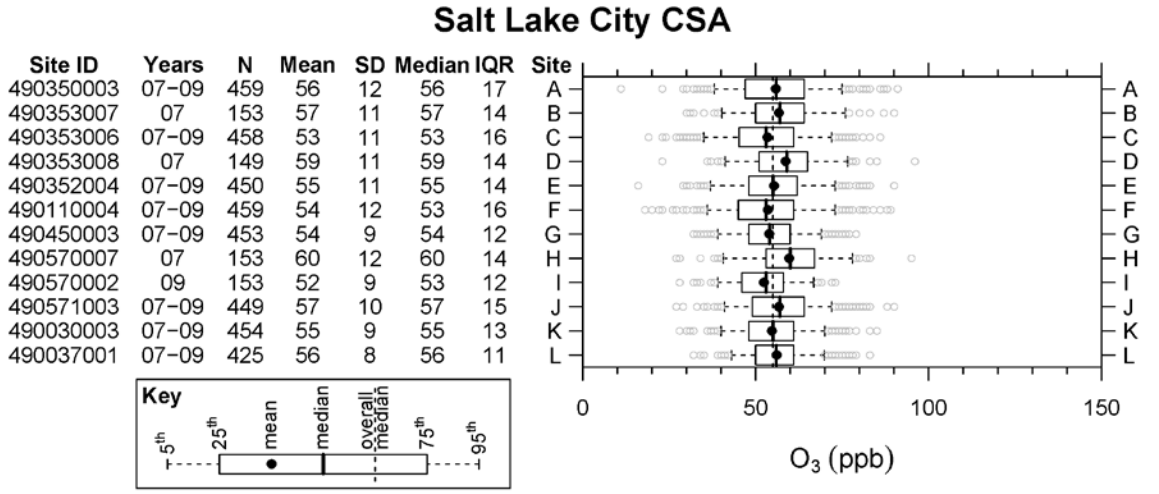


Figure 3-96 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Salt Lake City CSA.

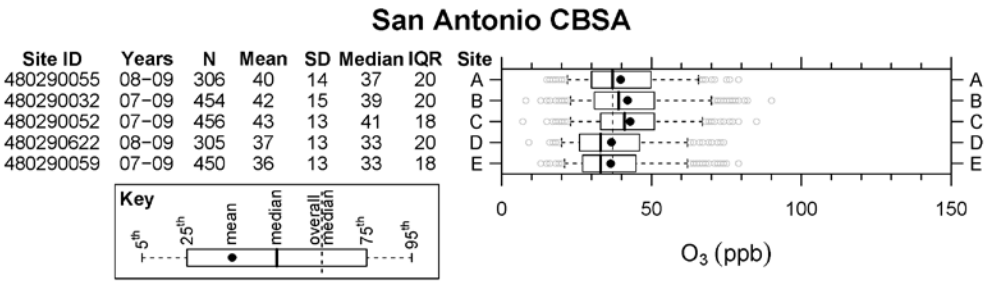


Figure 3-97 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the San Antonio CBSA.

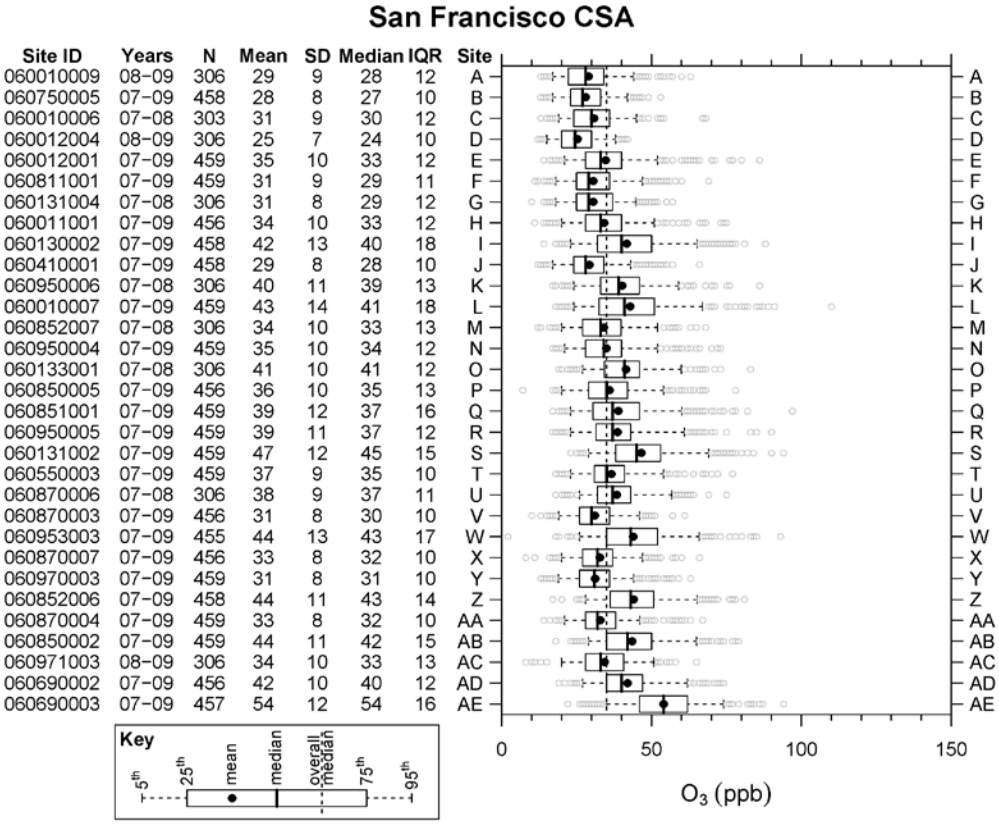


Figure 3-98 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the San Francisco CSA.

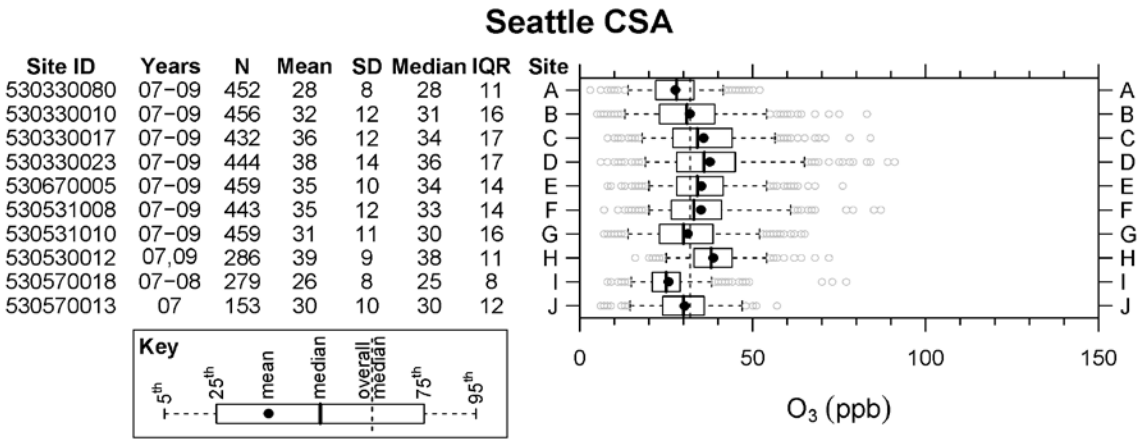


Figure 3-99 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Seattle CSA.

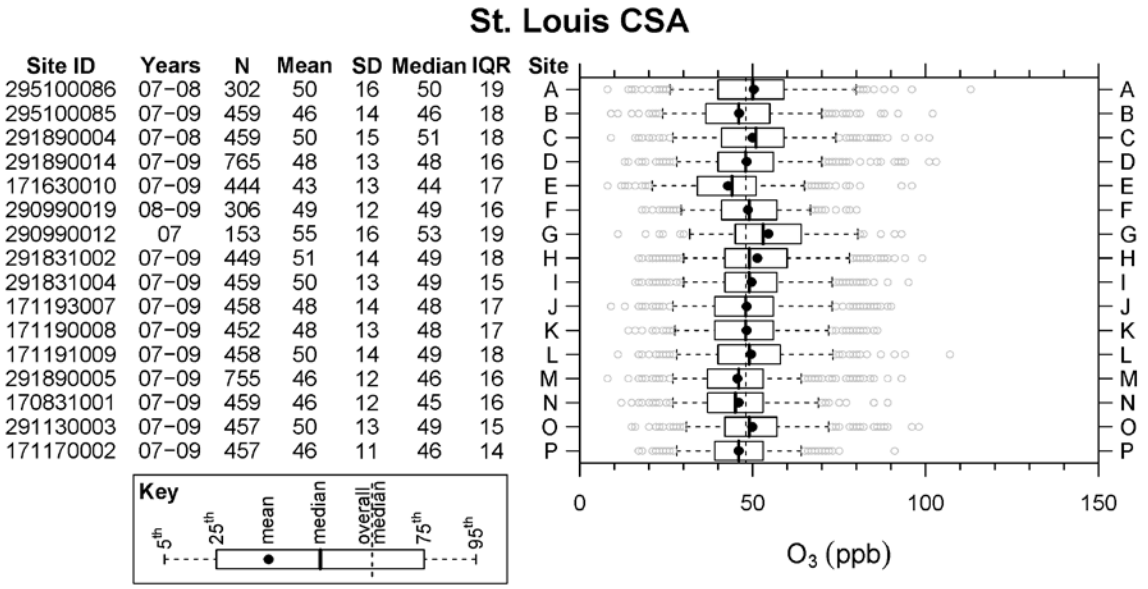
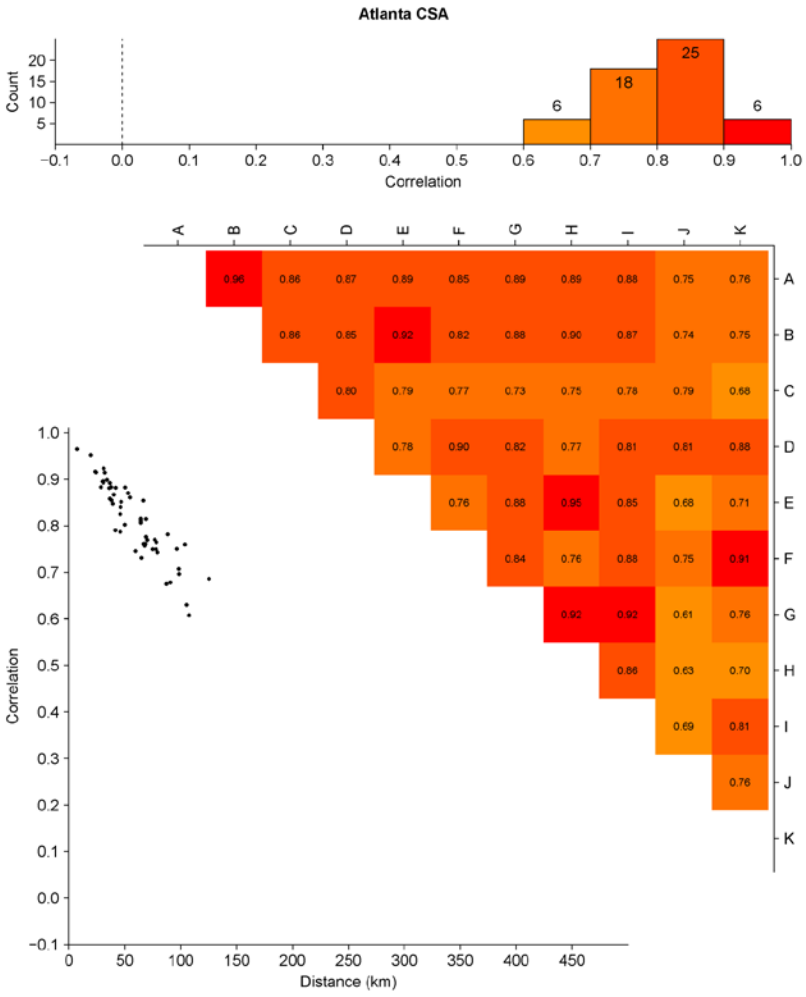


Figure 3-100 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the St. Louis CSA.

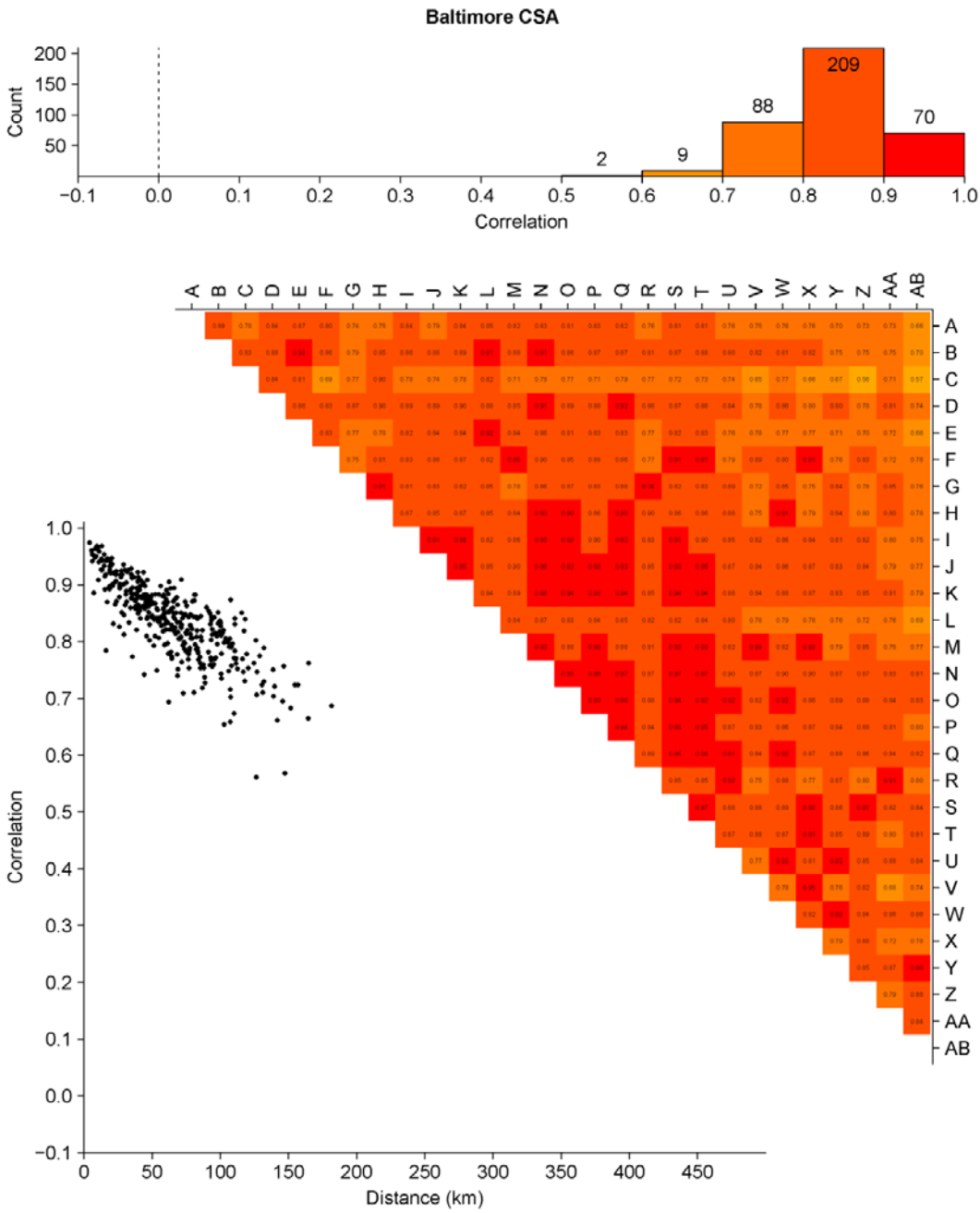
3.10.3 Ozone Concentration Relationships for the Urban Focus Cities

This section contains histograms and contour matrices of the Pearson correlation coefficient (R) and the coefficient of divergence (COD) between 8-h daily max O_3 concentrations from each monitor pair within the 20 urban focus cities discussed in Section 3.6.2.1. These figures also contain scatter plots of R and COD as a function of straight-line distance between monitor pairs.



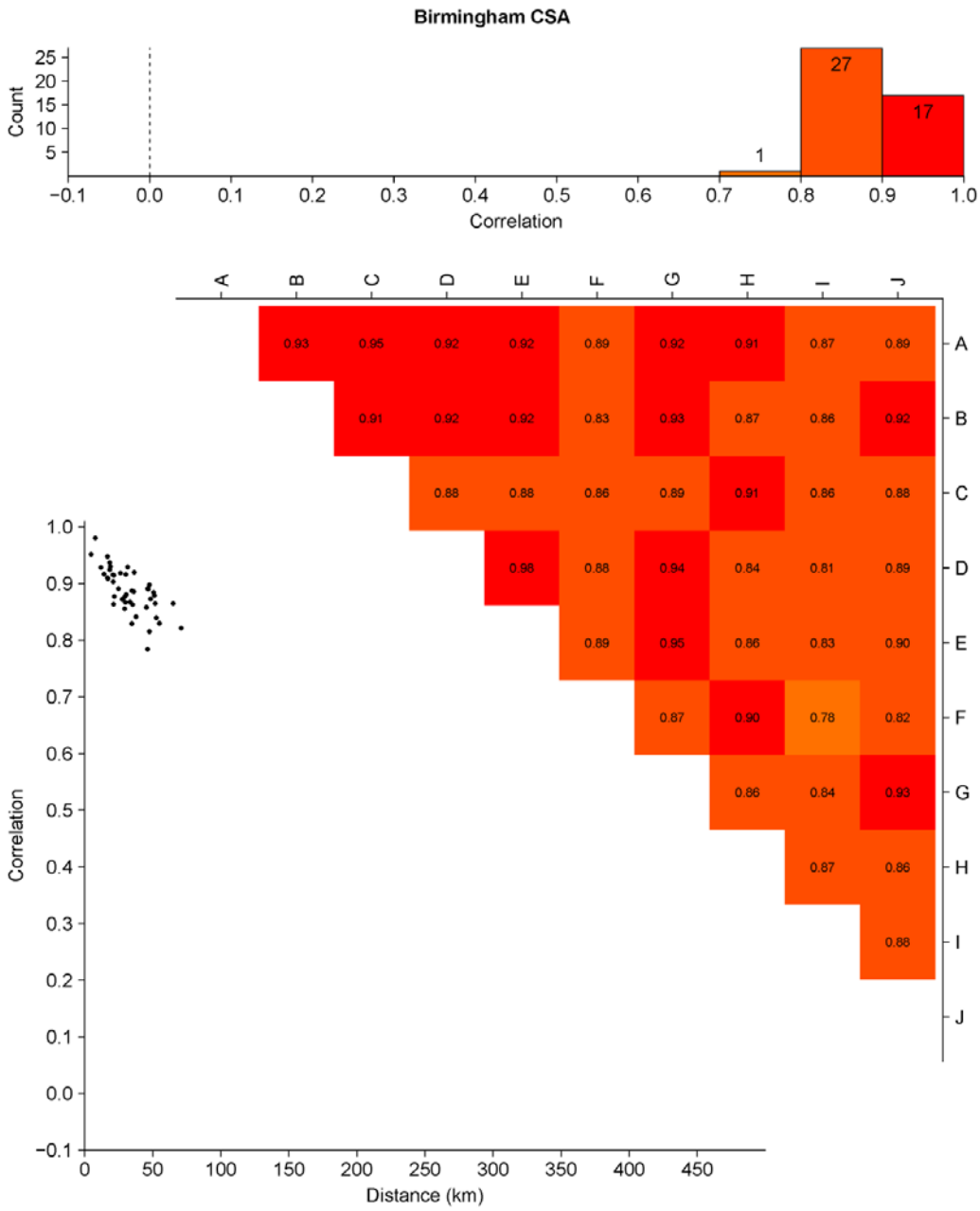
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-101 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Atlanta CSA.



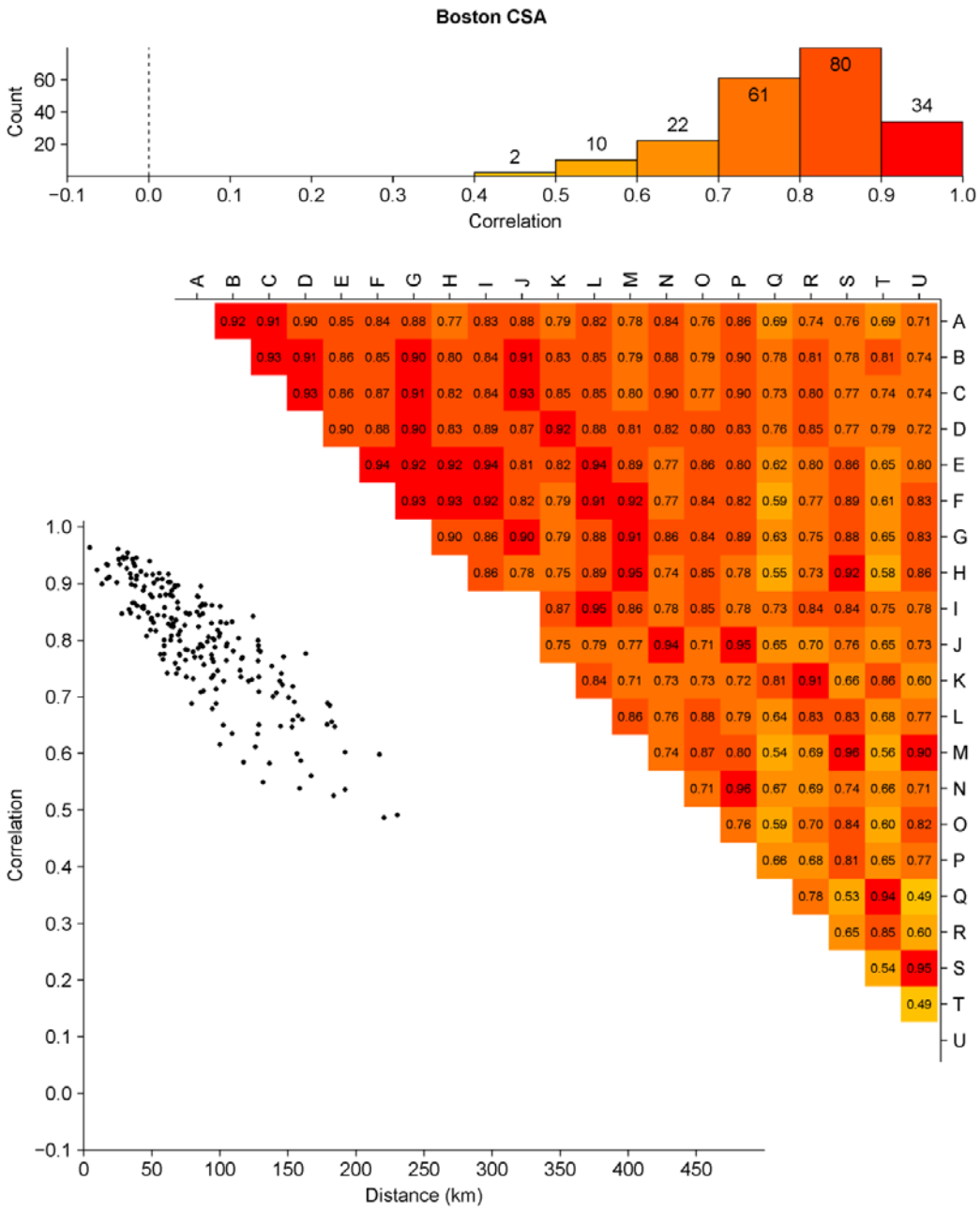
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-102 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Baltimore CSA.



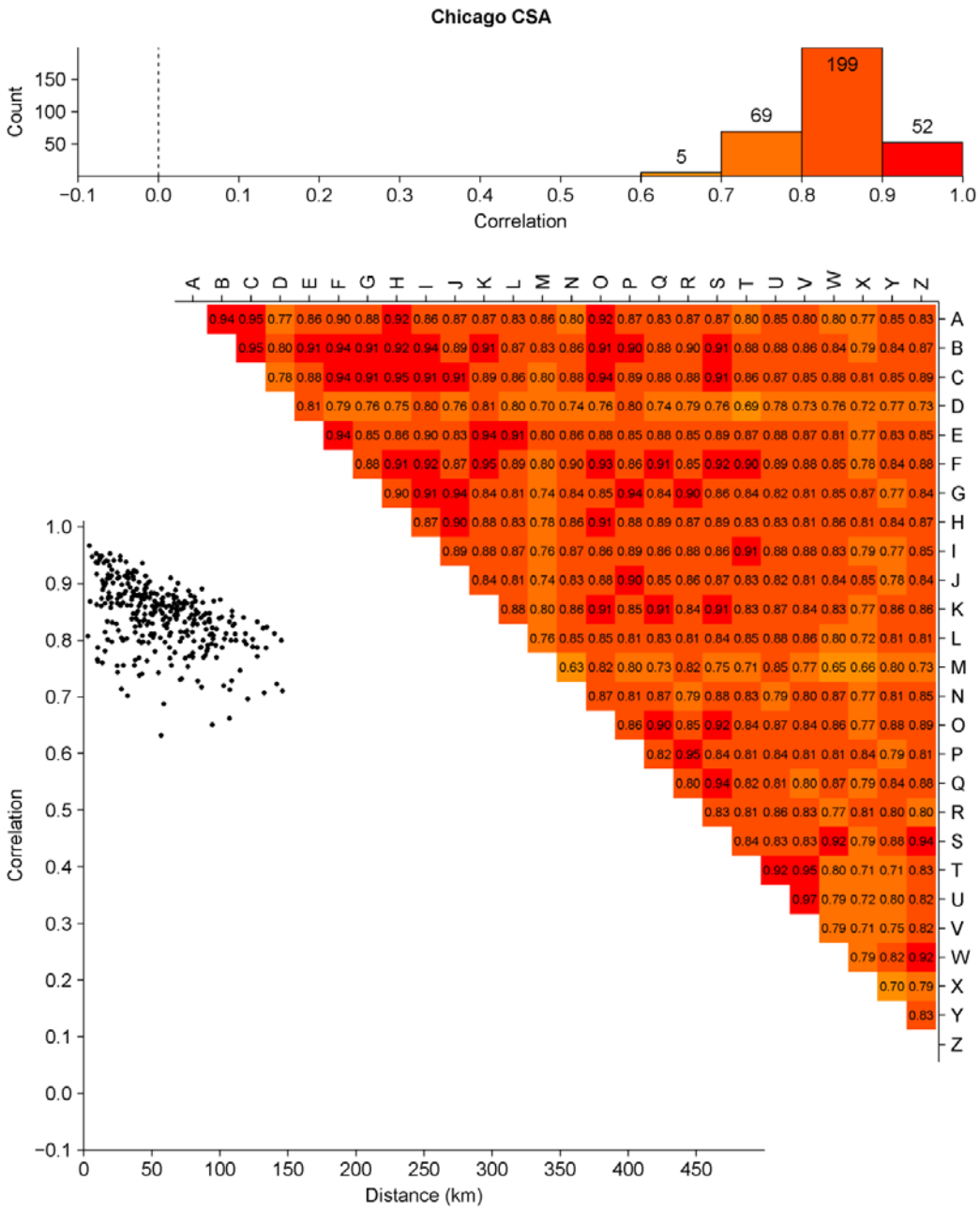
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-103 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Birmingham CSA.



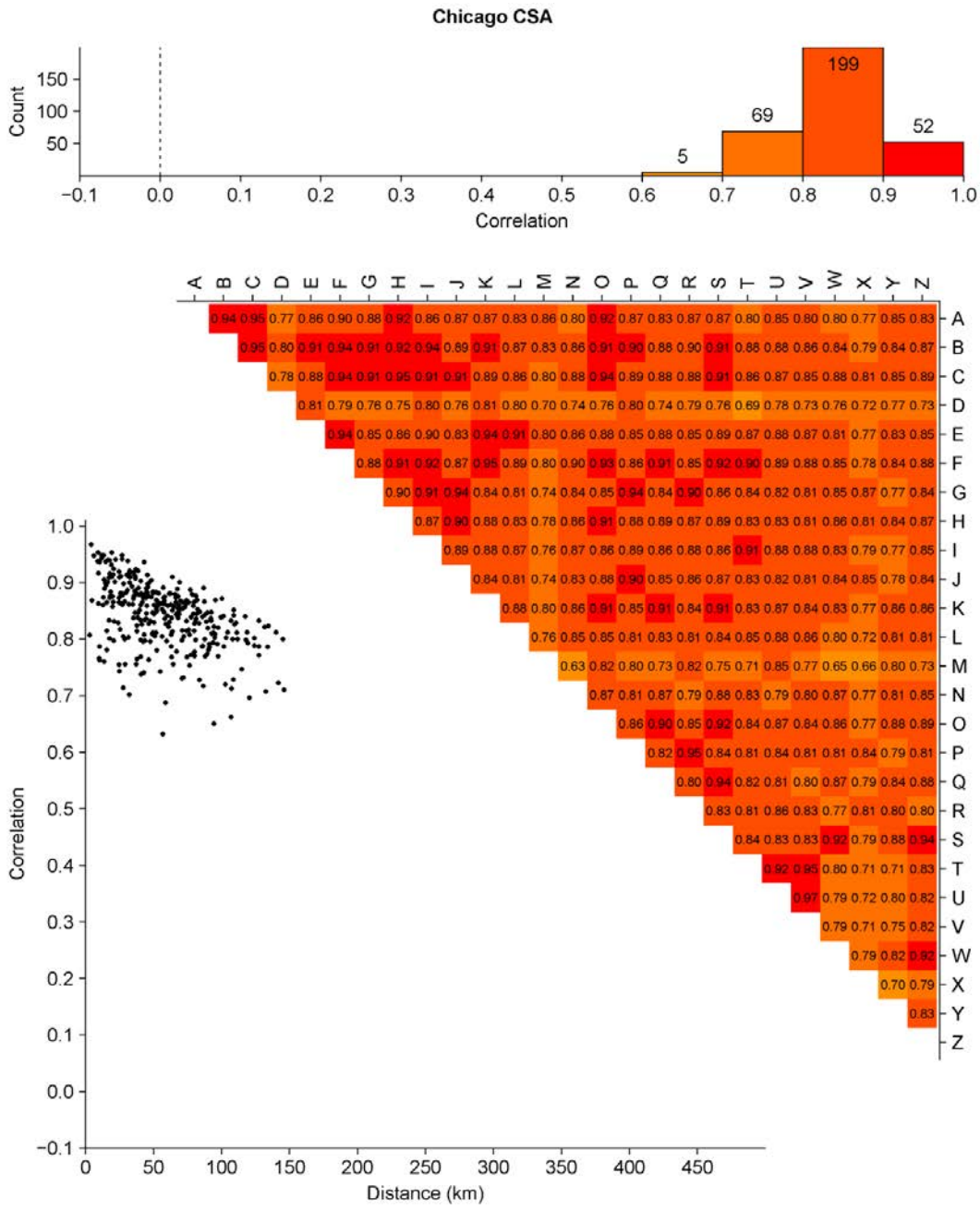
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-104 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Boston CSA.



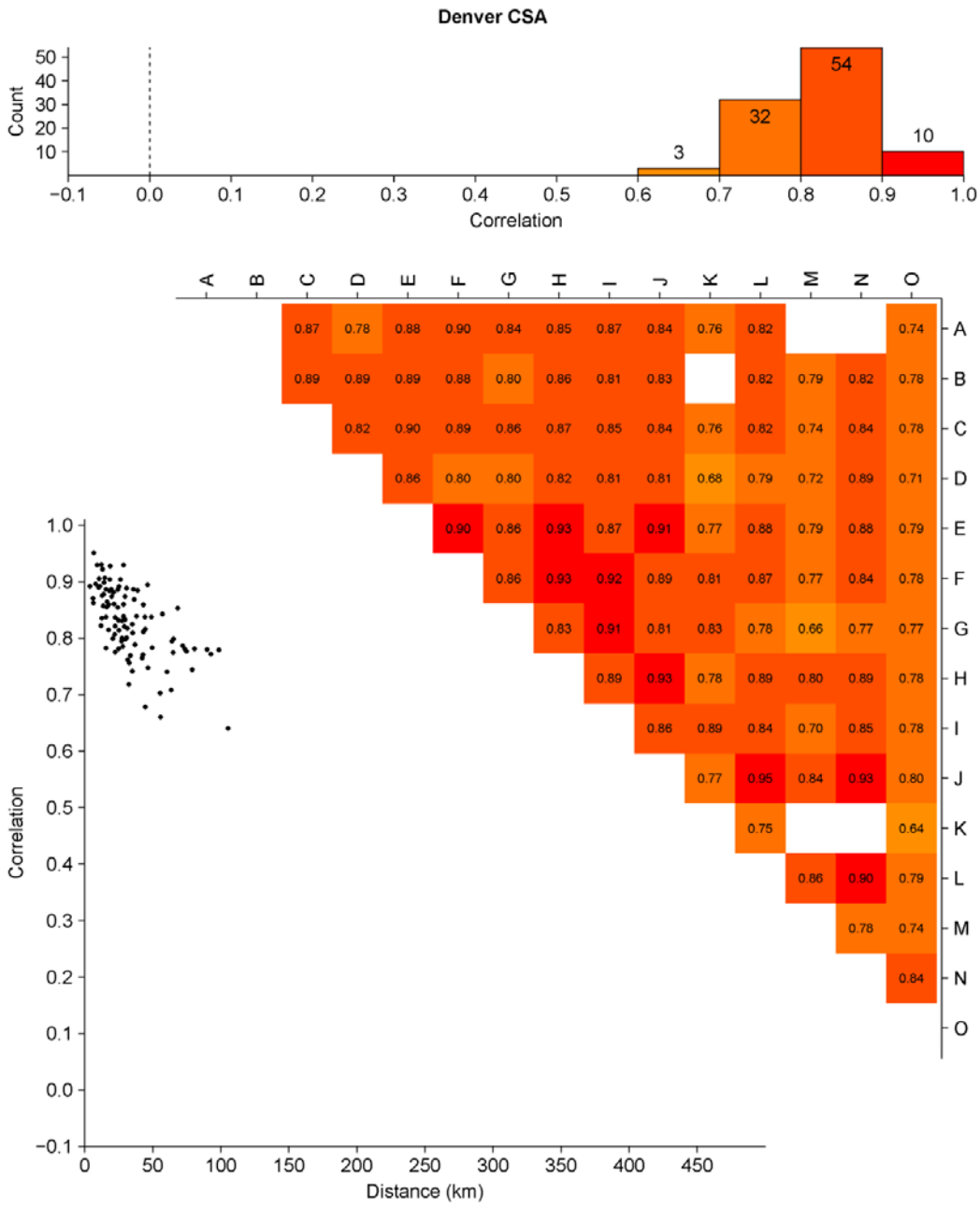
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-105 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Chicago CSA.



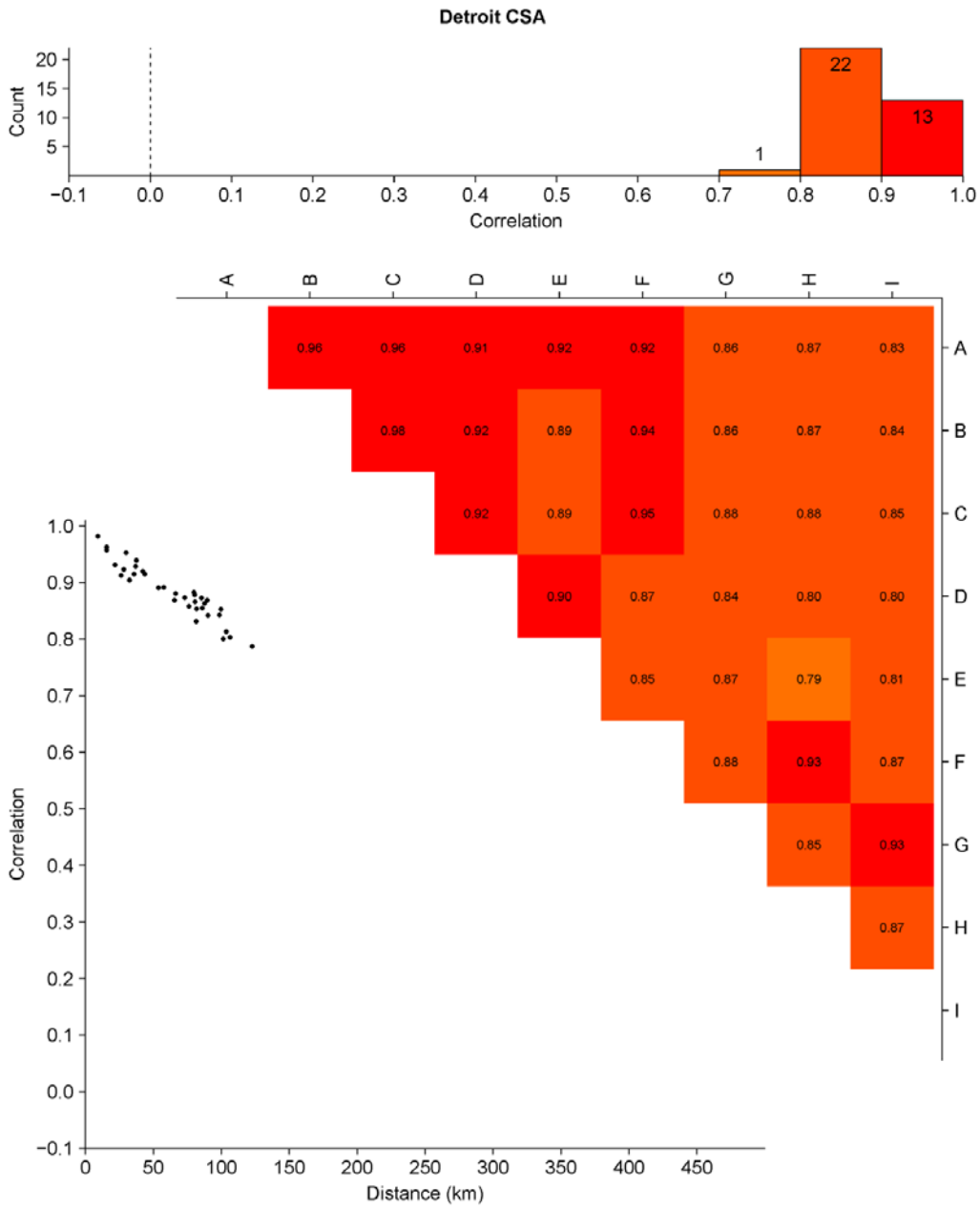
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-106 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Dallas CSA.



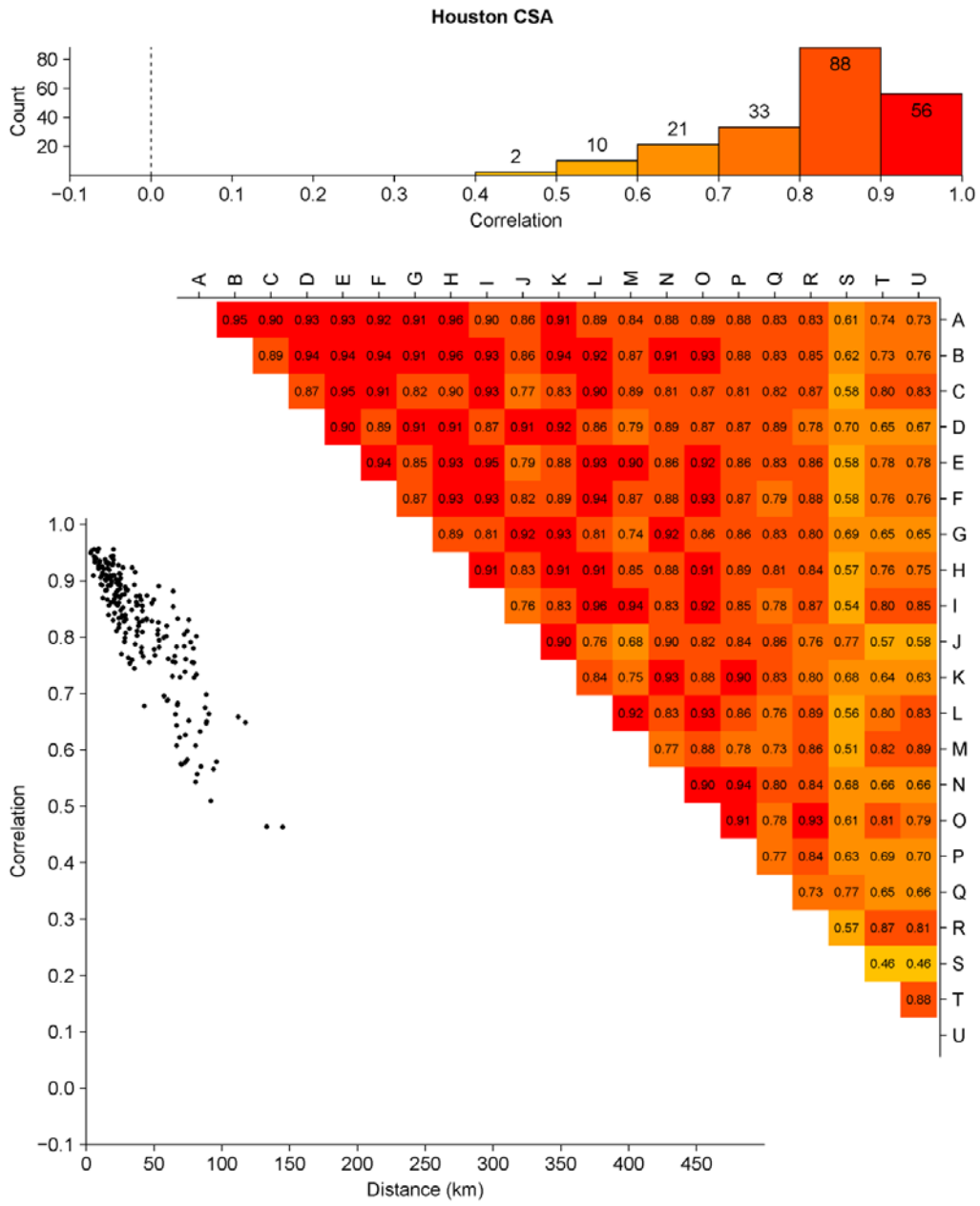
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-107 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Denver CSA.



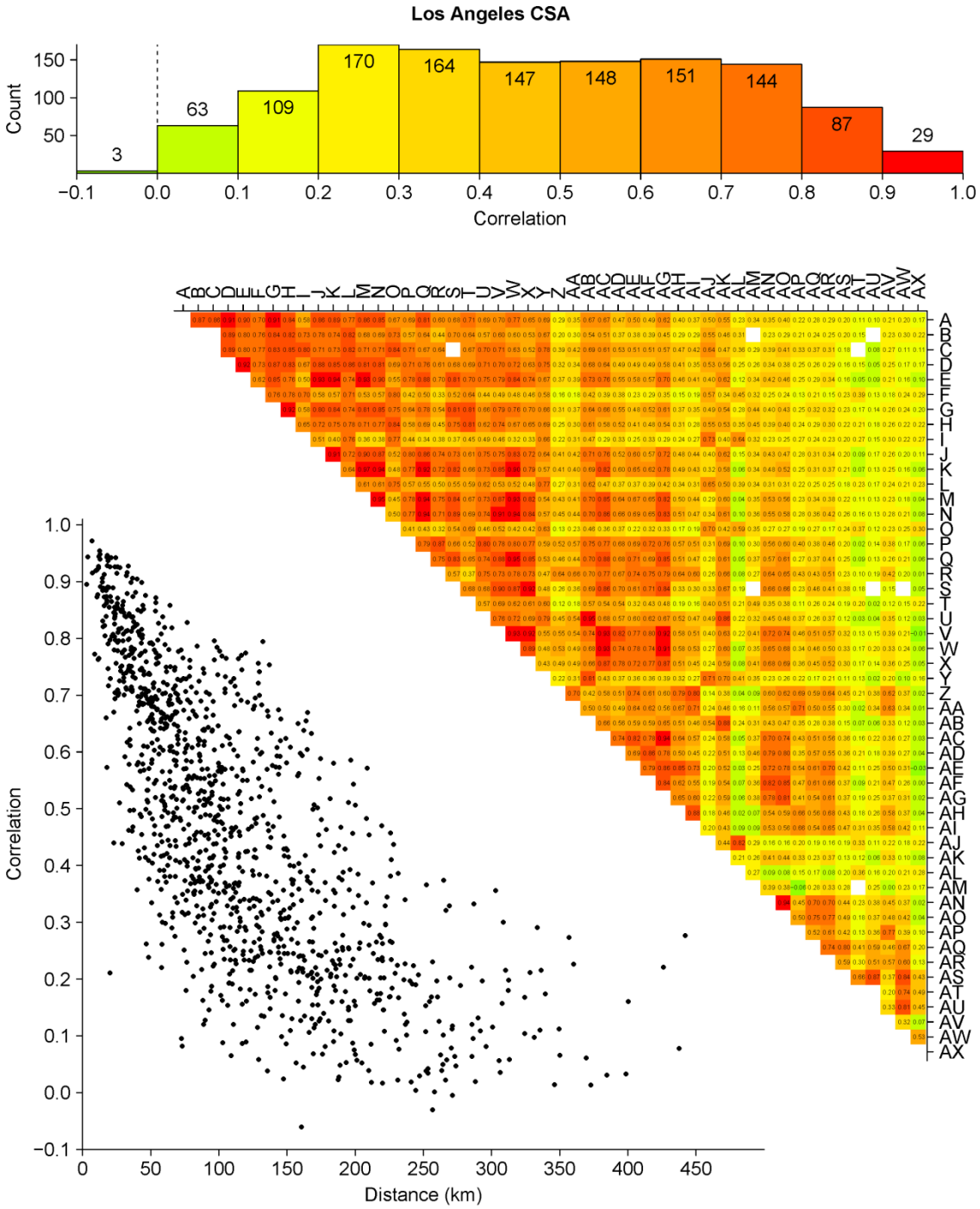
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-108 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Detroit CSA.



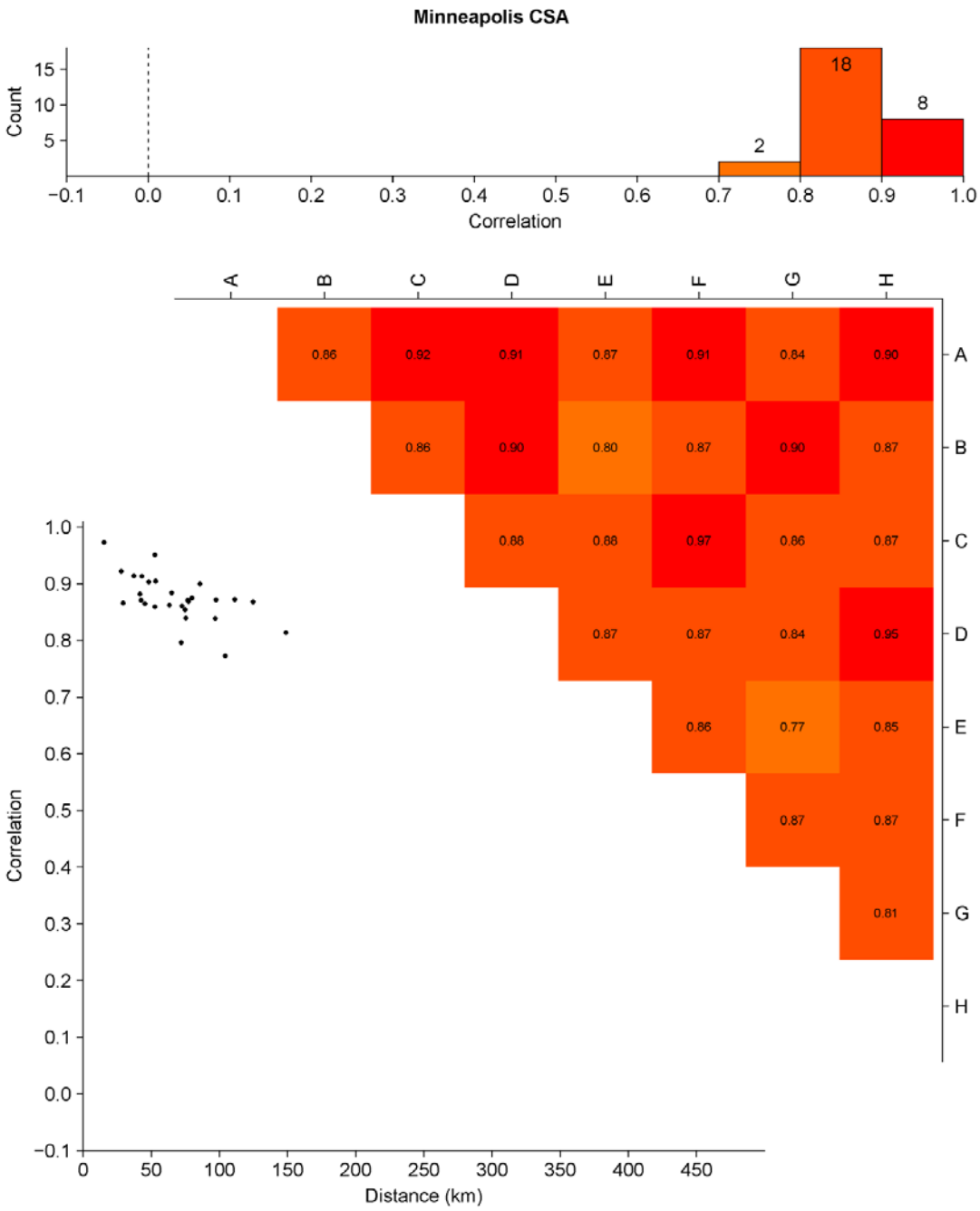
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-109 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Houston CSA.



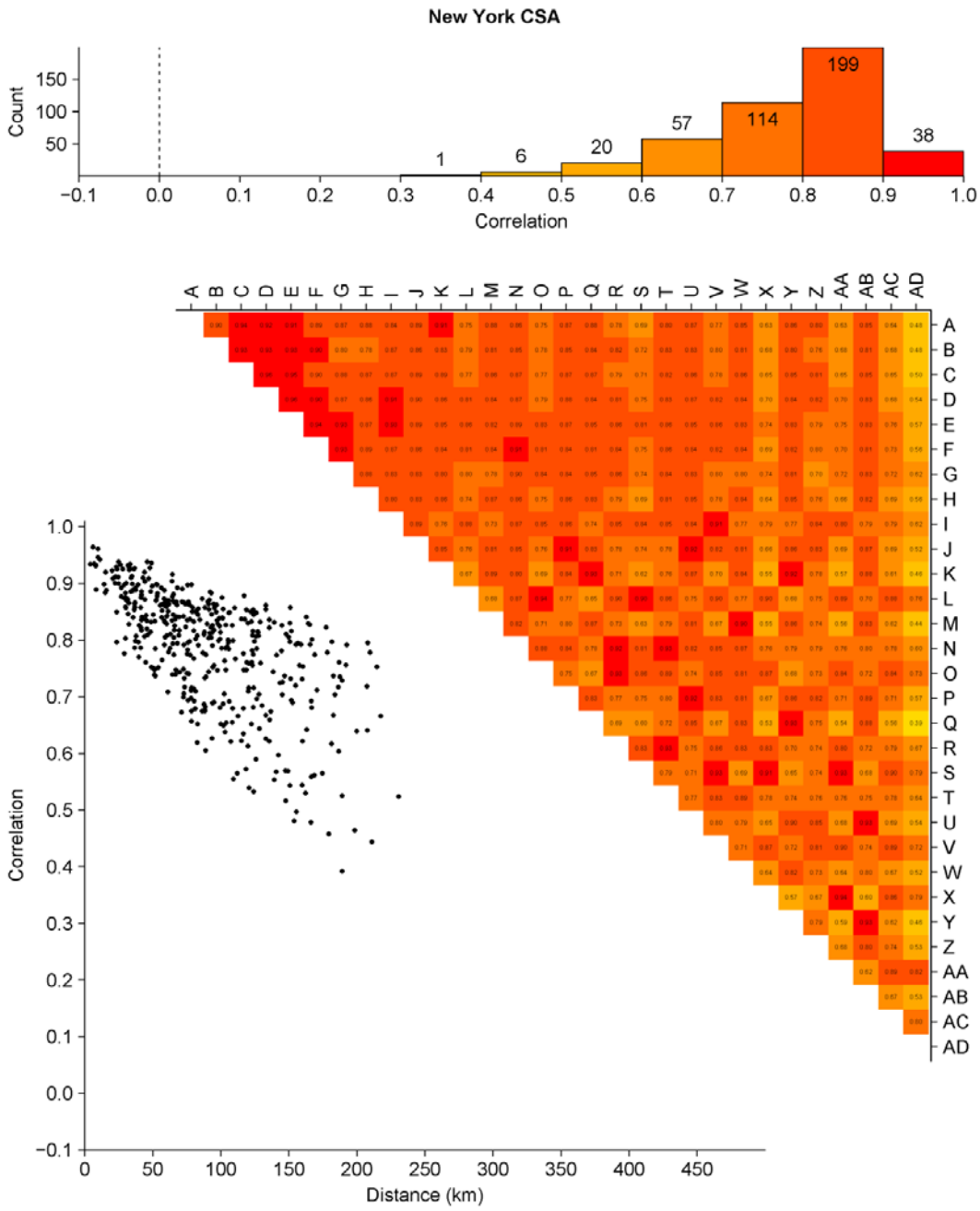
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-110 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Los Angeles CSA.



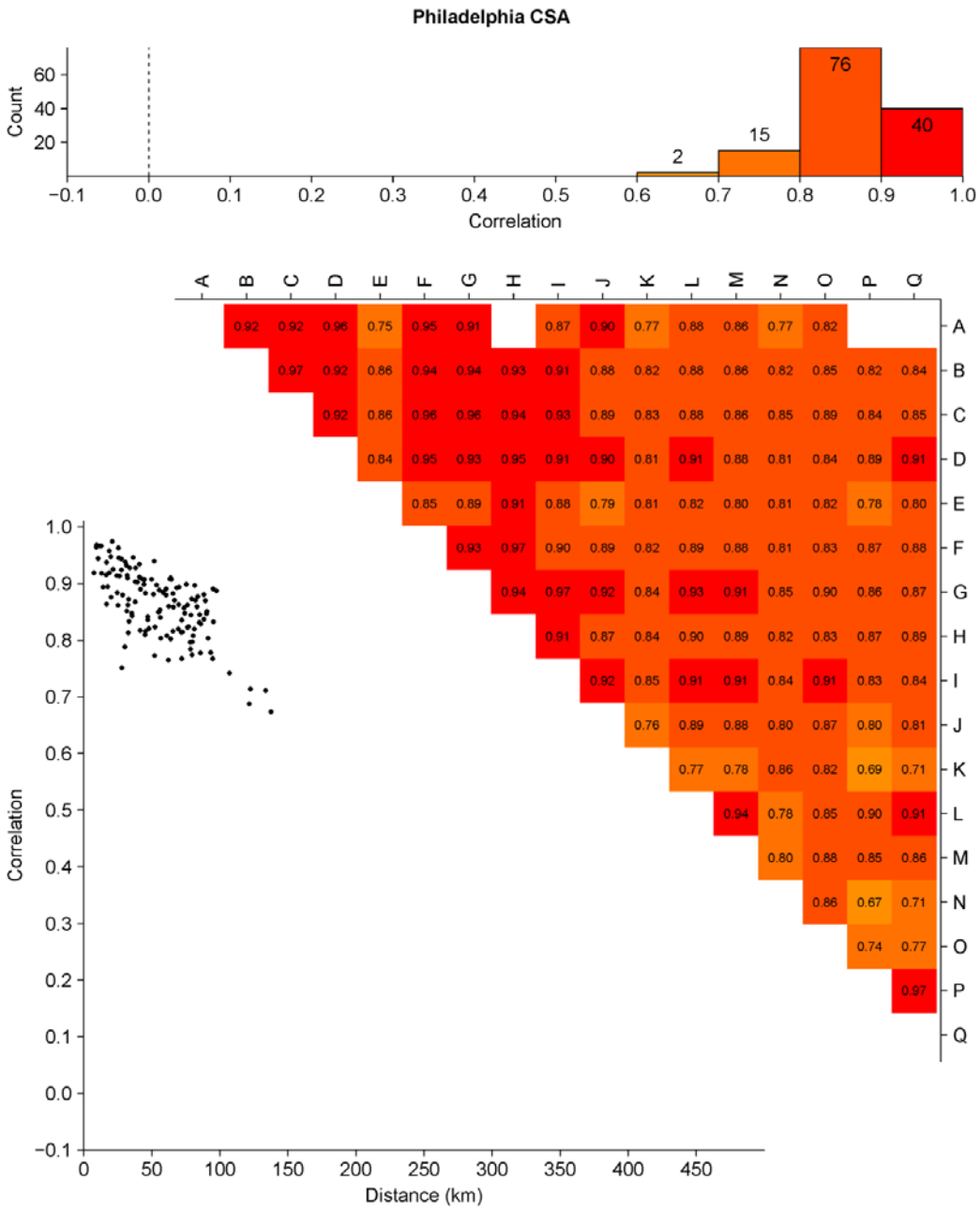
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-111 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Minneapolis CSA.



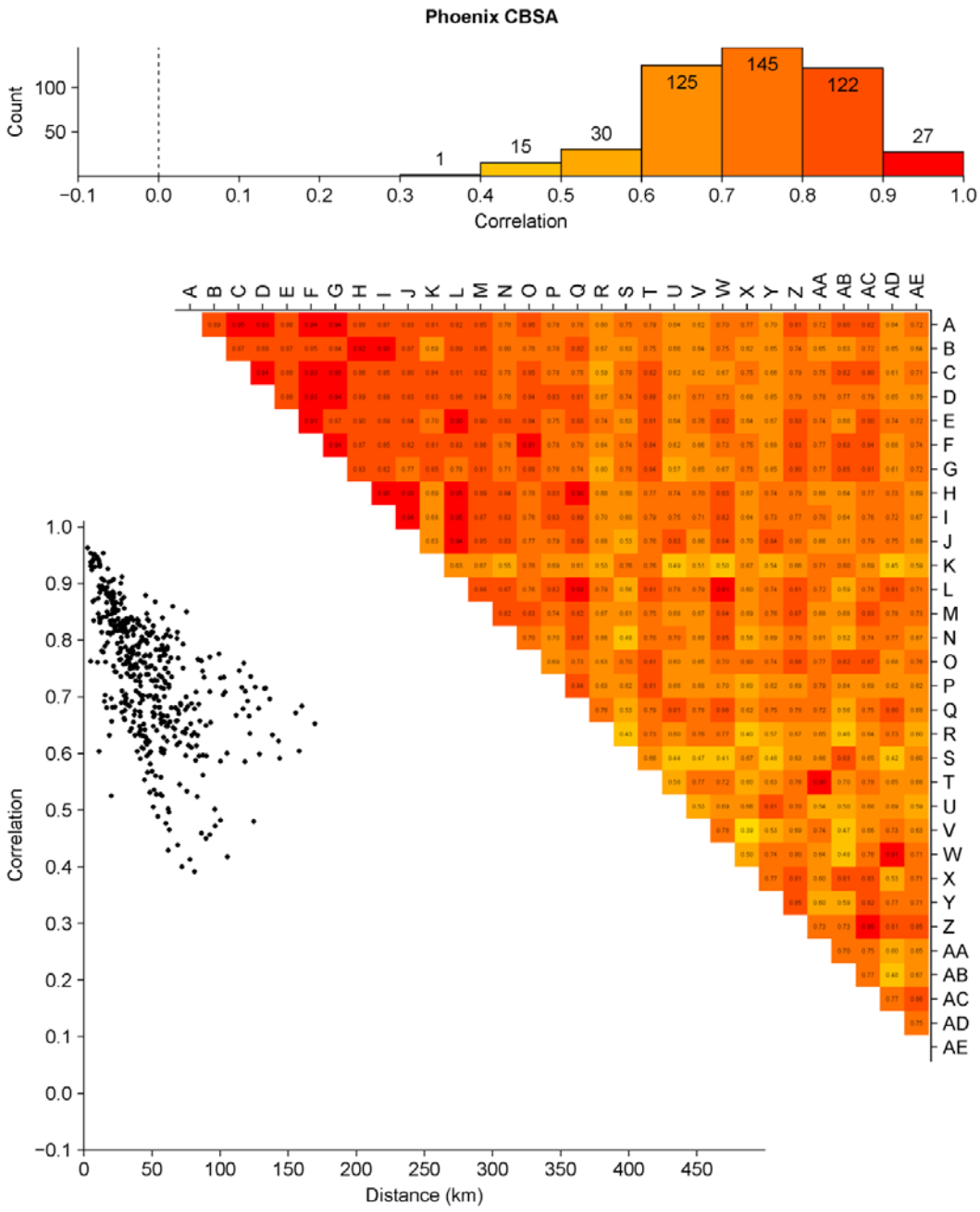
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-112 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the New York CSA.



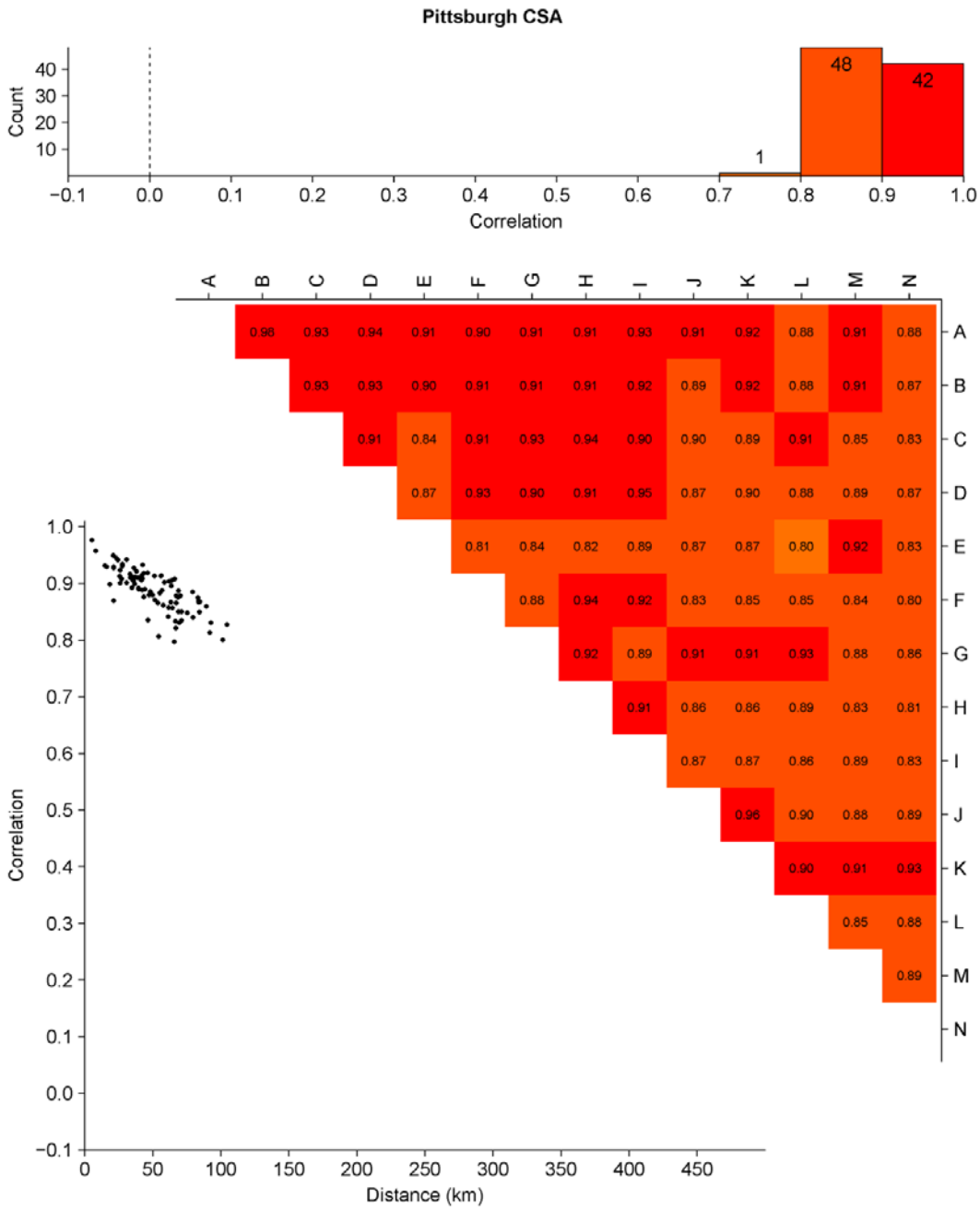
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-113 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Philadelphia CSA.



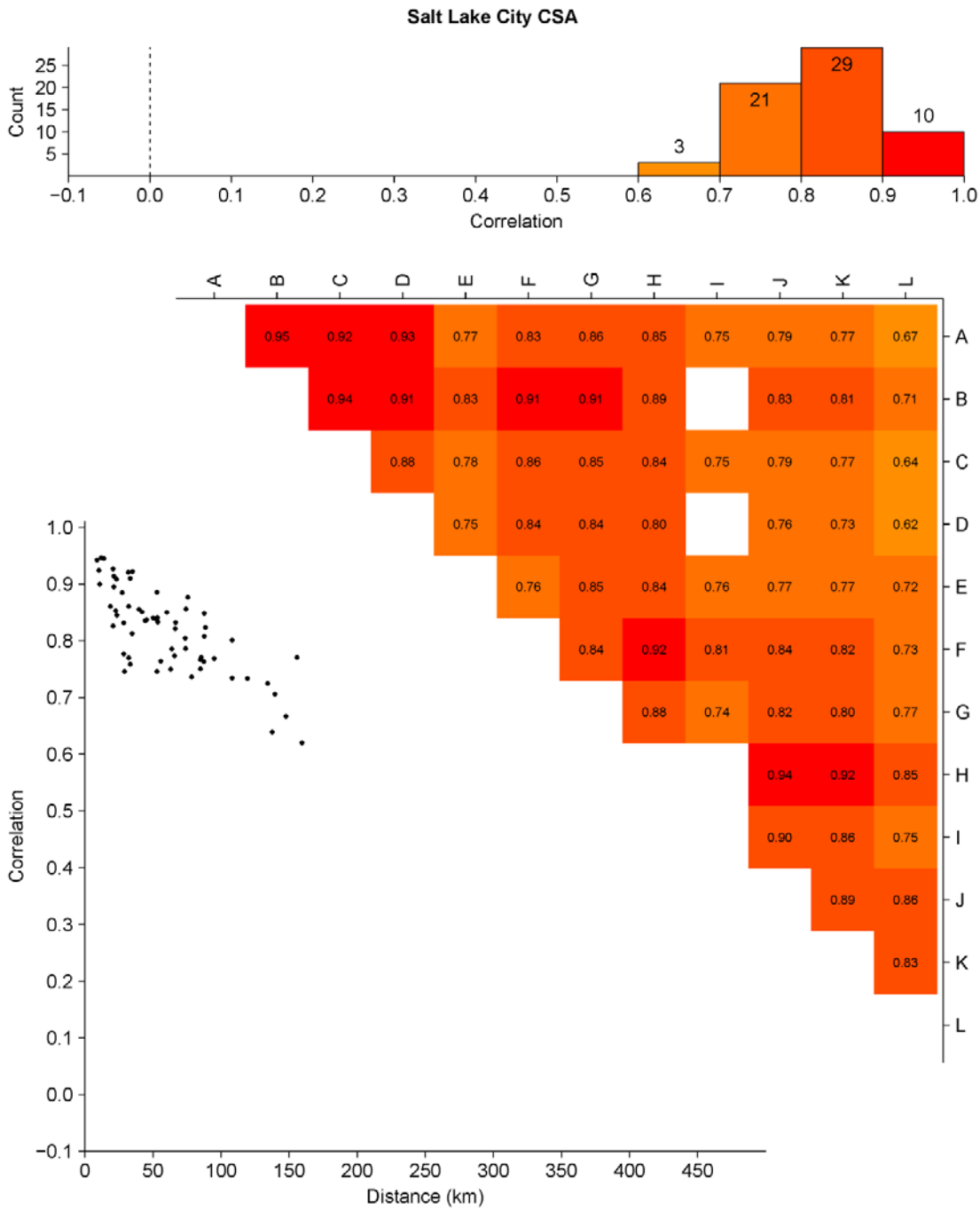
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-114 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Phoenix CBSA.



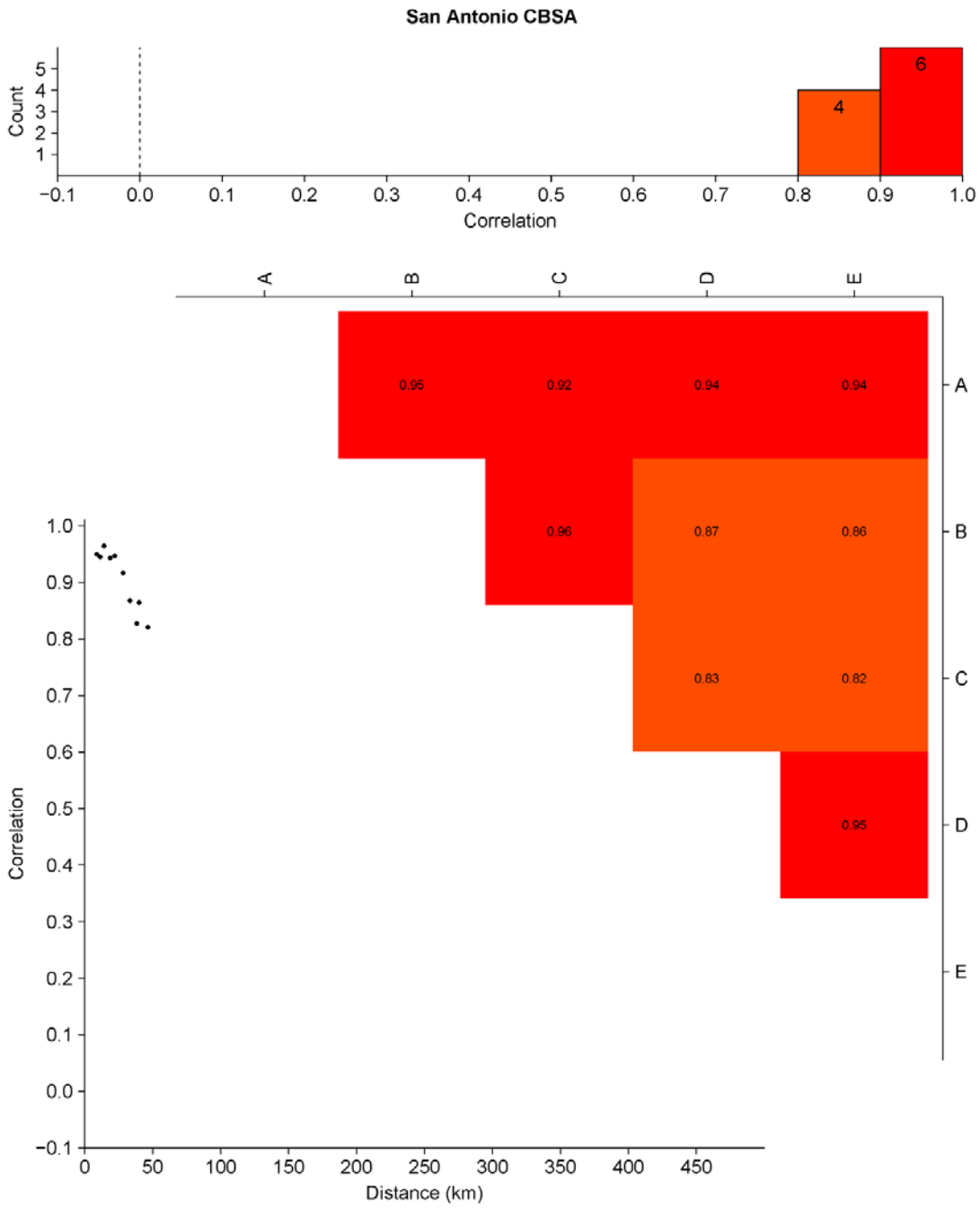
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-115 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Pittsburgh CSA.



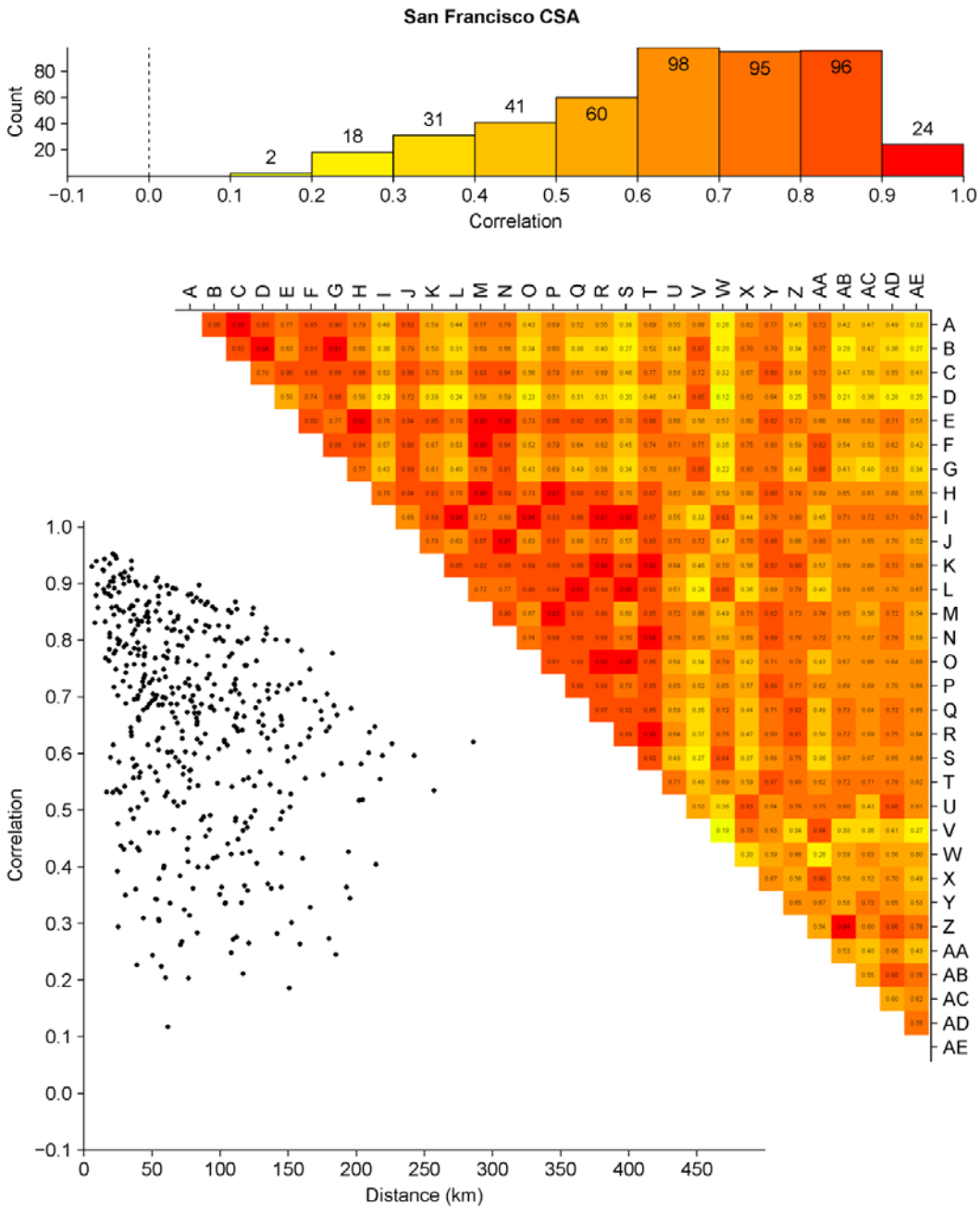
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-116 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Salt Lake City CSA.



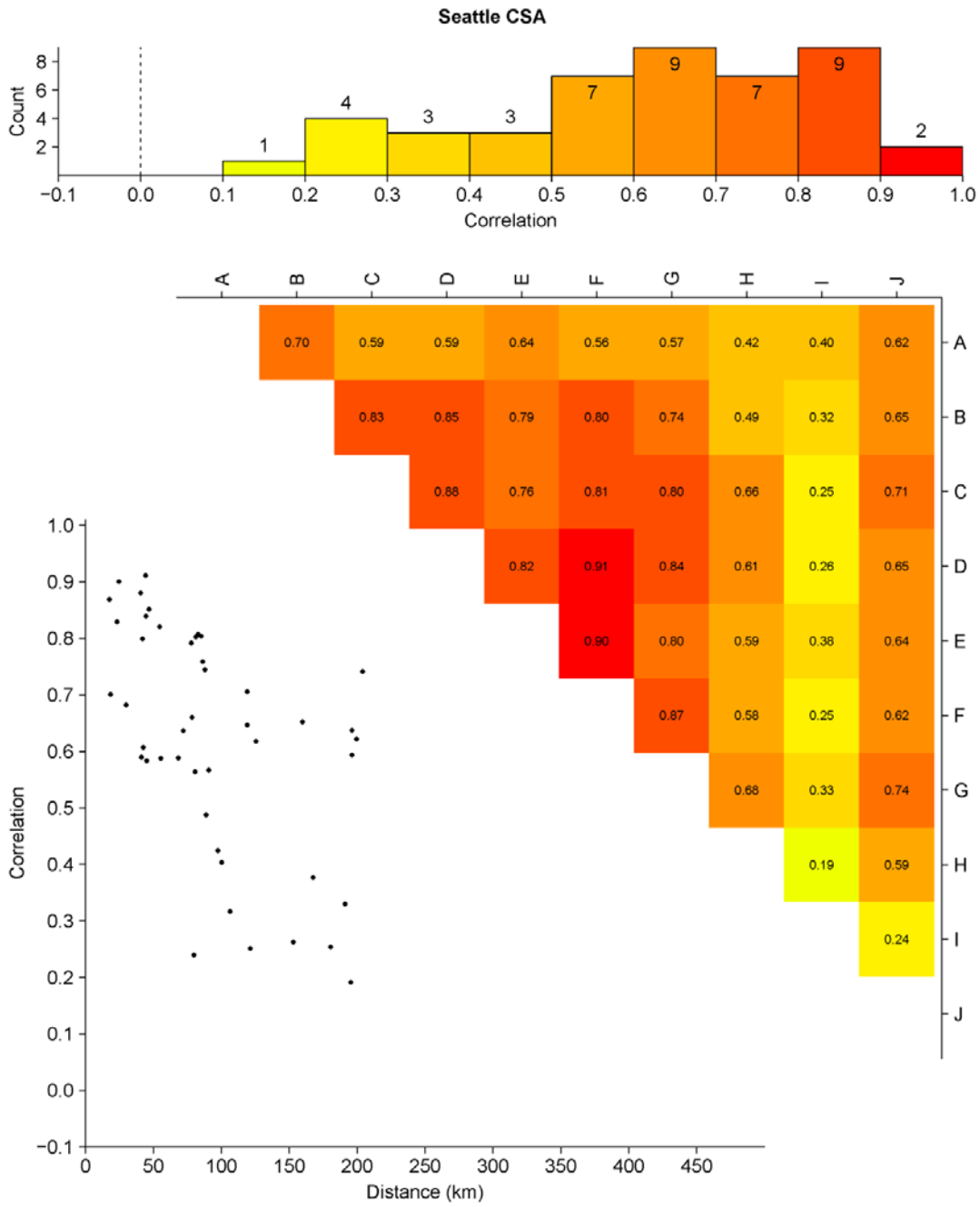
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-117 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the San Antonio CBSA.



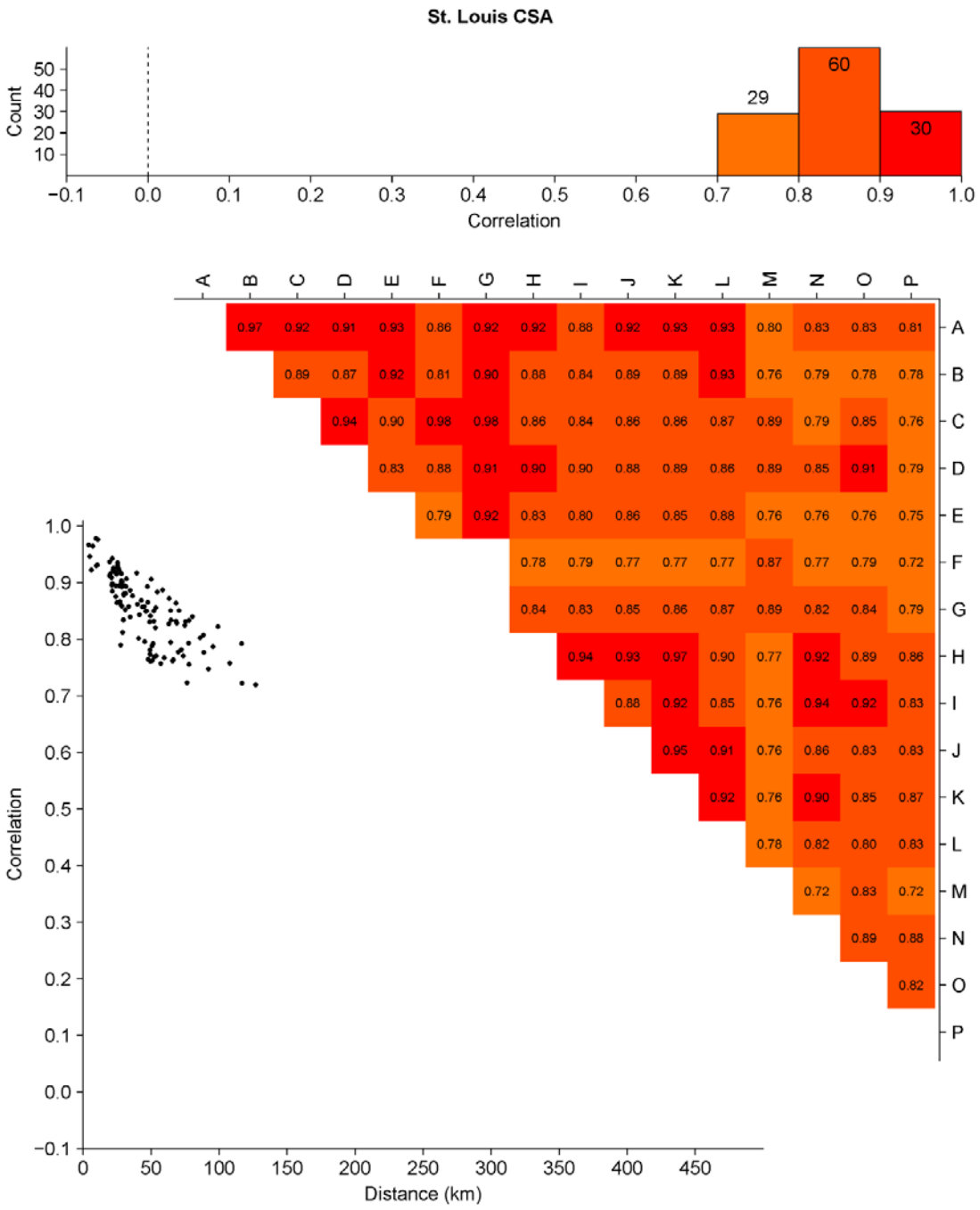
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-118 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the San Francisco CSA. of R.



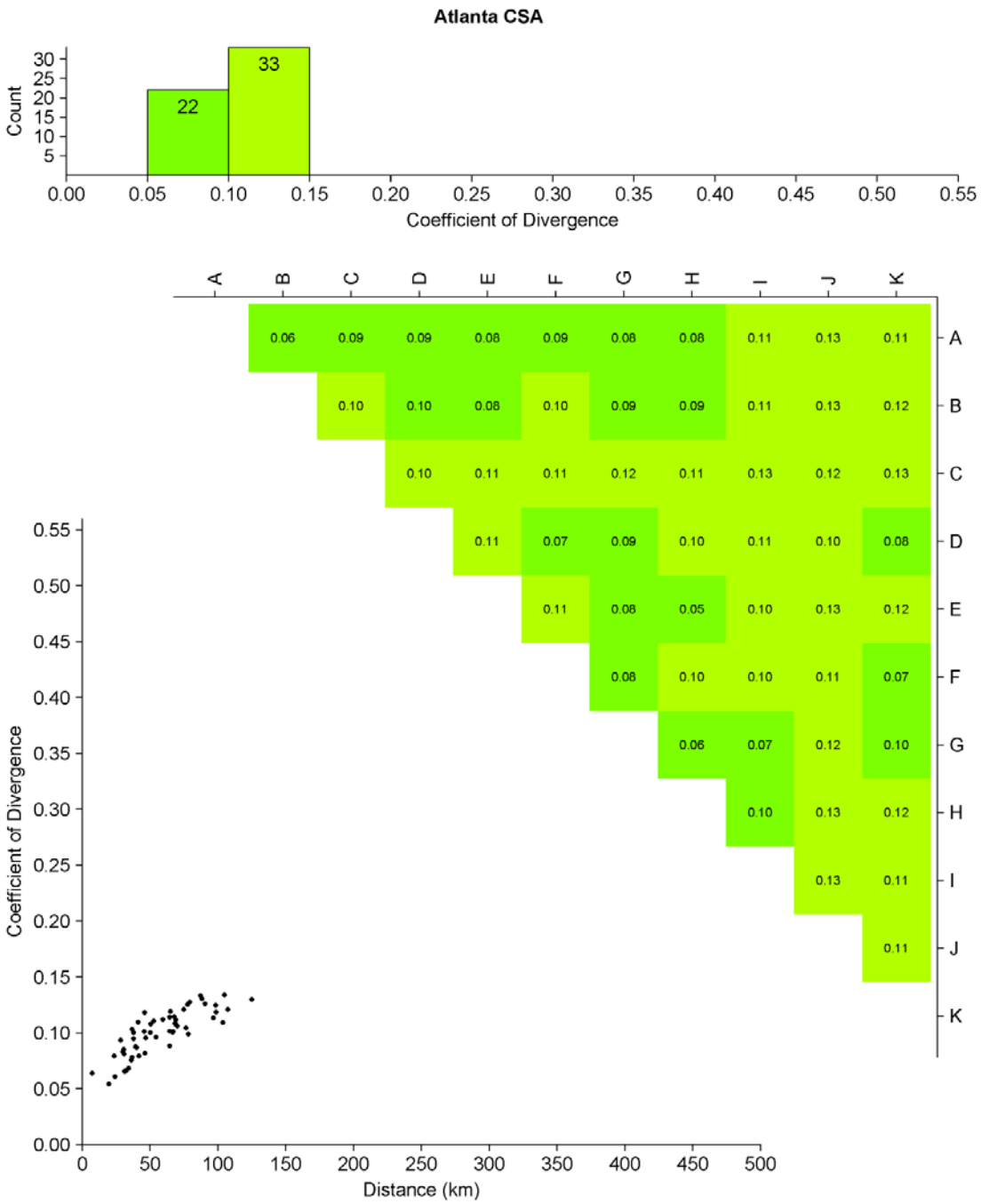
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-119 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Seattle CSA.



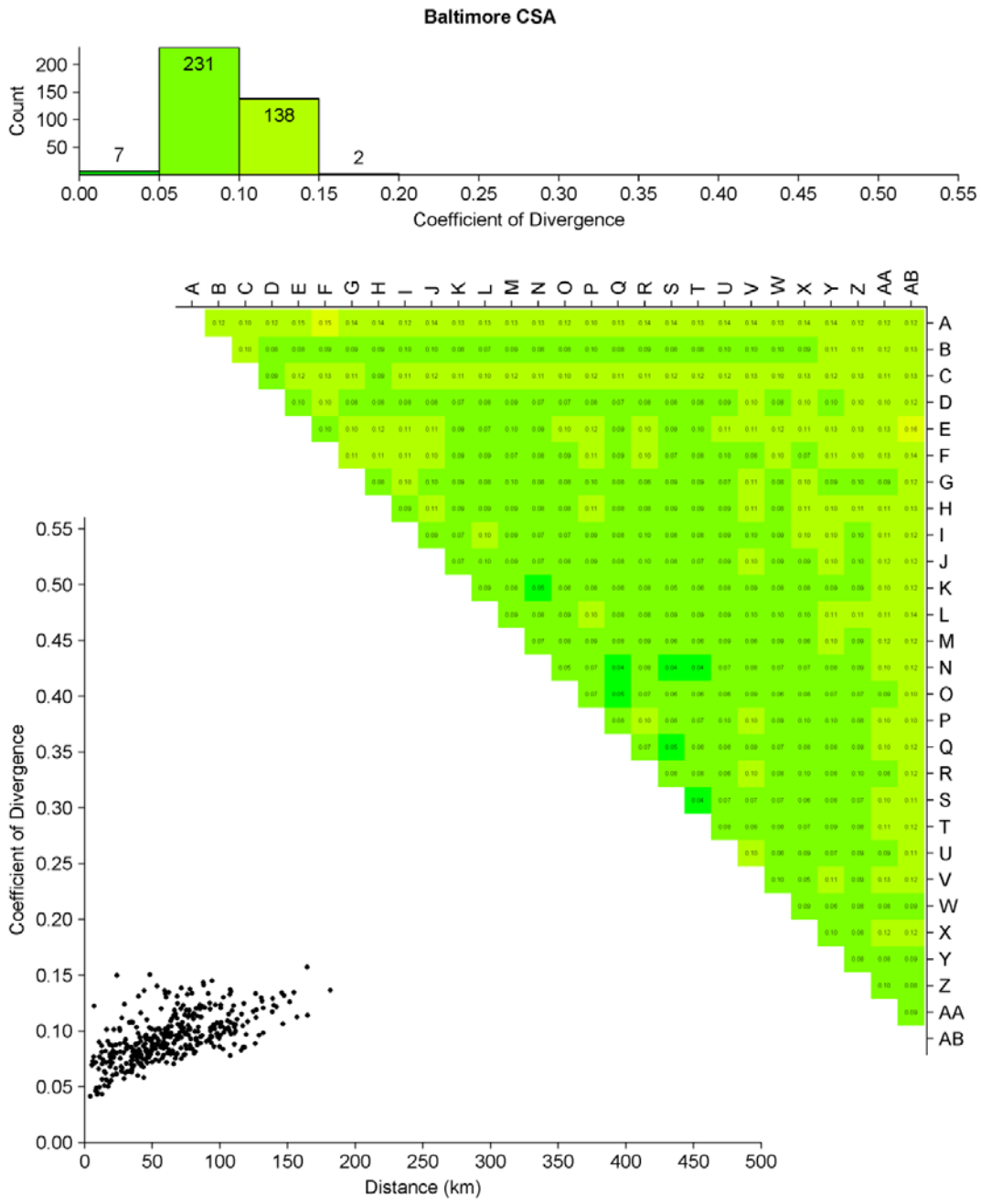
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-120 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the St. Louis CSA.



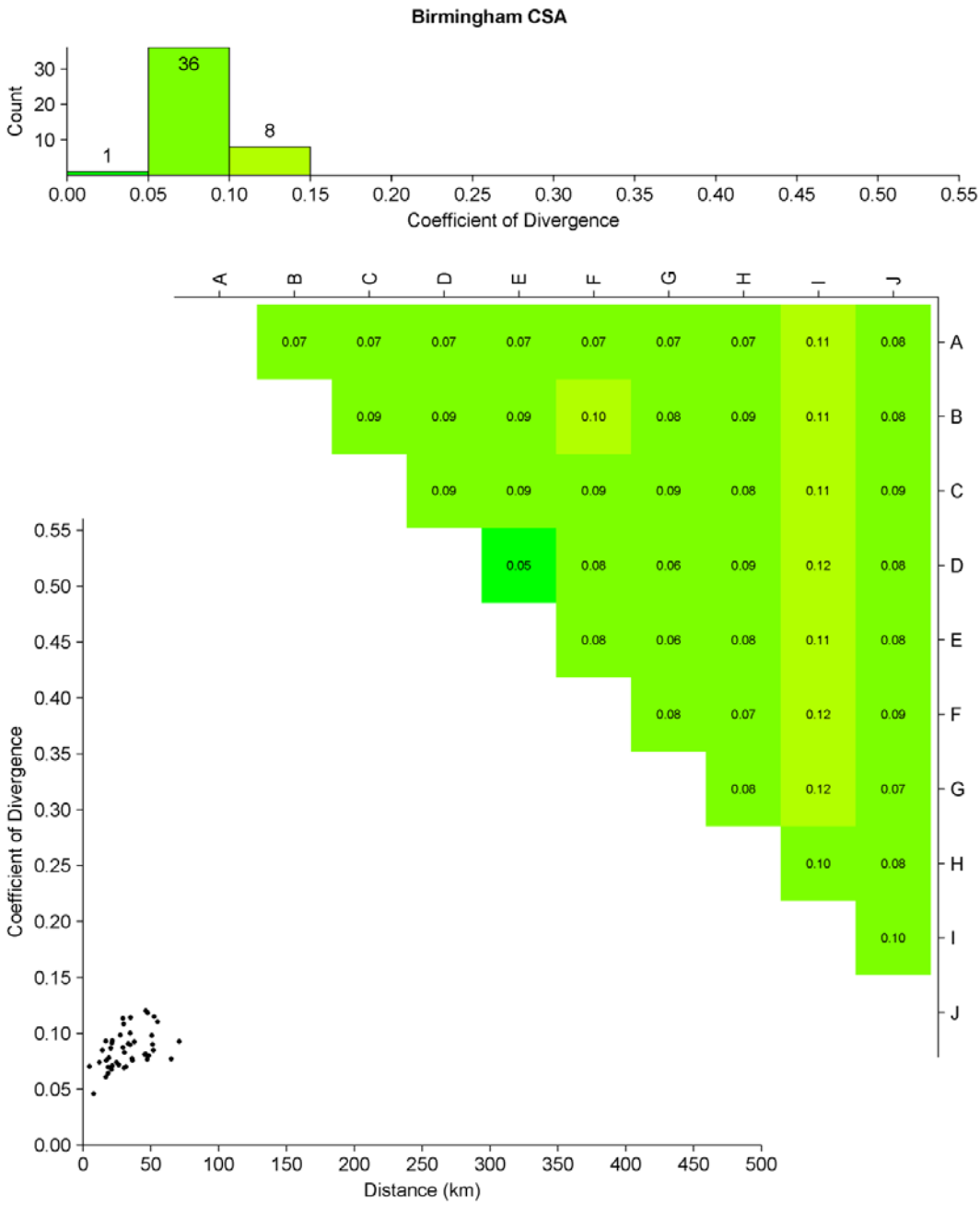
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-121 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Atlanta CSA.



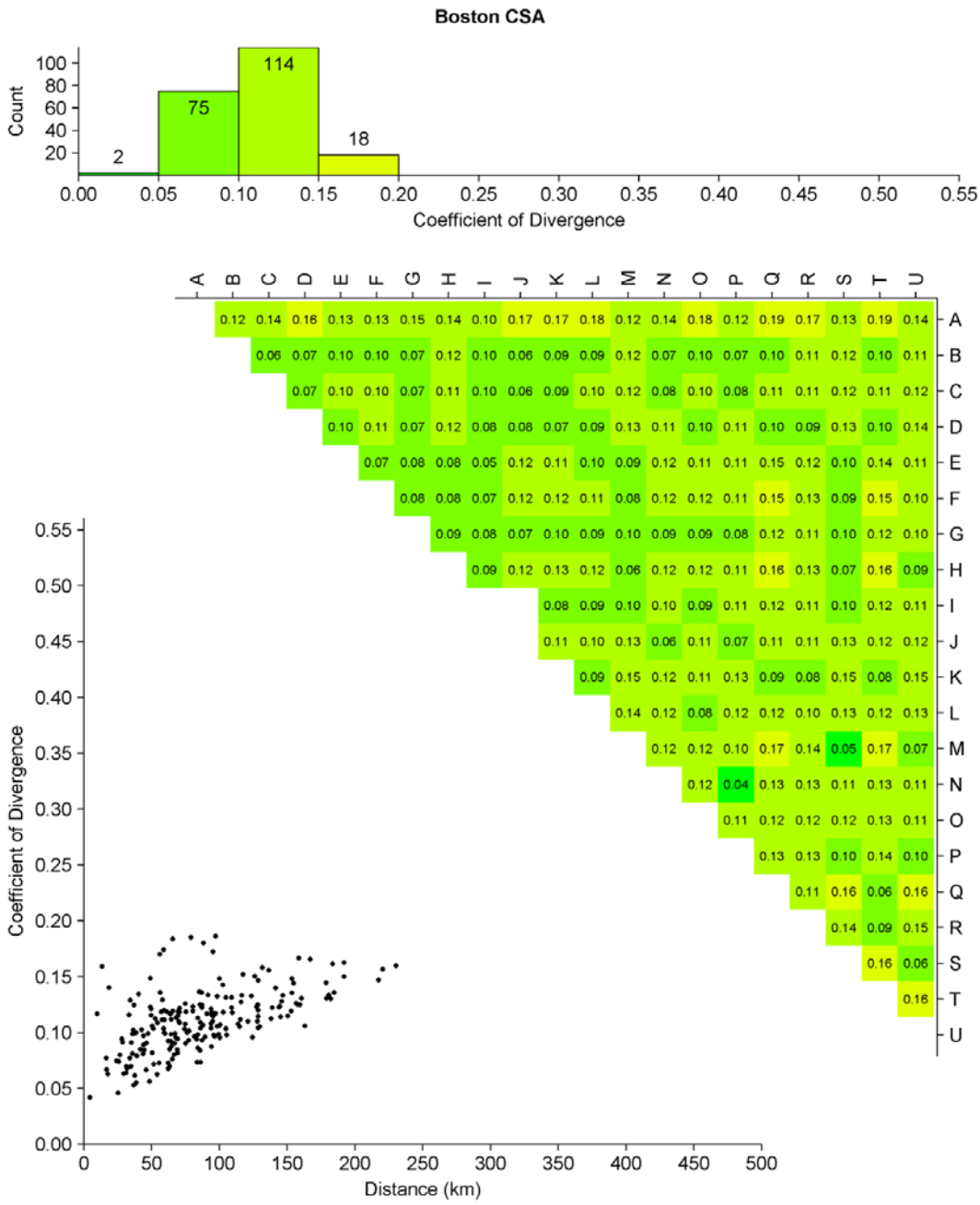
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-122 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Baltimore CSA.



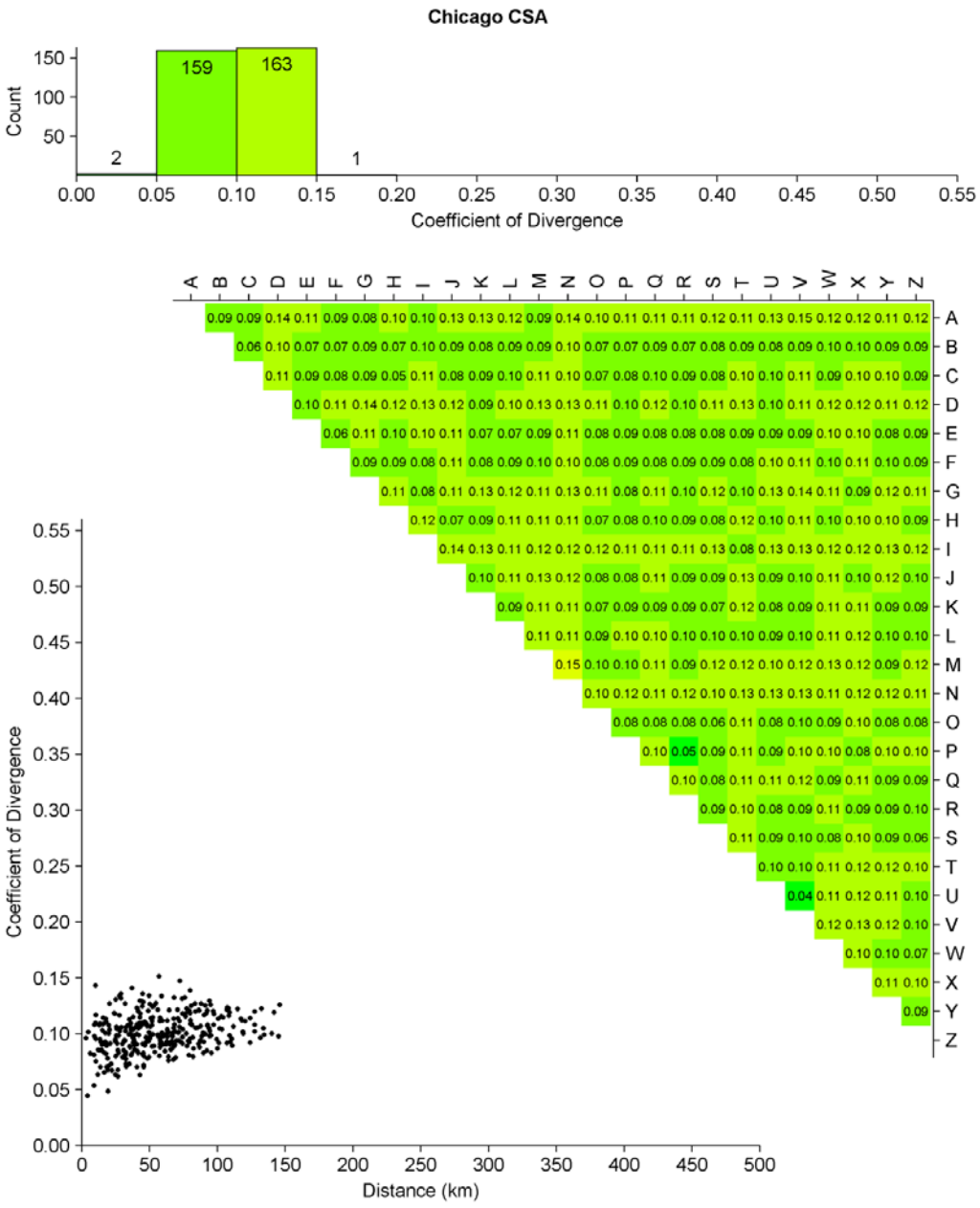
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-123 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Birmingham CSA.



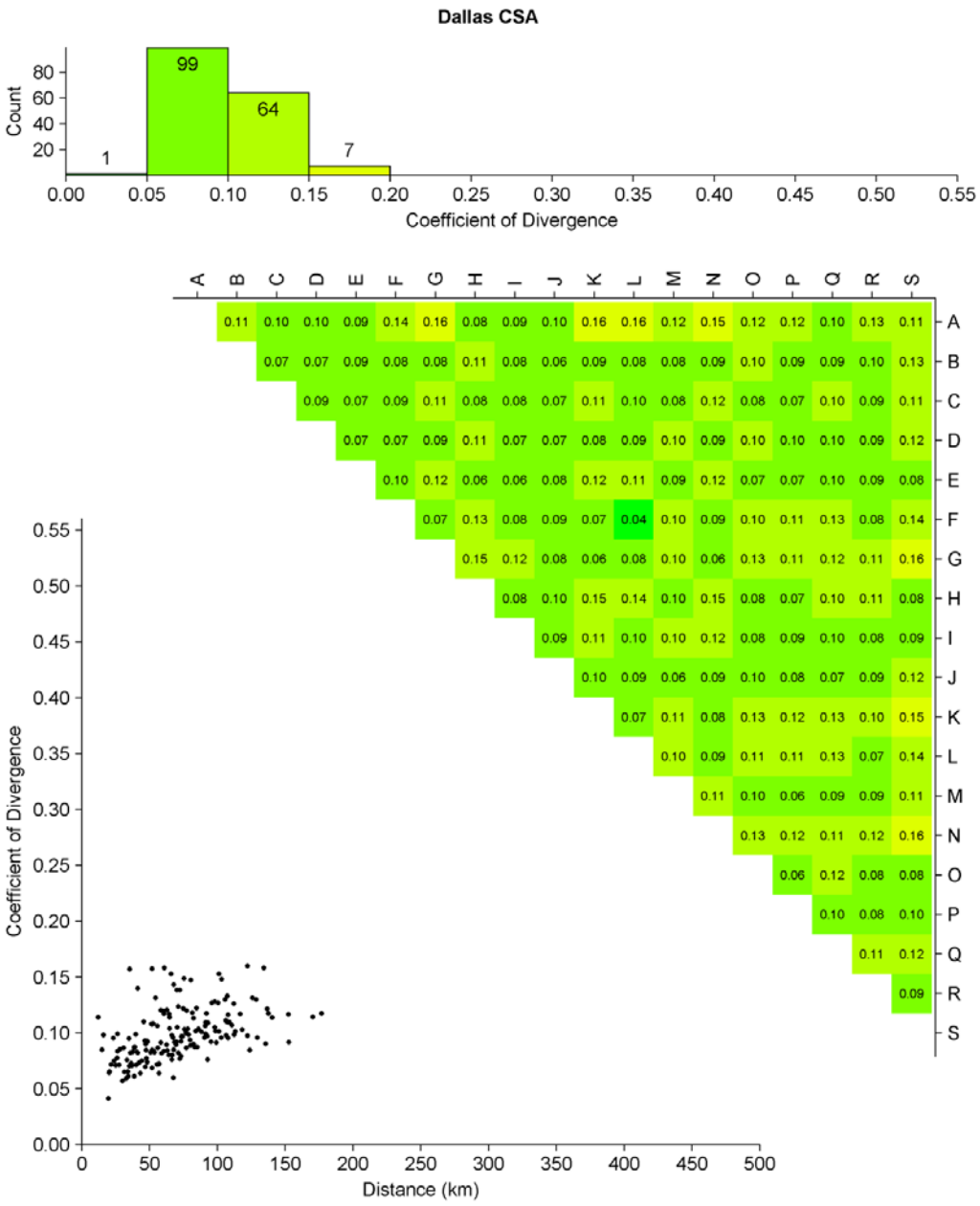
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-124 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Boston CSA.



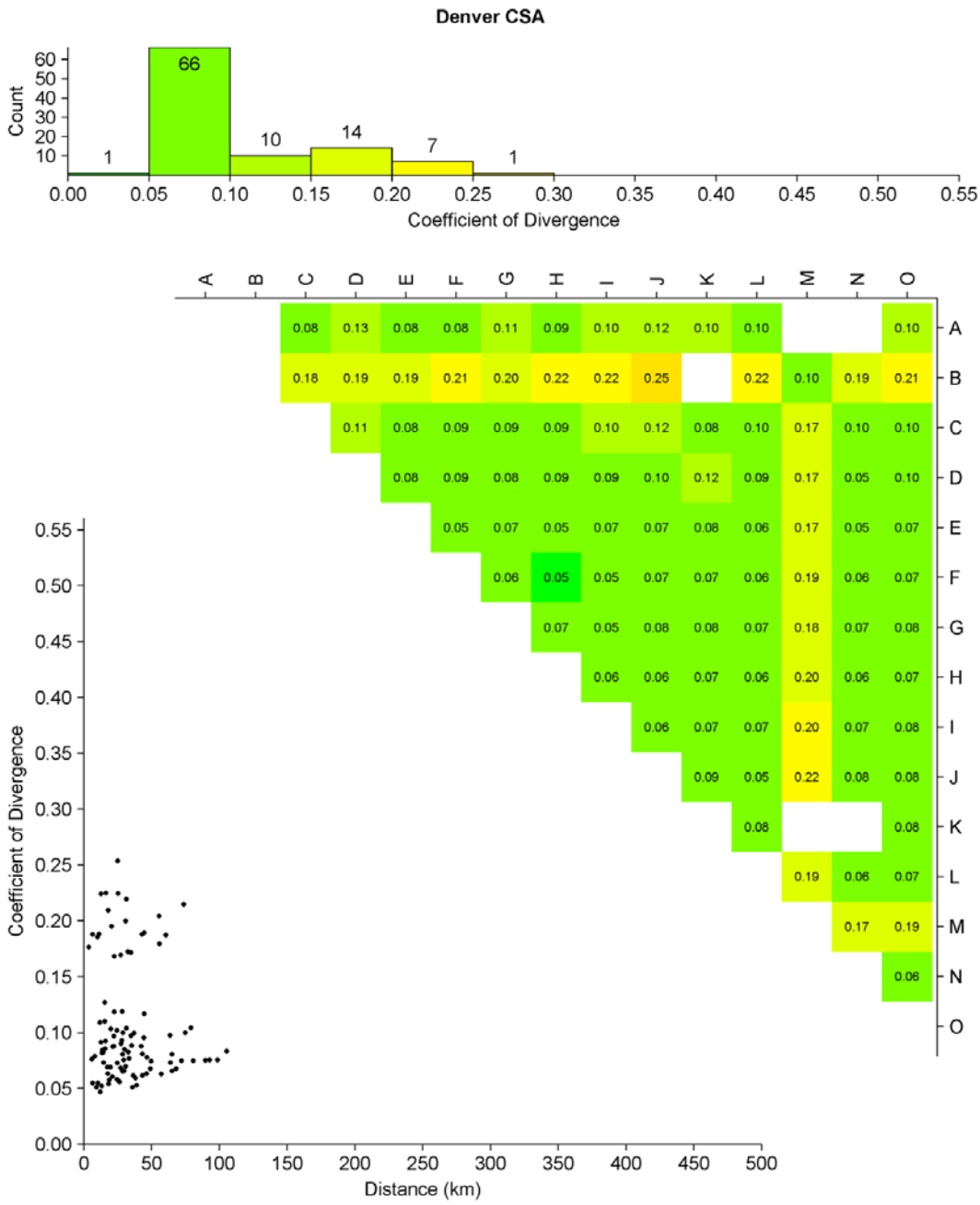
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-125 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Chicago CSA.



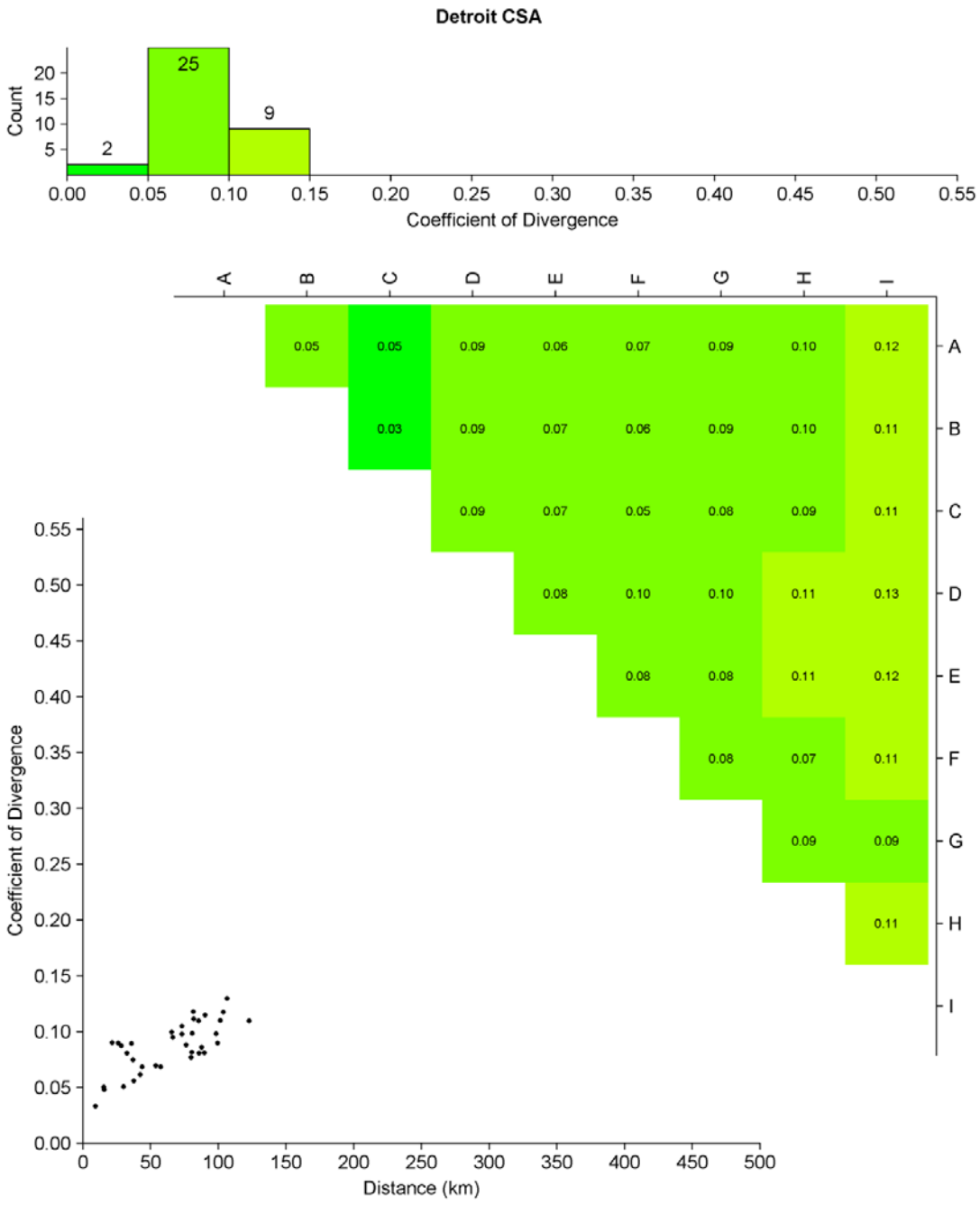
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-126 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Dallas CSA.



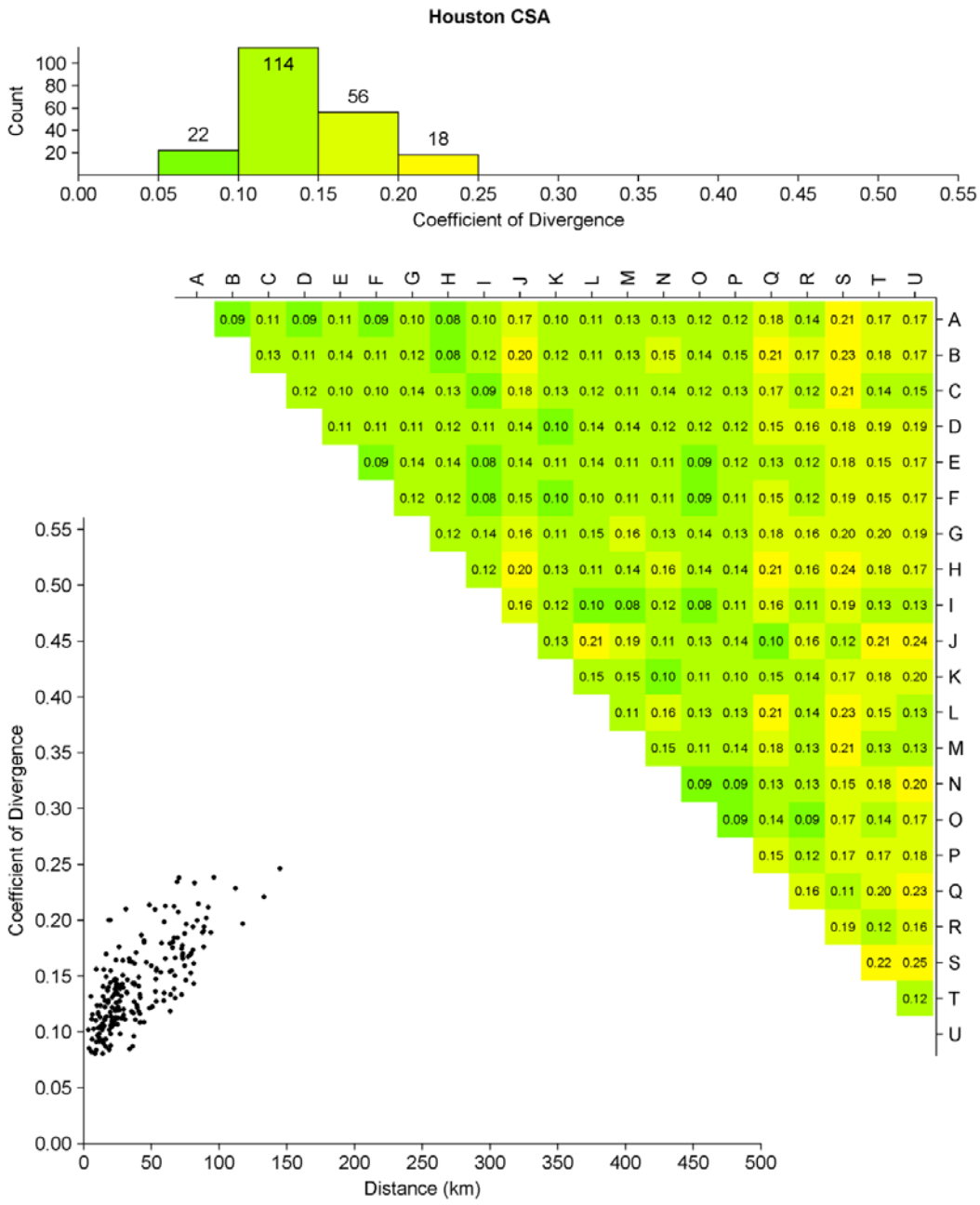
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-127 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Denver CSA.



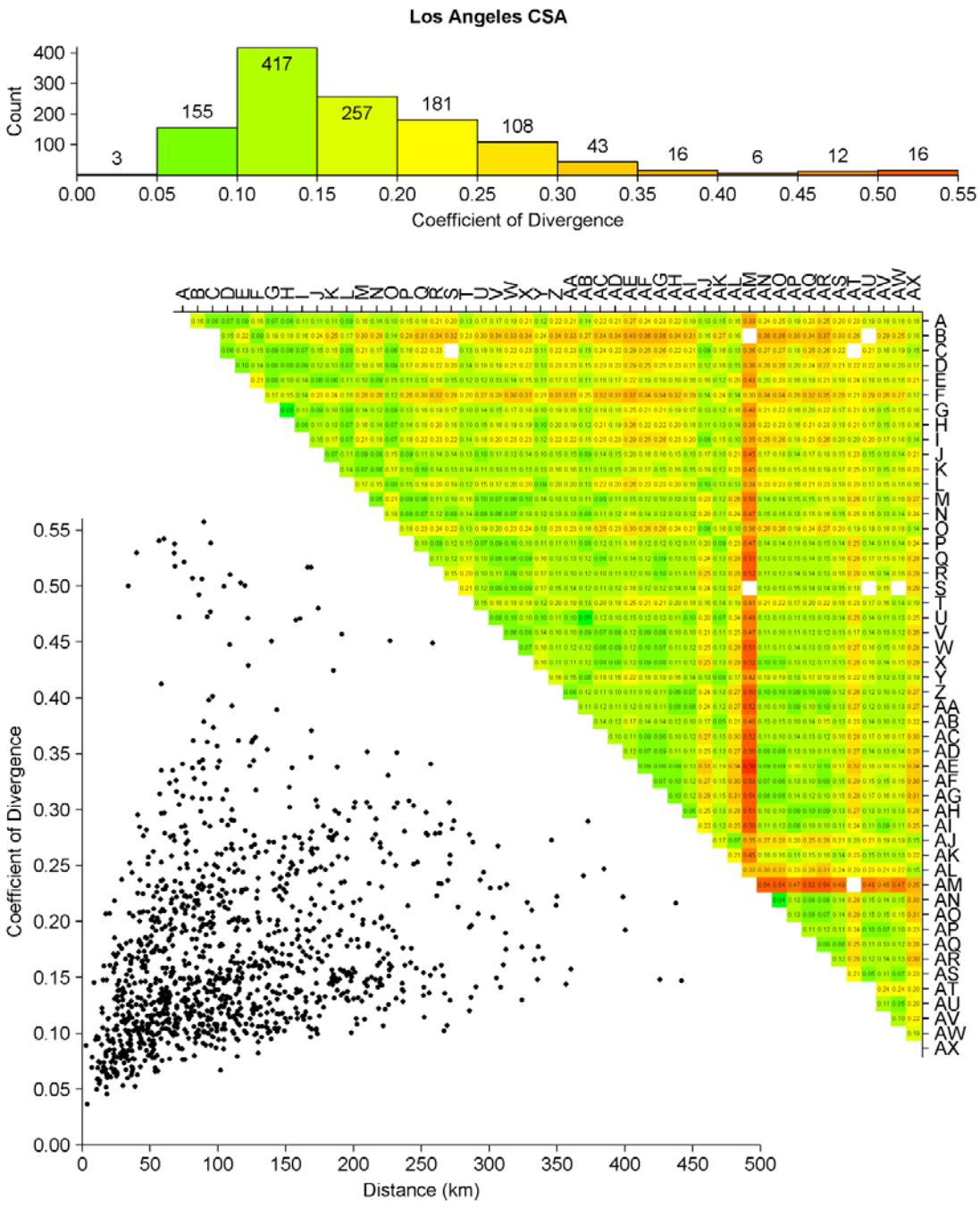
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-128 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Detroit CSA.



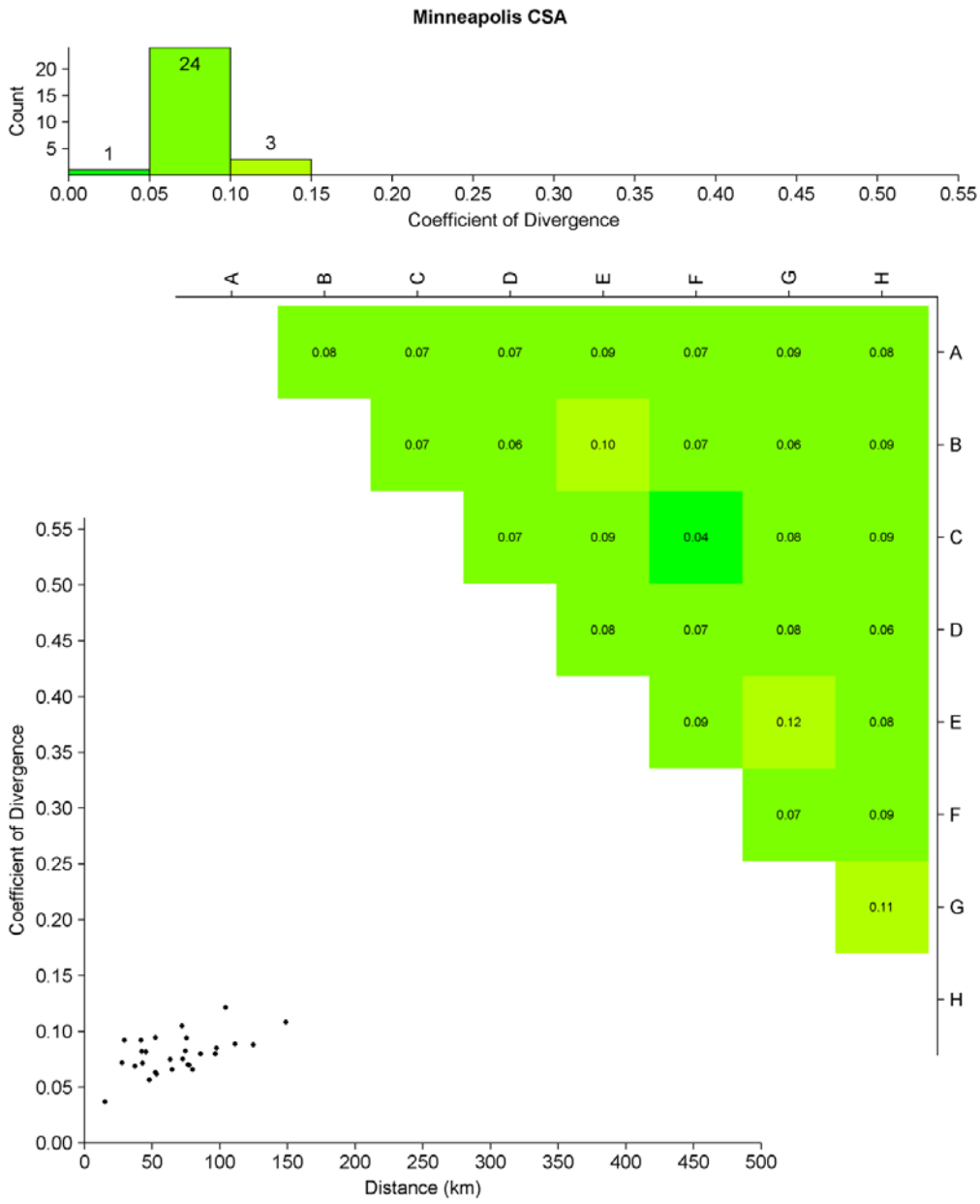
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-129 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Houston CSA.



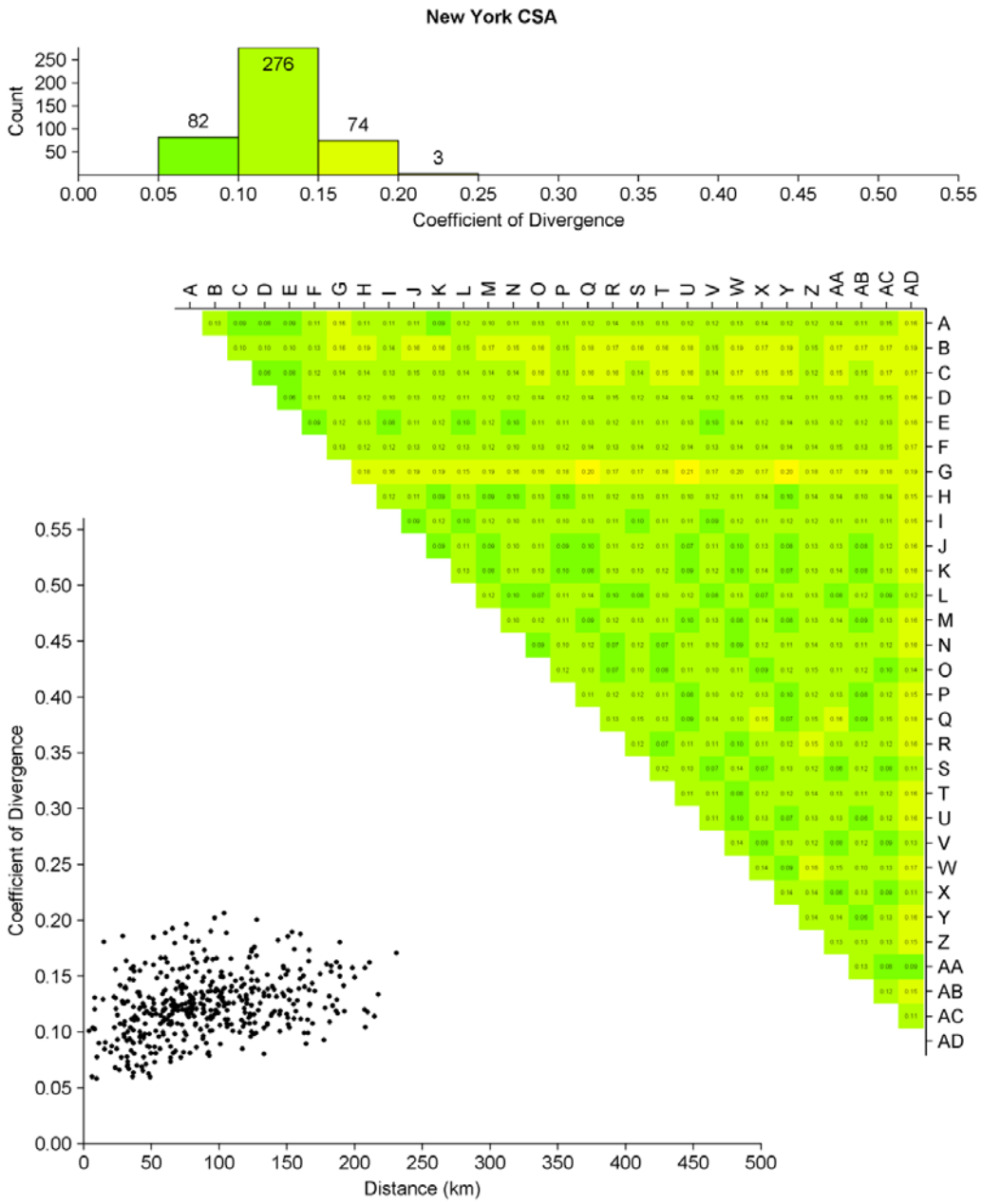
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-130 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Los Angeles CSA.



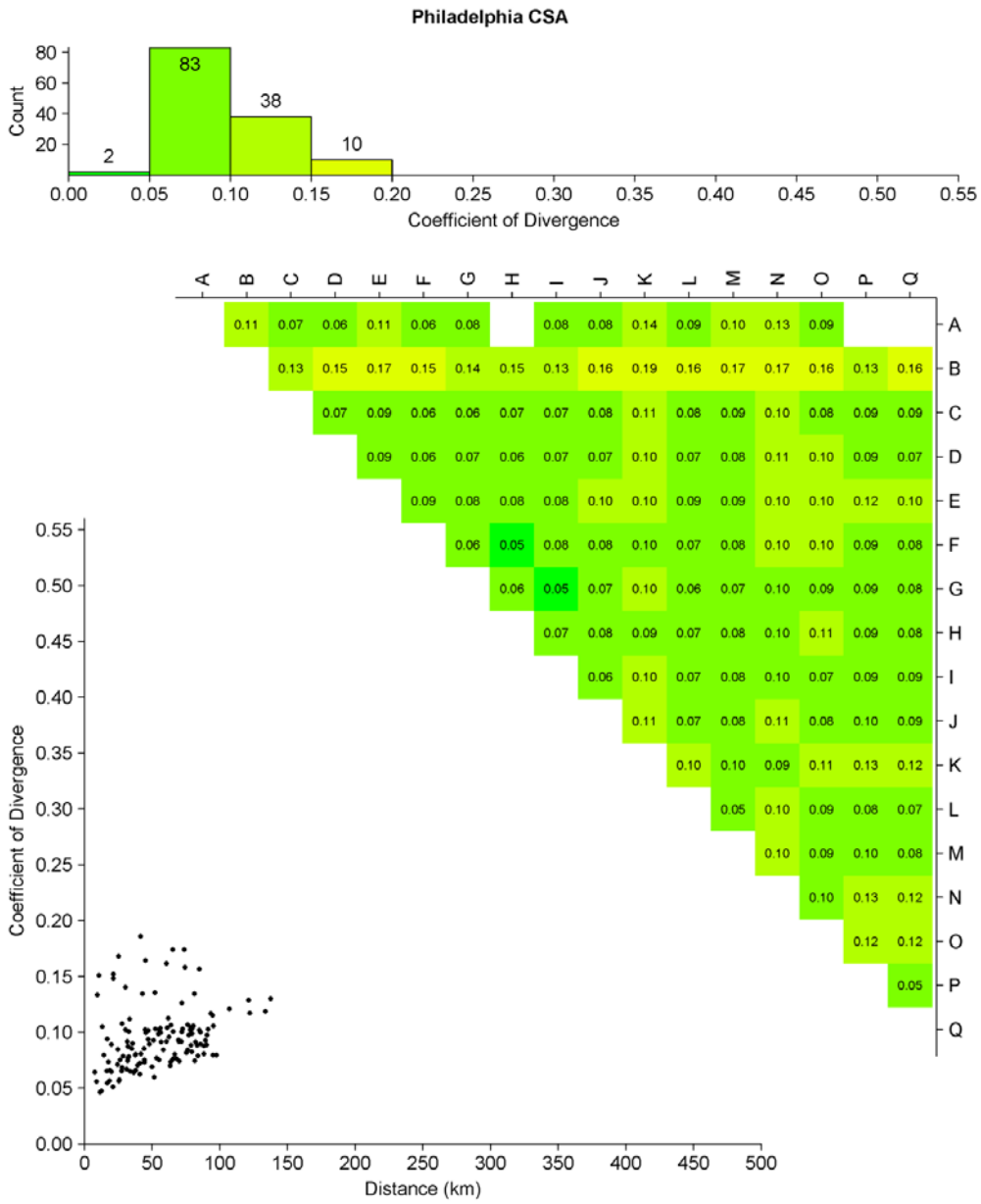
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-131 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Minneapolis CSA.



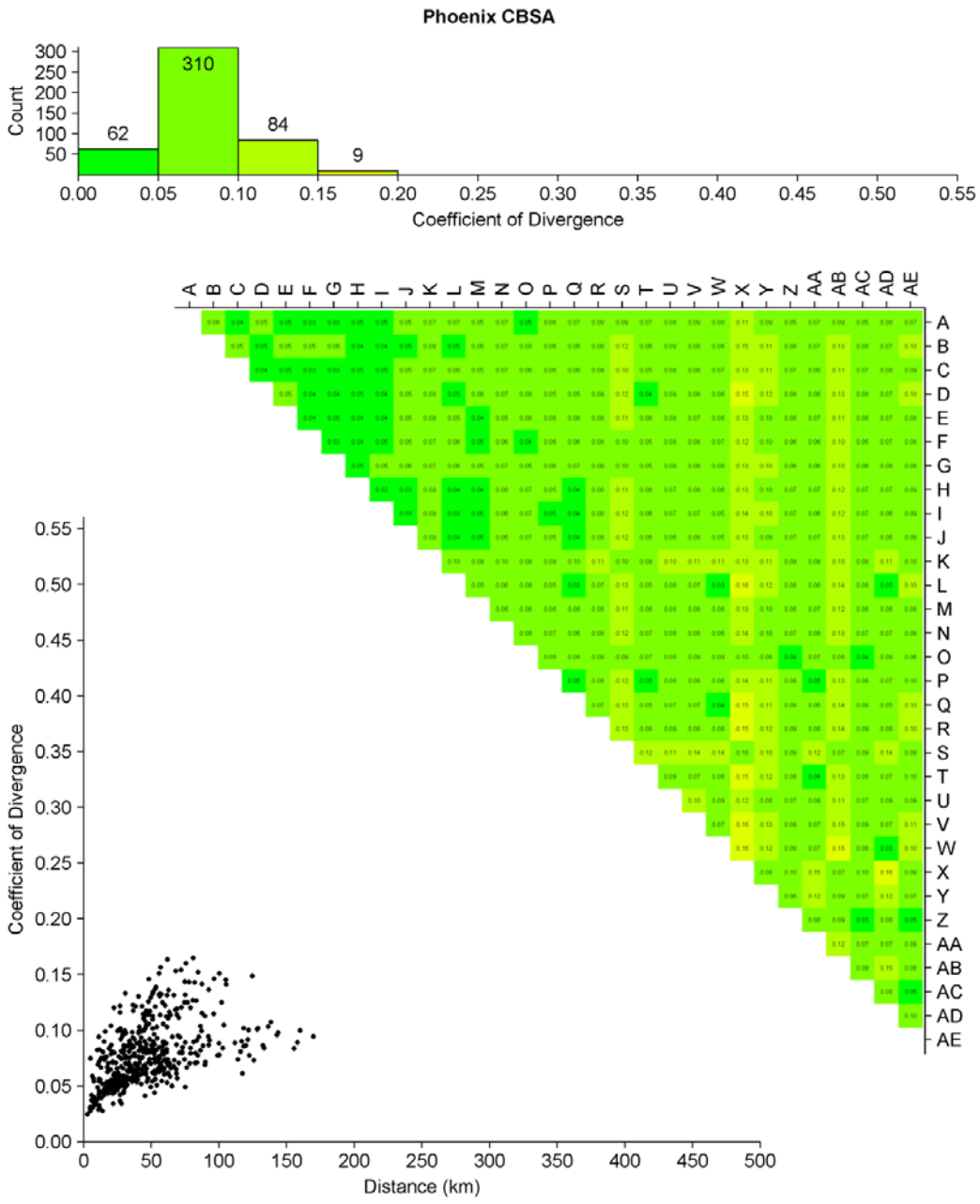
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-132 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the New York CSA.



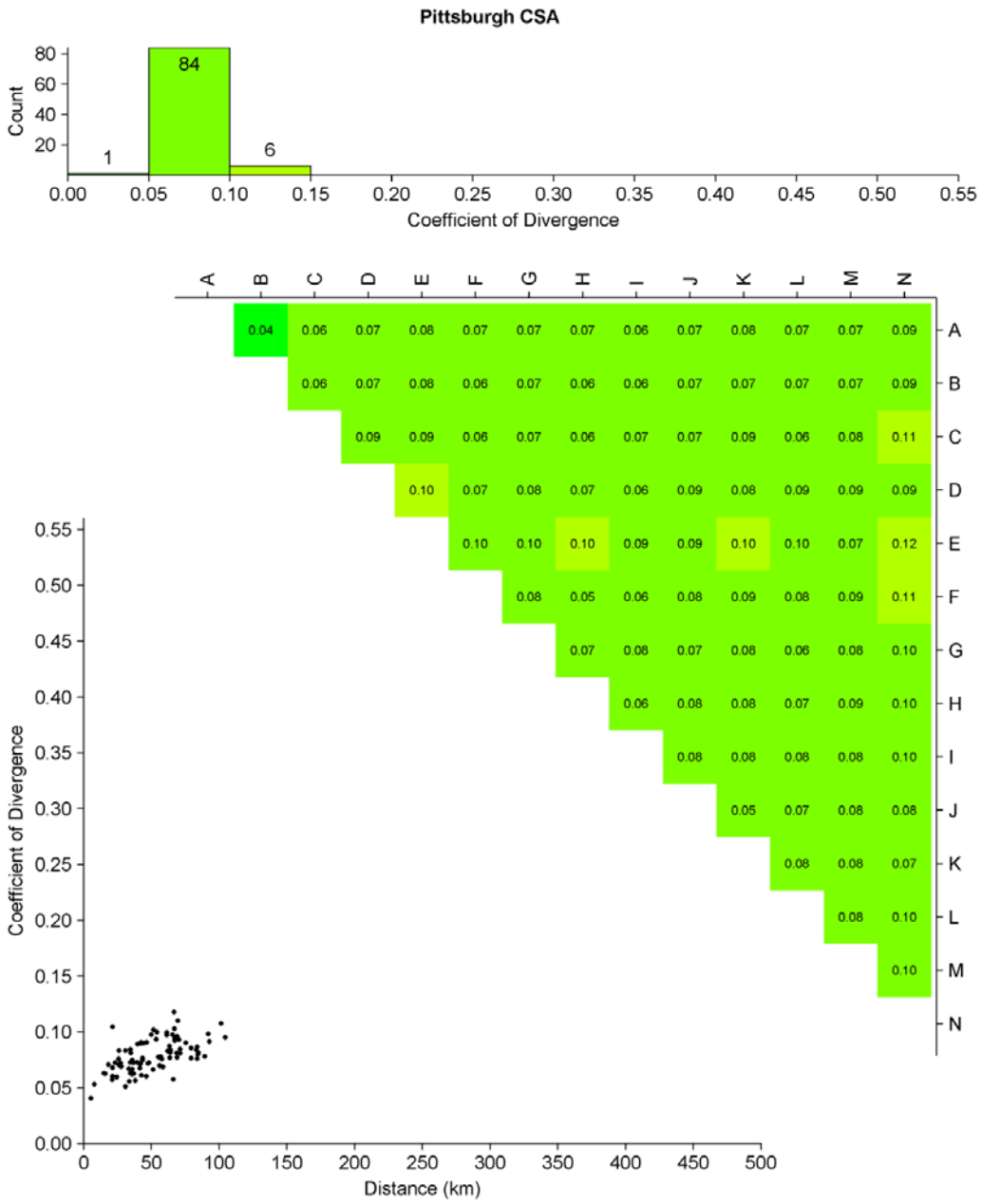
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-133 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Philadelphia CSA.



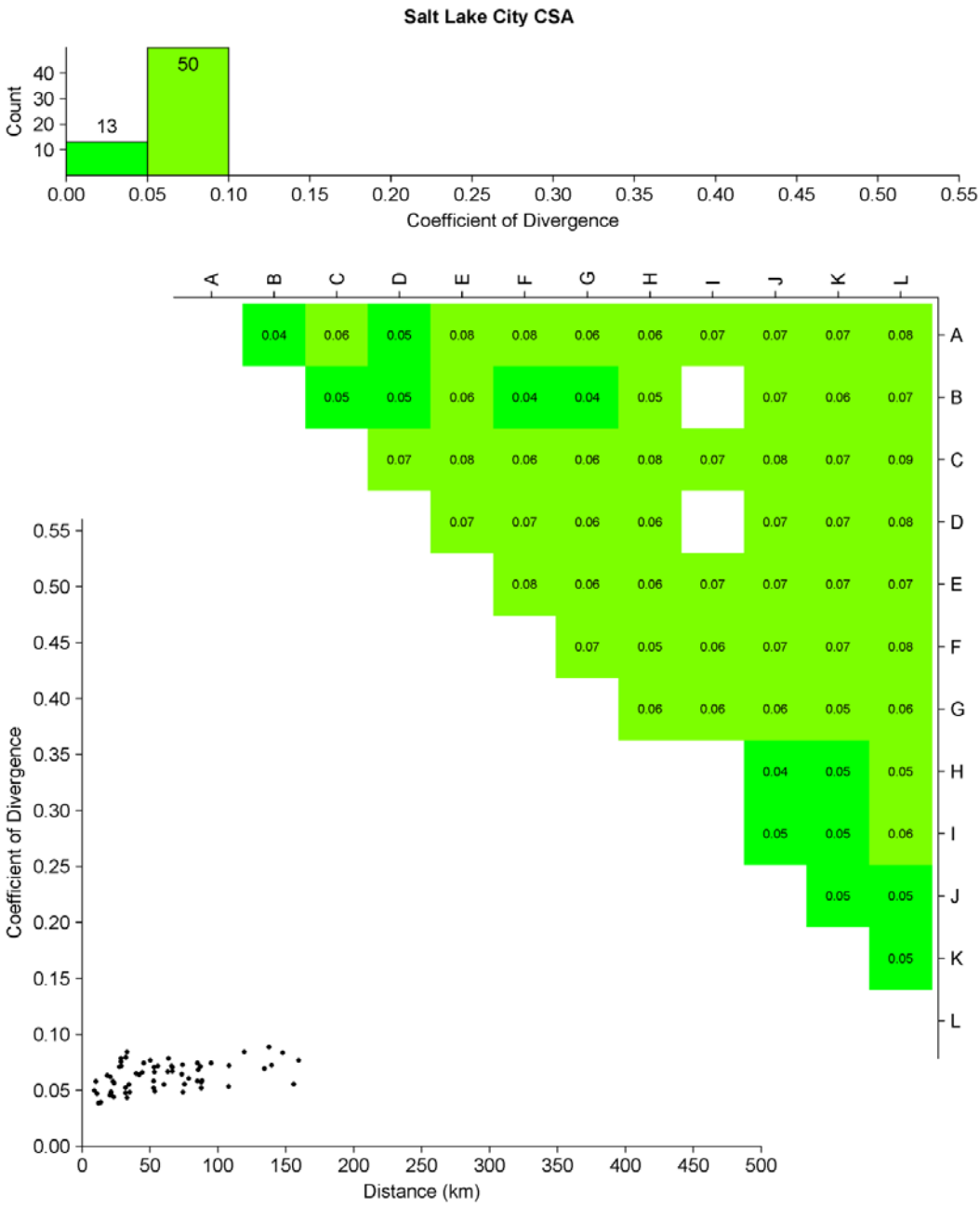
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-134 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Phoenix CBSA.



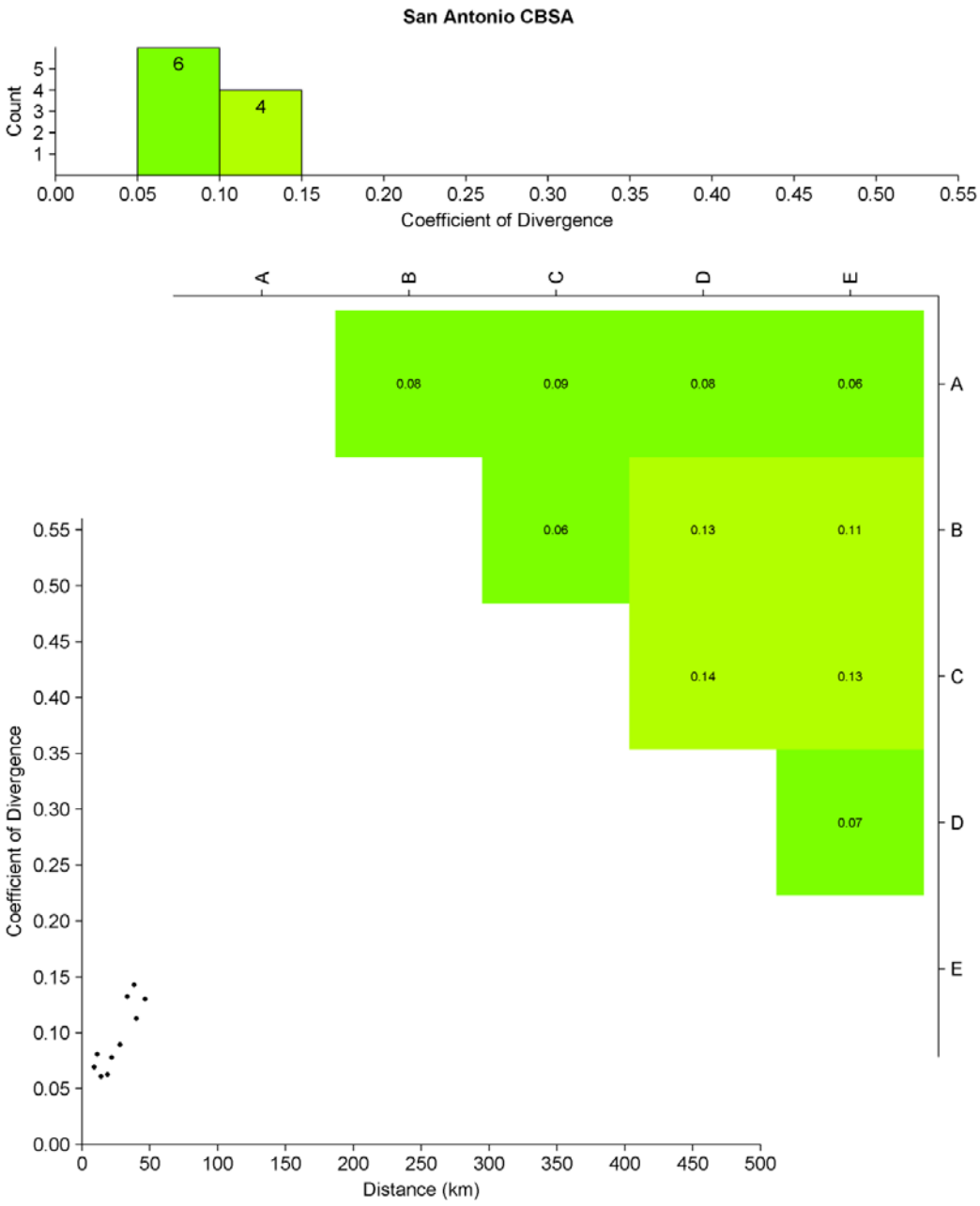
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-135 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Pittsburgh CSA.



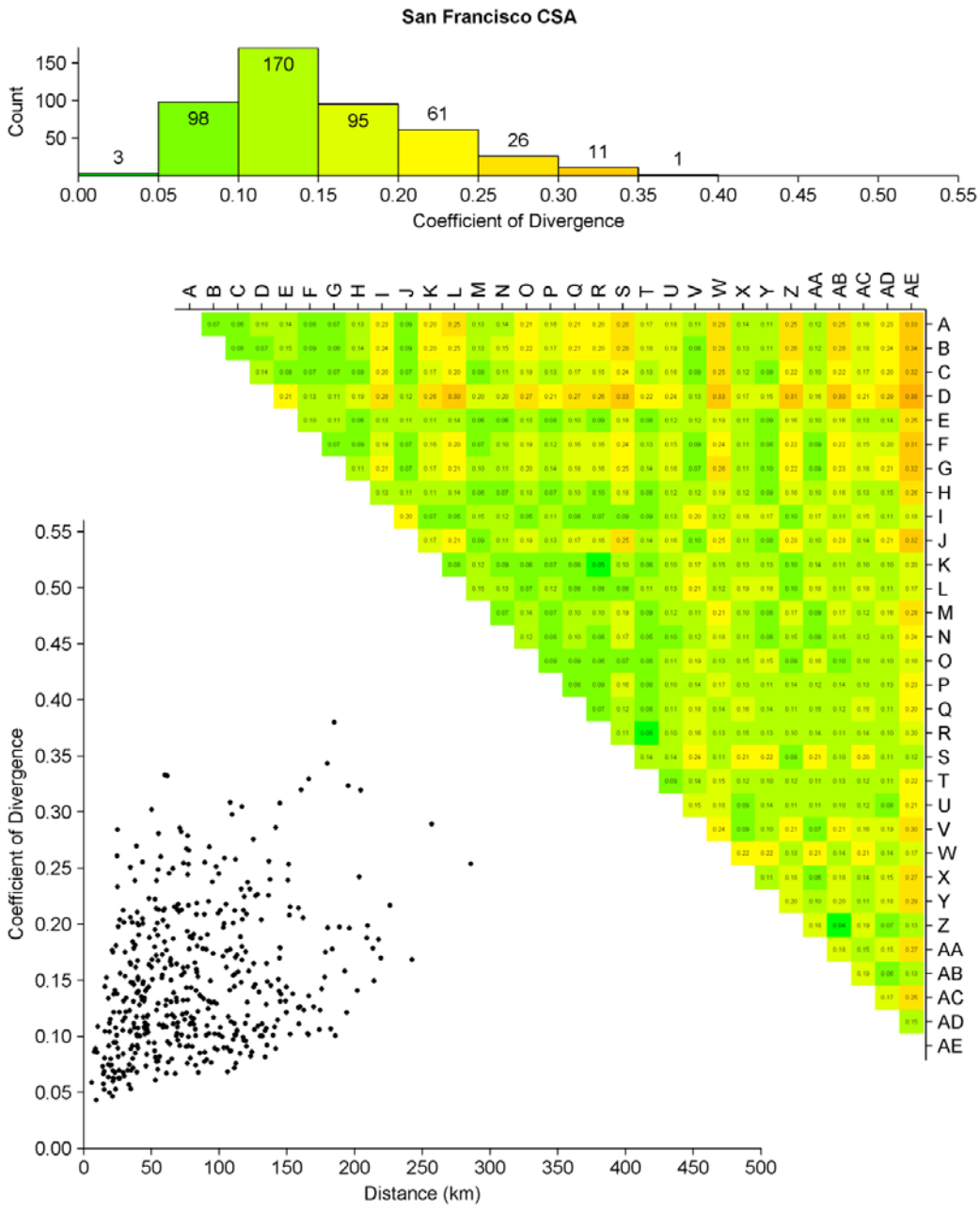
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-136 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Salt Lake City CSA.



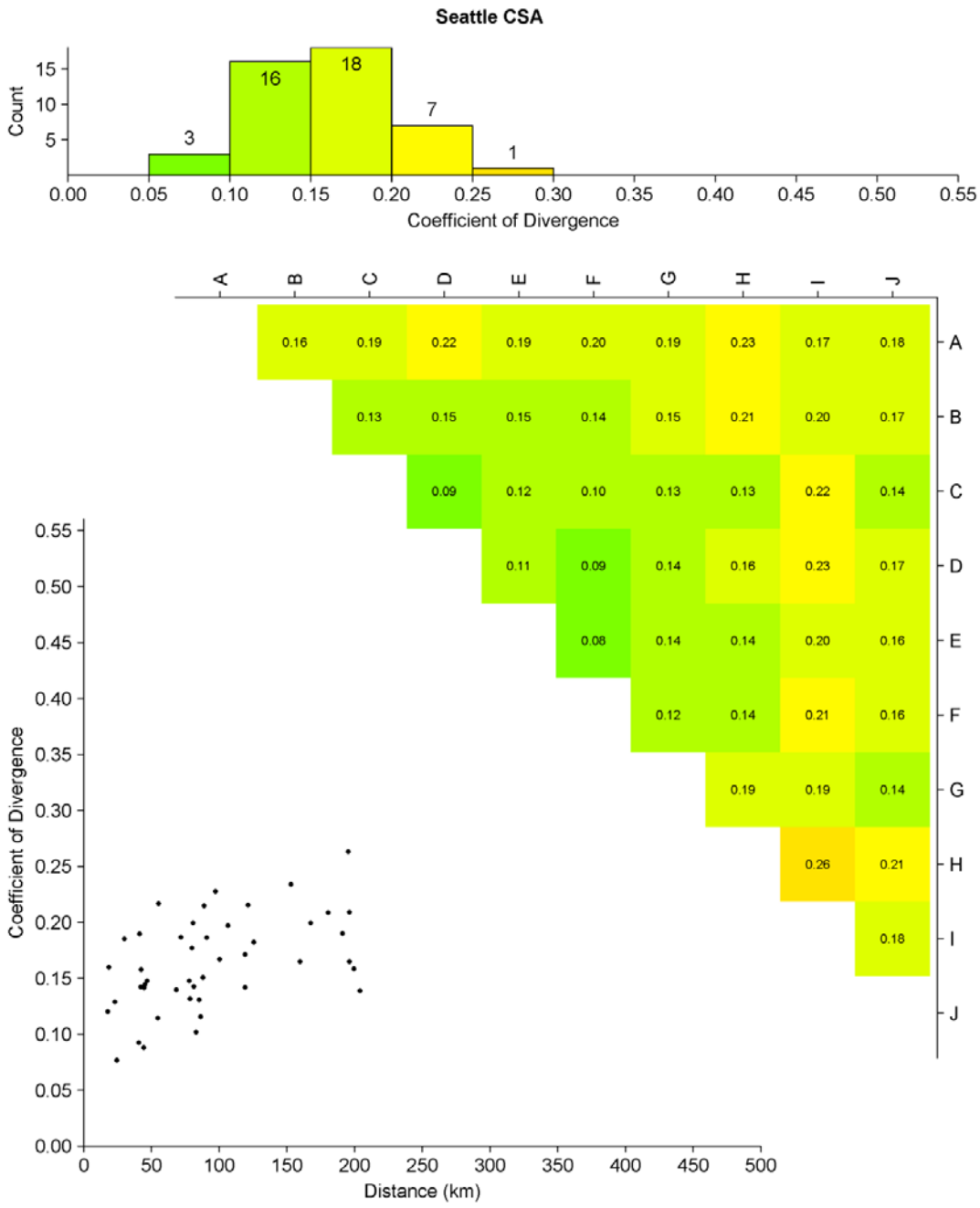
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-137 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the San Antonio CBSA.



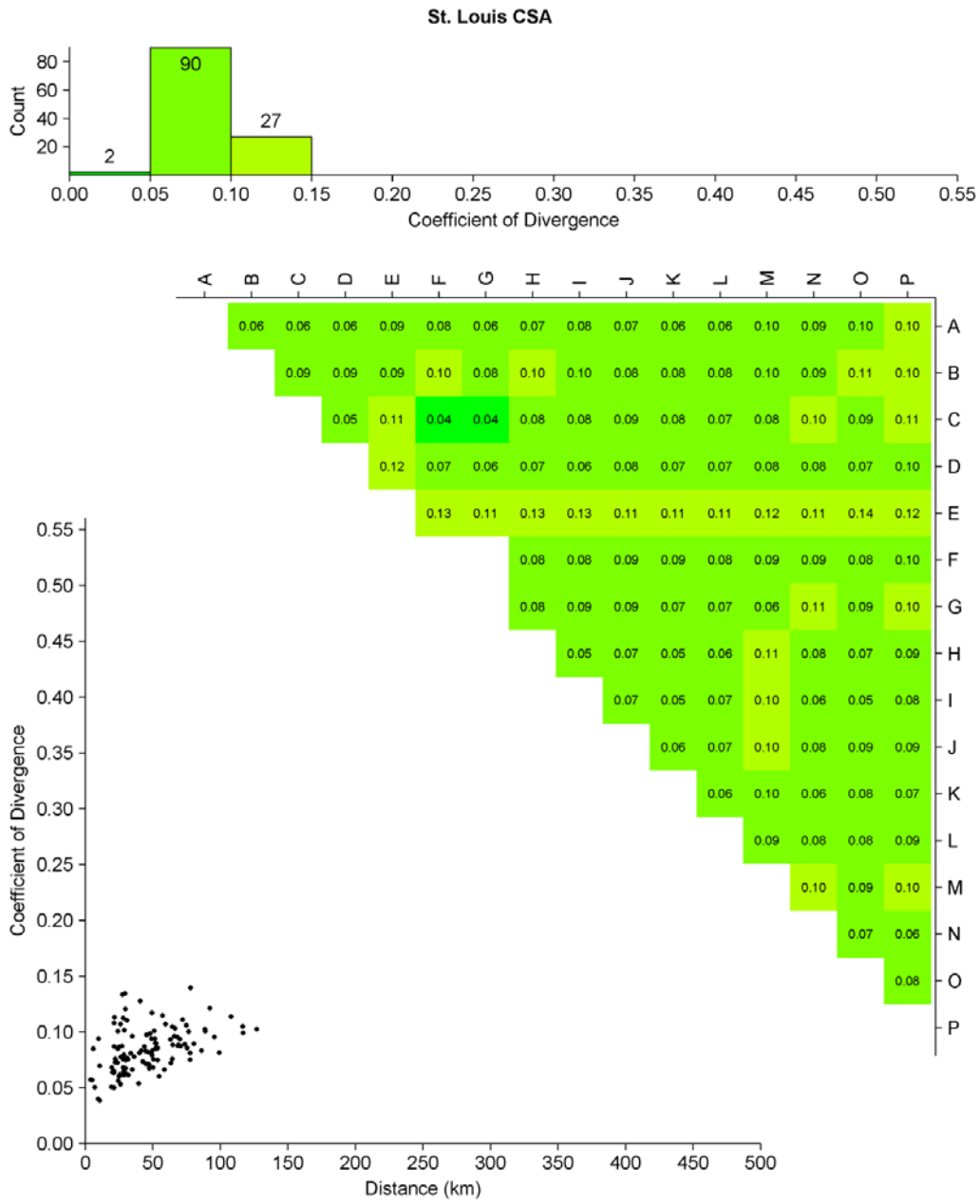
The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-138 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the San Francisco CSA.



The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-139 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Seattle CSA.

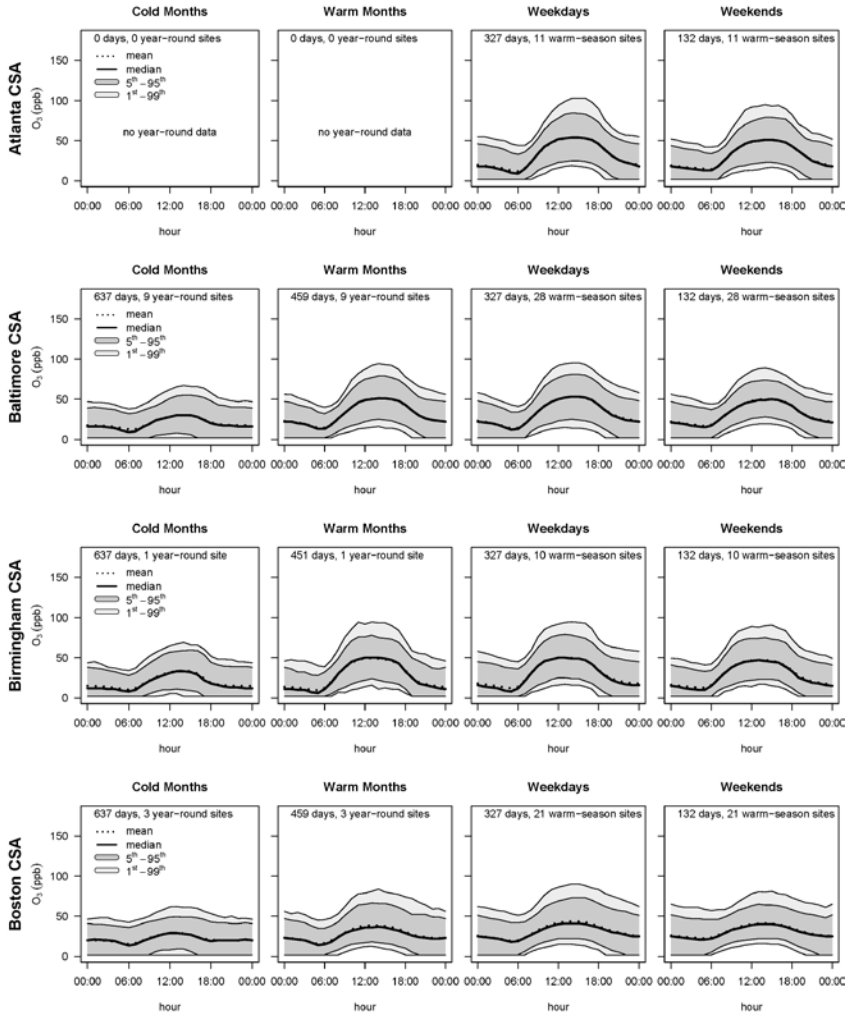


The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-140 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the St. Louis CSA.

3.10.4 Hourly Variations in Ozone for the Urban Focus Cities

This section contains diel plots of 1-h avg O_3 data to supplement the discussion on hourly variations in O_3 concentrations from Section 3.6.3.2 using data from the 20 urban focus cities first introduced in Section 3.6.2.1. Comparisons are made between cold months (October-April) and warm months (May-September), using the year-round data set, and between weekdays (Mon-Fri) and weekends (Sat-Sun) using the warm-season data set.



No year-round monitors were available for the cold month/warm month comparison in the Atlanta CSA.

Figure 3-141 Diel patterns in 1-h avg ozone for select CSAs between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).

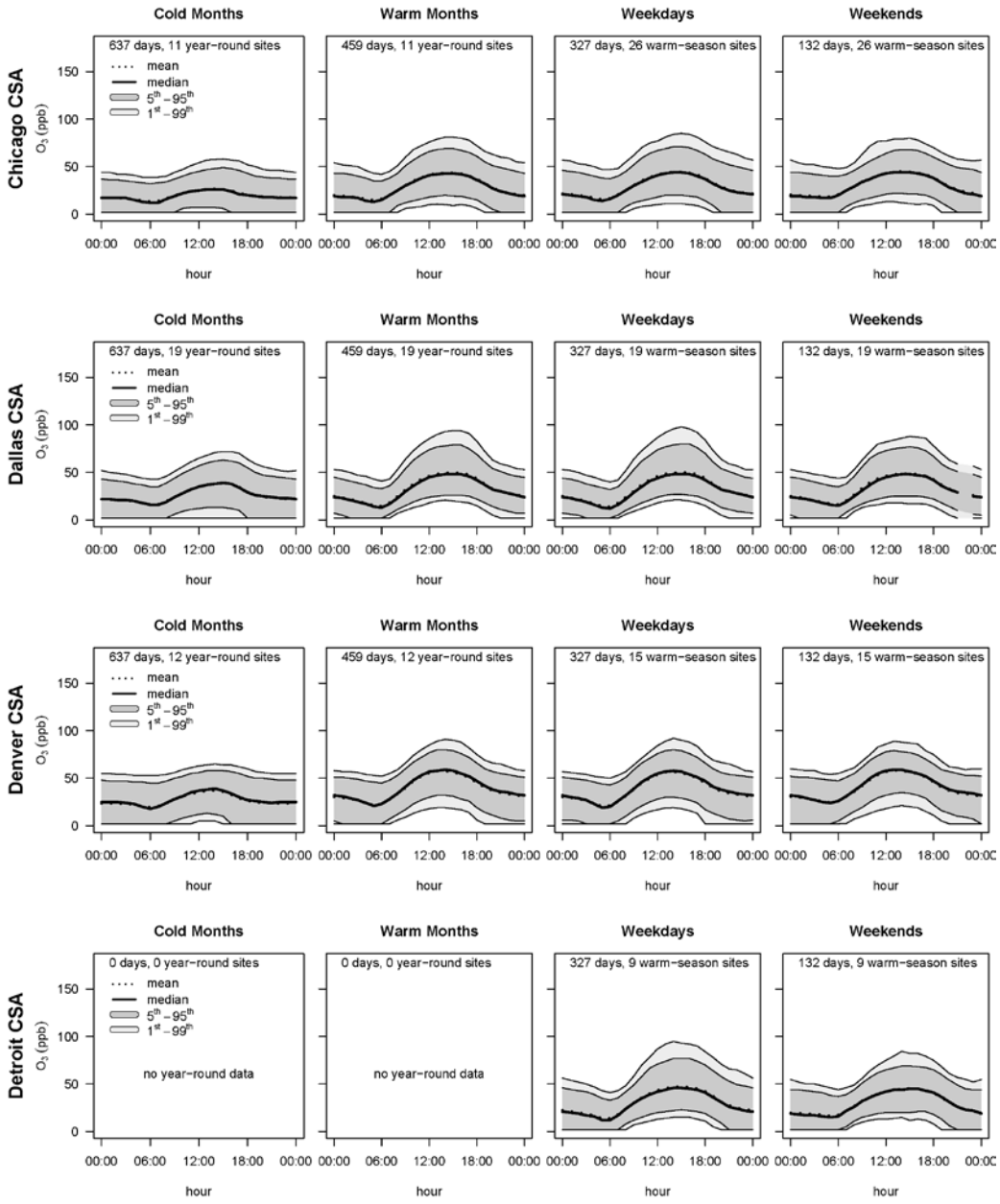


Figure 3-142 Diel patterns in 1-h avg ozone for select CSAs between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half). No year-round monitors were available for the cold month/warm month comparison in the Detroit CSA.

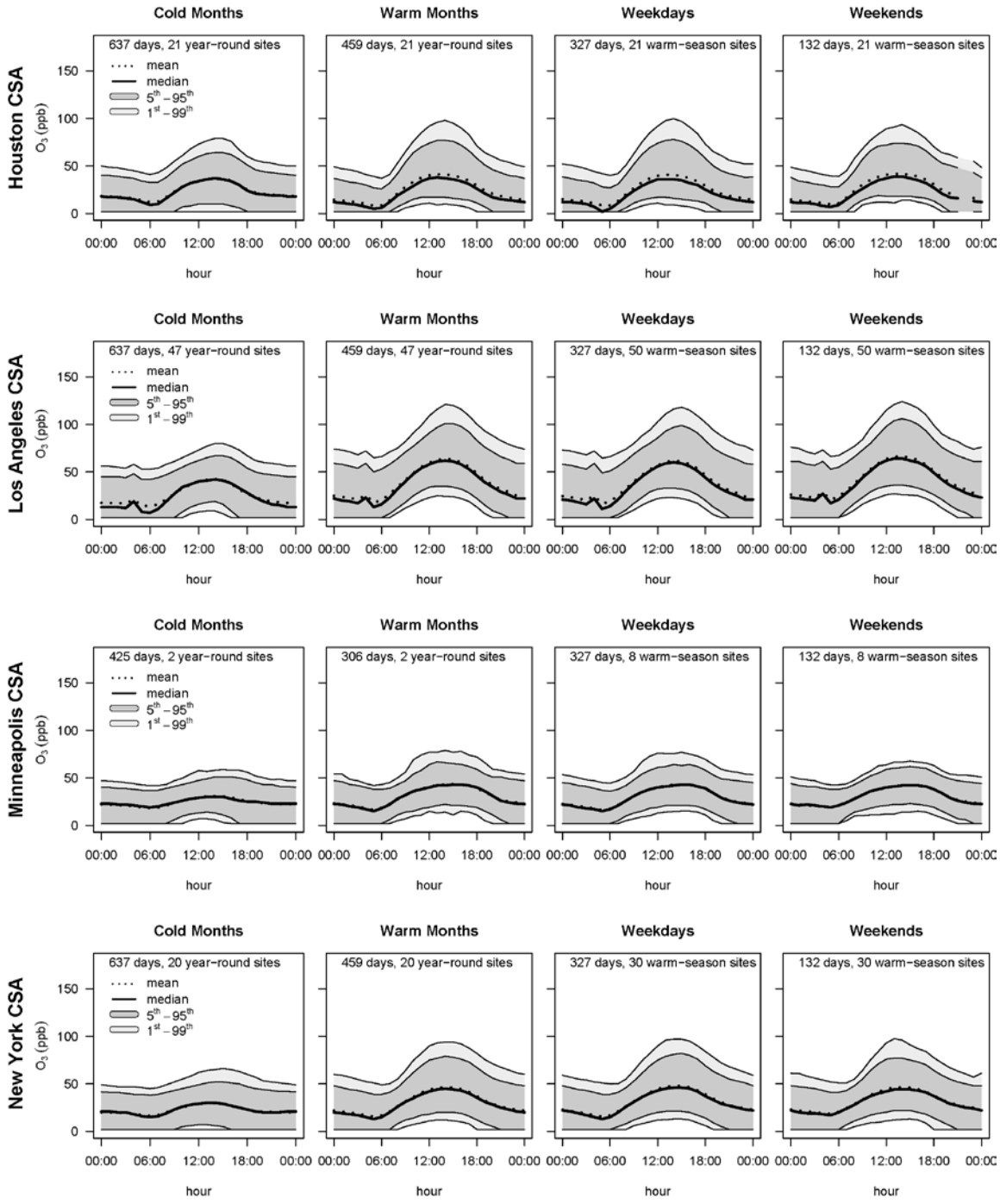


Figure 3-143 Diel patterns in 1-h avg ozone for select CSAs between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).

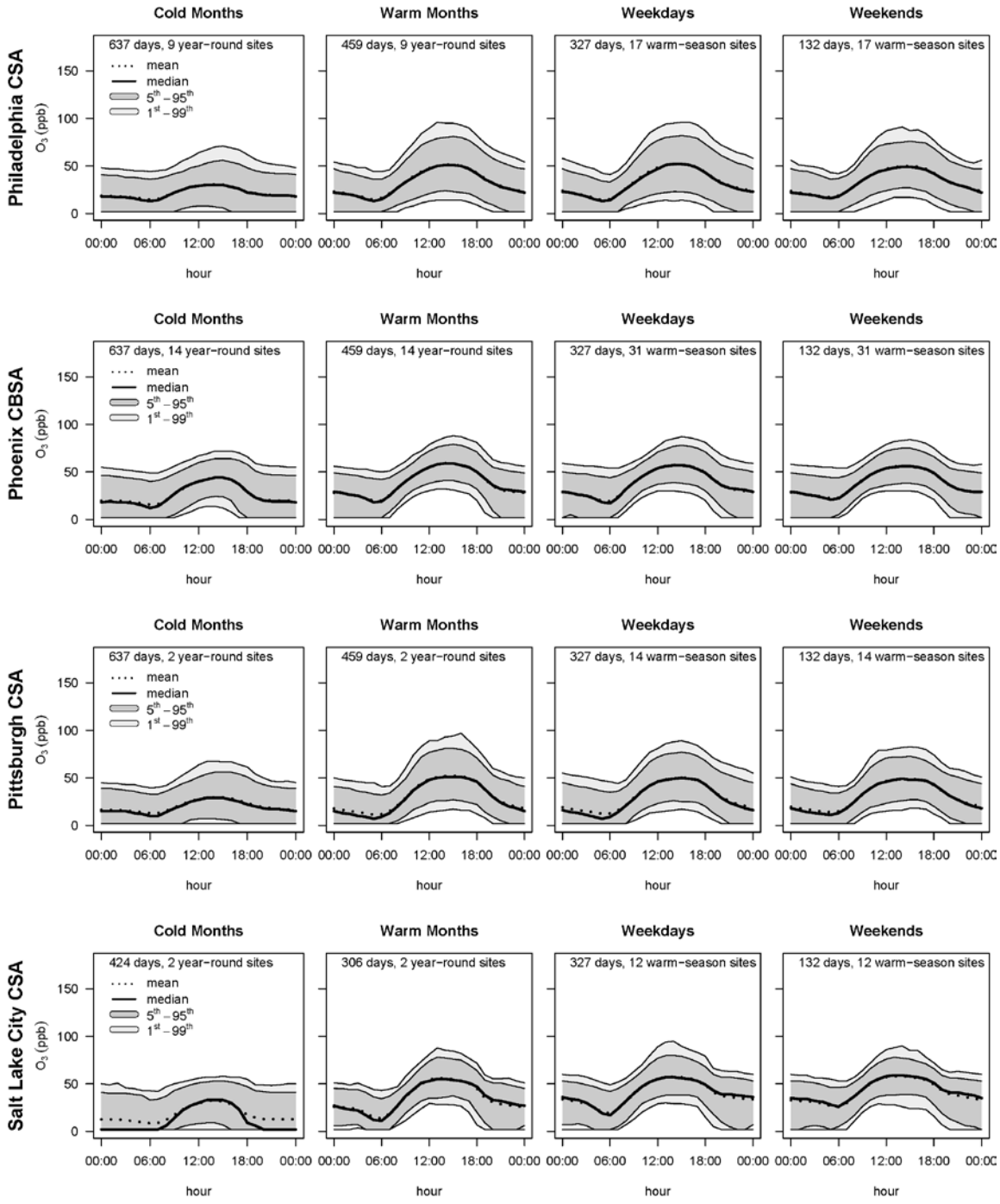


Figure 3-144 Diel patterns in 1-h avg ozone for select CSAs/CBSAs between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).

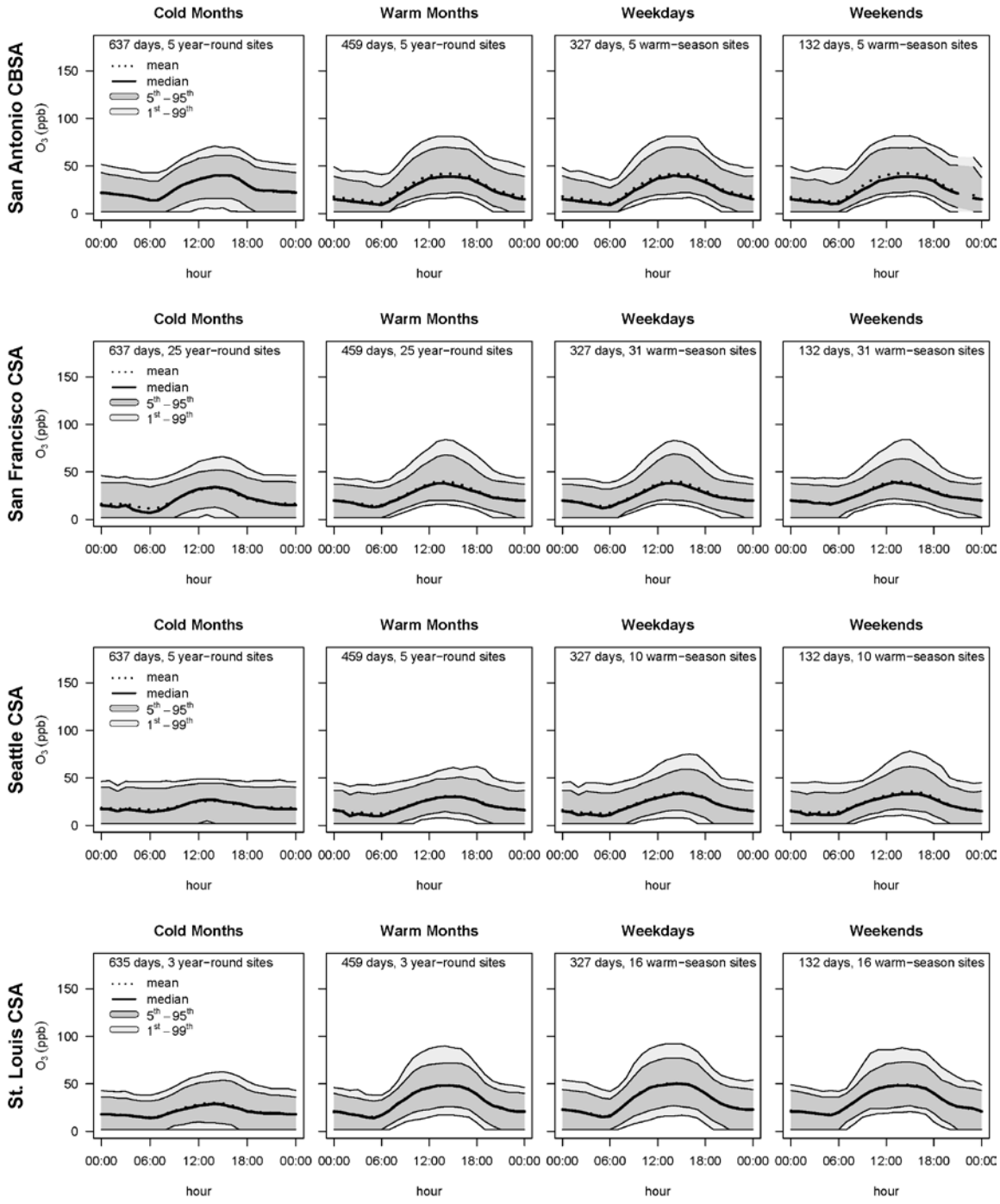


Figure 3-145 Diel patterns in 1-h avg ozone for select CSAs/CBSAs between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).

3.11 References

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4 EXPOSURE TO AMBIENT OZONE

4.1 Introduction

The 2006 O_3 AQCD evaluated O_3 concentrations and exposures in multiple microenvironments, discussed methods for estimating personal and population exposure via monitoring and modeling, analyzed relationships between personal exposure and ambient concentrations, and discussed the implications of using ambient O_3 concentrations as an estimate of exposure in epidemiologic studies. This chapter presents new information regarding exposure to ambient O_3 in the context of existing relevant information summarized in the 2006 O_3 AQCD, which in many areas remains definitive. A brief summary of findings from the 2006 O_3 AQCD is presented at the beginning of each section as appropriate.

Section 4.2 presents general exposure concepts describing the relationship between ambient pollutant concentrations and personal exposure. Section 4.3 describes exposure measurement techniques and studies that measured personal, ambient, indoor, and outdoor concentrations of O_3 and related pollutants. Section 4.4 presents material on parameters relevant to exposure estimation, including activity patterns, averting behavior, and population proximity to ambient monitors. Section 4.5 describes techniques for modeling local O_3 concentrations, air exchange rates, microenvironmental concentrations, and personal and population exposure. Section 4.6 discusses the implications of using ambient O_3 concentrations to estimate exposure in epidemiologic studies, including several factors that contribute to exposure error.

4.2 General Exposure Concepts

A theoretical model of personal exposure is presented to highlight measurable quantities and the uncertainties that exist in this framework. An individual's time-integrated total exposure to O_3 can be described based on a compartmentalization of the person's activities throughout a given time period:

$$E_T = \int C_j \, dt$$

Equation 4-1

where E_T = total (T) exposure over a time-period of interest, C_j = airborne O_3 concentration at microenvironment j, and dt = portion of the time-period spent in

microenvironment *j*. Equation 4-1 can be decomposed into a model that accounts for exposure to O_3, of ambient (E_a) and nonambient (En_a) origin of the form:

$$E_T = E_a + E_{na}$$

Equation 4-2

Ambient O_3 is formed through photochemical reactions involving NO_X, VOCs, and other compounds, as described in Chapter 3. Although nonambient sources of O_3 exist, such as O_3 generators and laser printers, these sources are specific to individuals and may not represent important sources of population exposure. Ozone concentrations generated by ambient and nonambient sources are subject to spatial and temporal variability that can affect estimates of exposure and influence epidemiologic effect estimates. Exposure parameters affecting interpretation of epidemiologic studies are discussed in Section 4.5.

This assessment focuses on the ambient component of exposure because this is more relevant to the NAAQS review. Assuming steady-state outdoor conditions, E_a can be expressed in terms of the fraction of time spent in various outdoor and indoor microenvironments (Wallace et al., 2006; Wilson et al., 2000):

$$E_a = \sum f_o C_o + \sum f_i \mathcal{F}_{inf_i} C_{o,i}$$

Equation 4-3

where f = fraction of the relevant time period (equivalent to dt in Equation 4-1), subscript o = index of outdoor microenvironments, subscript i = index of indoor microenvironments, subscript o,i = index of outdoor microenvironments adjacent to a given indoor microenvironment i, and $F_{inf,i}$ = infiltration factor for indoor microenvironment *(i)*. Equation 4-3 is subject to the constraint $\Sigma f_o + \Sigma f_i = 1$ to reflect the total exposure over a specified time period, and each term on the right hand side of the equation has a summation because it reflects various microenvironmental exposures. Here, "indoors" refers to being inside any aspect of the built environment, e.g., home, office buildings, enclosed vehicles (automobiles, trains, buses), and/or recreational facilities (movies, restaurants, bars). "Outdoor" exposure can occur in parks or yards, on sidewalks, and on bicycles or motorcycles. F_{inf} is a function of the building air exchange characteristics. Assuming steady state ventilation conditions, the infiltration factor is a function of the penetration (P) of O_3 into the microenvironment, the air exchange rate (a) of the microenvironment, and the rate of O_3 loss (k) in the microenvironment; $F_{inf} = Pa/(a+k)$.

In epidemiologic studies, the central-site ambient concentration, C_a, is often used in lieu of outdoor microenvironmental data to represent these exposures based on the availability

of data. Thus it is often assumed that $C_o = C_a$ and that the fraction of time spent outdoors can be expressed cumulatively as f_o; the indoor terms still retain a summation because infiltration differs among different microenvironments. If an epidemiologic study employs only C_a, then the assumed model of an individual's exposure to ambient O_3, first given in Equation 4-3, is re-expressed solely as a function of C_a:

$$E_a = \left(f_o + \sum f_i \mathcal{F}_{inf_i}\right) C_a$$

Equation 4-4

The spatial variability of outdoor O_3 concentrations due to meteorology, varying precursor emissions and O_3 formation rates; design of the epidemiologic study; and other factors determine whether or not Equation 4-4 is a reasonable approximation for Equation 4-3. Errors and uncertainties inherent in use of Equation 4-4 in lieu of Equation 4-3 are described in Section 4.6 with respect to implications for interpreting epidemiologic studies. Epidemiologic studies often use concentration measured at a central site monitor to represent ambient concentration; thus α, the ratio between personal exposure to ambient O_3 and the ambient concentration of O_3, is defined as:

$$\alpha = \frac{E_a}{C_a}$$

Equation 4-5

Combination of Equation 4-4 and Equation 4-5 yields:

$$\alpha = f_o + \sum f_i \mathcal{F}_{inf_i}$$

Equation 4-6

where α varies between 0 and 1. If a person's exposure occurs in a single microenvironment, the ambient component of a microenvironmental O_3 concentration can be represented as the product of the ambient concentration and F_{inf}. Wallace et al. (2006) note that time-activity data and corresponding estimates of F_{inf} for each microenvironmental exposure are needed to compute an individual's α with accuracy. In epidemiologic studies, α is assumed to be constant in lieu of time-activity data and estimates of F_{inf}, which can vary with building and meteorology-related air exchange characteristics. If local outdoor sources and sinks exist and are significant but not captured by central site monitors, then the ambient component of the local outdoor concentration may be estimated using dispersion models, land use regression models, receptor models, fine scale CTMs or some combination of these techniques. These techniques are described in Section 4.5.

4.3 Exposure Measurement

This section describes techniques that have been used to measure microenvironmental concentrations of O_3 and personal O_3 exposures as well as results of studies using those techniques. Previous studies from the 2006 O_3 AQCD are described along with newer studies that evaluate indoor-outdoor concentration relationships, associations between personal exposure and ambient monitor concentration, and multipollutant exposure to other pollutants in conjunction with O_3. Tables are provided to summarize important study results.

4.3.1 Personal Monitoring Techniques

As described in the 2006 O_3 AQCD, passive samplers have been developed and deployed to measure personal exposure to O_3 (Grosjean and Hisham, 1992; Kanno and Yanagisawa, 1992). Widely used versions of these samplers utilize a filter coated with nitrite, which is converted to nitrate by O_3 and then quantified by a technique such as ion chromatography (Koutrakis et al., 1993). This method has been licensed and marketed by Ogawa, Inc., Japan (Ogawa and Co, 2007). The cumulative sampling and the detection limit of the passive badges makes them mainly suitable for monitoring periods of 24 hours or greater, which limits their ability to measure short-term daily fluctuations in personal O_3 exposure. Longer sampling periods give lower detection limits; use of the badges for a 6-day sampling period yields a detection limit of 1 ppb, while a 24-hour sampling period gives a detection limit of approximately 5-10 ppb. This can result in a substantial fraction of daily samples being below the detection limit (Sarnat et al., 2006b; Sarnat et al., 2005), which is a limitation of past and current exposure studies. Development of improved passive samplers capable of shorter-duration monitoring with lower detection limits would enable more precise characterization of personal exposure in multiple microenvironments with relatively low participant burden.

The nitrite-nitrate conversion reaction has also been used as the basis for an active sampler consisting of a nitrite-coated glass tube through which air is drawn by a pump operating at 65 mL/min (Geyh et al., 1999; Geyh et al., 1997). The reported detection limit is 10 ppb-h, enabling the quantification of O_3 concentrations measured over a few hours rather than a full day (Geyh et al., 1999).

A portable active O_3 monitor based on the UV photometric technique used for stationary monitors (Chapter 3) has recently been approved as a FEM (75 FR 22126). This monitor includes a Nafion tube in the inlet line to equalize humidity, reducing the effect of humidity changes in different microenvironments (Wilson and Birks, 2006). Its size and

weight (approximately 10×20×30 cm; 2 kg) make it suitable for use in a backpack configuration. The monitors are currently used by the U.S. National Park service as stationary monitors to measure O_3 in several national parks (Chapter 3). Future improvements and continued miniaturization of real-time O_3 monitors can yield highly time-resolved personal measurements to further evaluate O_3 exposures in specific situations, such as near roadways or while in transit.

4.3.2 Indoor-Outdoor Concentration Relationships

Several studies summarized in the 2006 O_3 AQCD, along with some newer studies, have evaluated the relationship between indoor O_3 concentration and the O_3 concentration immediately outside the indoor microenvironment. These studies show that the indoor concentration is often substantially lower than the outdoor concentration unless indoor sources are present. Low indoor O_3 concentrations can be explained by reactions of O_3 with surfaces and airborne constituents. Studies have shown that O_3 is deposited onto indoor surfaces where reactions produce secondary pollutants such as formaldehyde (Reiss et al., 1995a; Reiss et al., 1995b). However, the indoor-outdoor relationship is greatly affected by the air exchange rate; under conditions of high air exchange rate, such as open windows, the indoor O_3 concentration may approach the outdoor concentration. Table 4-1 summarizes indoor-outdoor (I/O) ratios and correlations reported by older and more recent studies, with discussion of individual studies in the subsequent text. In general, I/O ratios range from about 0.1 to 0.4, with some evidence for higher ratios during the O_3 season when concentrations are higher.

O_3 concentrations near and below the monitor detection limit cause uncertainty in I/O ratios, because small changes in low concentration values cause substantial variation in resulting ratios. This problem is particularly acute in the non-ozone season when ambient O_3 concentrations are low. Further improvements in characterization of microenvironmental O_3 concentrations and I/O ratios will rely on improved monitoring. Until new monitoring techniques are available and can be used in the field, past studies summarized in the 2006 O_3 AQCD remain relevant to consider along with more recent studies in evaluating the relationship between indoor and outdoor O_3 concentrations.

Table 4-1 Relationships of Indoor and Outdoor Ozone Concentration

Study	Location	Years/Season	Population	Sample duration	Ratio[a]	Correlation	Micro-environment	Others
Geyh et al. (2000)	Upland, Southern California	June - September 1995 and May 1996	Children	6 day	0.24	NR	Home	Air-conditioned
		October 1995-April 1996			0.15			
	Mountain Communities, Southern California	June - September 1995 and May 1996			0.36			Opening windows
		October 1995-April 1996			0.08			
Avol et al. (1998b)	Southern California	February-December, 1994	NR	24 h	0.37 SD: 0.25	0.58	Home	
		Summer			0.43 SD: 0.29	NR		
		Non-summer			0.32 SD: 0.21	NR		
Romieu et al. (1998b)	Mexico City, Mexico	September 1993 - July 1994	Children	7 or 14 day	0.20 0.15[b] Range: 0.01-1.00	NR	Home	
Lee et al. (2004a)	Nashville, TN	Summer 1994	Children	1 week	0.1	NR	Home	
Héroux et al. (2010)	Regina, Saskatchewan, Canada	Summer 2007	All age groups	5 day	0.13	NR	Home	
López-Aparicio et al. (2011)	Prague, Czech Republic	July 2009 – March 2010	NR	1 month	0.10-0.30	NR	Home	No heating or air conditioning
Liu et al. (1995)	Toronto, Canada	Winter, 1992	All age groups	1 week	0.07 SD: 0.10	NR	Home	
		Summer, 1992			0.40 SD: 0.29			
		Summer, 1992		12 h	0.30 SD: 0.32			Daytime
		Summer, 1992			0.43 SD: 0.54			Nighttime
Romieu et al. (1998b)	Mexico City, Mexico	September 1993 - July 1994	Children	24 h/day, 14 days	0.15	NR	School	
			Children (during school hours)	5 h/day, 10 days	0.30-0.40			Immediately outside the schools
Blondeau et al. (2005)	La Rochelle, France	Spring, 2000	Children	NR	Range: 0.00-0.45	NR	School	
Riediker et al. (2003)	North Carolina	August - October 2001	Adults	9 h	0.51	NR	Vehicle	

[a] Mean value unless otherwise indicated
[b] Median
NR = not reported
SD = standard deviation

Geyh et al. (2000) measured 6-day indoor and outdoor concentrations at 116 homes in southern California, approximately equally divided between the community of Upland and several mountain communities. The extended sampling period resulted in a relatively low detection limit (1 ppb) for the passive samplers used. The Upland homes were nearly all air-conditioned, while the mountain community homes were ventilated by opening windows. During the O_3 season, the indoor O_3 concentration averaged over all homes was approximately 24% of the overall mean outdoor concentration in Upland (11.8 versus 48.2 ppb), while in the mountain communities, the indoor concentration was 36% of the outdoor concentration (21.4 versus 60.1 ppb). This is consistent with the increased air exchange rate expected in homes using window ventilation. In the non-ozone season, when homes are likely to be more tightly closed to conserve heat, the ratios

of indoor to outdoor concentration were 0.15 (3.2 versus 21.1 ppb) and 0.08 (2.8 versus 35.7 ppb) in Upland and the mountain communities, respectively. Avol et al. (1998b) observed a mean I/O ratio of 0.37 for 239 matched 24-h samples collected between February and December at homes in the Los Angeles area. The I/O ratio during summer was higher than the non-summer I/O ratio (0.43 versus 0.32). The authors also reported a correlation of 0.58 between the 24-h avg indoor concentration and the outdoor concentration, which was only slightly higher than the correlation between the indoor concentration and the concentration at the neighborhood fixed-site monitor (0.49). Substantially higher summer I/O ratios were reported in a study in Toronto (Liu et al., 1995), which found summer I/O ratios of 0.30-0.43, in comparison with a winter I/O ratio of 0.07. Romieu et al. (1998b) reported a mean I/O ratio of 0.20 in 145 homes in Mexico City for 7- or 14-day cumulative samples, with the highest ratios observed in homes where windows were usually open during the day and where there was no carpeting or air filters. Studies conducted in Nashville, TN and Regina, Saskatchewan reported mean residential I/O ratios of approximately 0.1 (Héroux et al., 2010; Lee et al., 2004a).

Investigators have also measured I/O ratios for non-residential microenvironments, including schools and vehicles. Romieu et al. (1998b) reported that O_3 concentrations measured during school hours (10-day cumulative sample, 5 h/day) were 30-40% of concentrations immediately outside the schools, while overall I/O ratios (14-day cumulative sample, 24 h/day) were approximately 15%. The authors attribute this discrepancy to increased air exchange during the school day due to opening doors and windows. Air exchange was also identified as an important factor in the I/O ratios measured at eight French schools (Blondeau et al., 2005). In this study, the I/O ratios based on simultaneous continuous measurements ranged from 0-0.45, increasing with decreasing building tightness. A historical library building in Prague, Czech Republic with no heating or air conditioning (i.e., natural ventilation) was observed to have ratios of one-month indoor and outdoor concentrations ranging from 0.10-0.30 during a nine-month sampling campaign, with the highest ratios reported in Nov-Dec 2009 and the lowest ratios during Jul-Aug 2009 (López-Aparicio et al., 2011). Indoor concentrations were relatively constant (approximately 3-7 ug/m^3 or 2-3 ppb), while outdoor concentrations were lower in the winter (9-10 ug/ m^3 or about 5 ppb) than in the summer (35-45 ug/ m^3 or about 20 ppb). This seasonal variation in outdoor concentrations coupled with homogeneous indoor concentrations, together with increased wintertime air exchange rate due to higher indoor-outdoor temperature differences, is likely responsible for the observed seasonal pattern in I/O ratios.

Exposures in near-road, on-road and in-vehicle microenvironments are likely to be highly variable and lower than those in other microenvironments due to reaction of O_3 with NO

and other combustion emissions. Depending on wind direction, O_3 concentrations near the roadway have been found to be 20-80% of ambient concentrations at sites 400 m or more distant from roads (Section 3.6.2.1). A study on patrol cars during trooper work shifts reported in-vehicle 9-h concentrations that were approximately 51% of simultaneously measured roadside concentrations (mean of 11.7 versus 22.4 ppb) (Riediker et al., 2003).

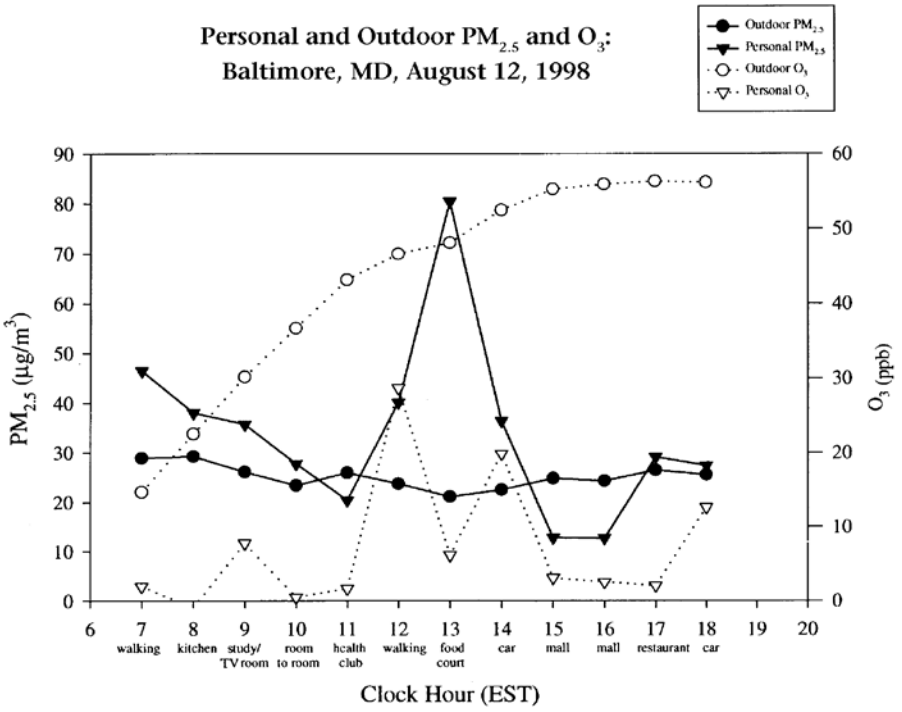
4.3.3 Personal-Ambient Concentration Relationships

Several factors influence the relationship between personal O_3 exposure and ambient concentration. Due to the lack of indoor O_3 sources, along with reduction of ambient O_3 that penetrates into enclosed microenvironments, indoor and in-vehicle O_3 concentrations are highly dependent on air exchange rate and therefore vary widely in different microenvironments. Ambient O_3 varies spatially due to reactions with other atmospheric species, especially near busy roadways where O_3 concentrations are decreased by reaction with NO (Section 3.6.2.1). This is in contrast with pollutants such as CO and NO_X, which show appreciably higher concentrations near the roadway than several hundred meters away (Karner et al., 2010). O_3 also varies temporally over multiple scales, with a generally increasing trend during the daytime hours, and higher O_3 concentrations during summer than in winter. An example of this variability is shown in Figure 4-1, taken from a personal exposure study conducted by Chang et al. (2000).

Hourly personal exposures are seen to vary from a few ppb in some indoor microenvironments to tens of ppb in vehicle and outdoor microenvironments. The increase in ambient O_3 concentration during the day is apparent from the outdoor monitoring data. In comparison, ambient $PM_{2.5}$ exhibits less temporal variability over the day than O_3, although personal exposure to $PM_{2.5}$ also varies by microenvironment. This combined spatial and temporal variability for O_3 results in varying relationships between personal exposure and ambient concentration.

Correlations between personal exposure to O_3 and corresponding ambient concentrations, summarized in Table 4-2, exhibit a wide range (generally 0.3-0.8, although both higher and lower values have been reported), with higher correlations generally observed in outdoor microenvironments, high building ventilation conditions, and during the summer season. Low O_3 concentrations indoors and during the winter lead to a high proportion of personal exposures below the sampler detection limit, which may partially explain the low correlations observed in some studies under those conditions. Ratios of personal exposure to ambient concentration, summarized in Table 4-3, are generally lower in magnitude (typically 0.1-0.3), and are also variable, with increasing time spent outdoors

associated with higher ratios. The next two subsections describe studies that have reported personal-ambient correlations and slopes for a variety of seasons, locations, and populations.



Source: Reprinted with permission of Air and Waste Management Association (Chang et al., 2000)
The notation below each clock hour shows the location or activity during that hour.

Figure 4-1 Variation in hourly personal and ambient concentrations of O_3 and $PM_{2.5}$ in various microenvironments during daytime hours.

O_3 concentrations near and below the passive sampler detection limit lead to uncertainty in personal-ambient correlations and ratios. Correlations are reduced in magnitude by values below the detection limit because noise obscures the underlying signal in the data, while ratios tend to fluctuate widely at low concentration since small changes in measured values cause large relative changes in resulting ratios. As with I/O ratios, this problem is particularly acute in the non-ozone season when ambient O_3 concentrations are low. Improved characterization of the relationship between personal exposure and ambient concentration will depend on improved monitoring techniques to accurately capture low O_3 concentrations, preferably at high time resolution to facilitate evaluation of the effect of activity pattern on exposure. Until new monitoring techniques are available, past studies summarized in the 2006 O_3 AQCD remain relevant to consider

along with more recent studies in evaluating personal-ambient concentration relationships.

Personal-Ambient Correlations. Correlations between personal exposure and ambient O_3 concentrations have been evaluated in several research studies, many of which were conducted prior to 2005 and are discussed in the 2006 O_3 AQCD. Some studies evaluated subject-specific, or longitudinal correlations, which describe multiple daily measurements for a single individual. These studies indicate the inter-individual variability of personal-ambient correlations. Another type of correlation is a pooled correlation, which combines data from multiple individuals over multiple monitoring periods (e.g., days), providing an overall indicator of the personal-ambient relationship for all study subjects. A third type of correlation is a community-average correlation, which correlates average exposure across all study subjects with fixed-site monitor concentrations. Community-average correlations are particularly informative for interpreting time-series epidemiologic studies, in which ambient concentrations are used as a surrogate for community-average exposure. However, few studies report this metric; this represents another opportunity for improvement of future personal exposure studies. Table 4-2 summarizes studies reporting personal-ambient correlations, and the studies in the table are discussed in the subsequent text.

The results of these studies indicate that personal exposures are moderately well correlated with ambient concentrations, and that the ratio of personal exposure to ambient concentration is higher in outdoor microenvironments and during the summer season. In situations where a lack of correlation was observed, this may be due in part to a high proportion of personal measurements below the detection limit. The effect of season is unclear, with mixed evidence on whether higher correlations are observed during the O_3 season. Chang et al. (2000) measured hourly personal exposures in multiple microenvironments and found that the pooled correlation between personal exposure and ambient concentration was highest for outdoor microenvironments (r = 0.68-0.91). In-vehicle microenvironments showed moderate to high correlations (0.57-0.72). Correlations in residential indoor microenvironments were very low (r = 0.05-0.09), with moderate correlations (0.34-0.46) in other indoor microenvironments such as restaurants and shopping malls. Liard et al. (1999) evaluated community-average correlations based on 4-day mean personal O_3 exposure measurements for adults and children and found a relatively high correlation (r = 0.83) with ambient concentrations, even though 31-82% of the personal measurements were below the detection limit. Sarnat et al. (2000) studied a population of older adults in Baltimore and found that longitudinal correlations between 24-h personal exposure and ambient concentration varied by subject and season, with somewhat higher correlations observed in this study during summer (mean = 0.20) than in winter (mean = 0.06). Some evidence was presented that subjects living in well-

ventilated indoor environments have higher correlations than those living in poorly ventilated indoor environments, although exceptions to this were also observed. Ramirez-Aguilar et al. (2008) measured 48- to 72-h personal exposures of four groups of asthmatic children aged 6-14 in Mexico City during 1998-2000. A moderate pooled correlation (r = 0.35) was observed between these exposures and corresponding ambient concentrations.

Table 4-2 Correlations between Personal and Ambient Ozone Concentration

Study	Location	Years/Season	Population	Sample duration	Correlation	Study Type	Others
Chang et al. (2000)	Baltimore, MD	Summer 1998	Older adults	1 h	0.91	Pooled	Outdoor near roadway
		Winter 1999			0.77		
		Summer 1998			0.68		Outdoor away from road
		Winter 1999			0.86		
		Summer 1998			0.72		In vehicle
		Winter 1999			0.57		
		Summer 1998			0.09		Indoors-residence
		Winter 1999			0.05		
		Summer 1998			0.34		Indoors-other
		Winter 1999			0.46		
Liard et al. (1999)	Paris, France	Summer 1996	All age groups	4 day	0.83	Community-averaged	
Sarnat et al. (2000)	Baltimore, MD	Summer	Older adults	24 h	0.20	Longitudinal	
		Winter			0.06		
Linn et al. (1996)	Southern California	All seasons from 1992 to 1993	Children	24 h	0.61	Community-averaged	
Brauer and Brook (1997)	Vancouver, Canada	Summers 1992 and 1993	Health clinic workers	24 h	0.60	Pooled	0-25% of time outdoors
			Camp counselors	24 h	0.42	Pooled	7.5-45% of time outdoors
			Farm workers	24 h	0.64	Pooled	100% of time outdoors
Ramírez-Aguilar et al. (2008)	Mexico City, Mexico	December 1998-April 2000	Asthmatic children	48 h to 72 h	0.35	Pooled	

NR = not reported

Consistent with hourly microenvironment-specific results from the Chang et al. (2000) study described above, studies have found moderate to high personal-ambient correlations for individuals spending time outdoors. A moderate pooled correlation of 0.61 was reported between 24-h avg personal and central-site measurements by Linn et al. (1996) for a population of southern California schoolchildren who spent an average of 101-136 minutes per day outdoors. The authors also report a correlation of 0.70 between central-site measurements and concentrations outside the children's schools. Although the average school outdoor concentration (34 ppb) was higher than the average central-site concentration (23 ppb) and the average personal exposure concentration was lower

(5 ppb) than the central-site value, the similarity between the correlations indicate that central-site monitor concentrations can represent personal exposures in addition to representing local outdoor concentrations. A study in Vancouver, BC provided another illustration of the effect of outdoor microenvironments on personal-ambient relationships by comparing three groups spending different amounts of time outdoors: health clinic workers (0-25% of time outdoors), camp counselors (7.5-45% of time outdoors), and farm workers (100% of time outdoors) (Brauer and Brook, 1997). Health clinic workers and camp counselors were monitored 24 h/day, while farm workers were monitored during their work shift (6-14 hours). In this study, the pooled correlations between personal exposure and fixed-site concentration not substantially different among the groups (r = 0.60, 0.42, and 0.64, respectively). The ratios of personal exposure to fixed-site monitor concentration increased among the groups with increasing amount of time spent outdoors (0.35, 0.53, and 0.96, respectively). This indicates that temporal variations in personal exposure to O_3 are driven by variations in ambient concentration, even for individuals that spend little time outdoors.

Personal-Ambient Ratios. Studies indicate that the ratio between personal O_3 exposure and ambient concentration varies widely, depending on activity patterns, housing characteristics, and season. Higher personal-ambient ratios are generally observed with increasing time spent outside, higher air exchange rate, and in seasons other than winter. Table 4-3 summarizes the results of several such studies discussed in the 2006 O_3 AQCD together with newer studies showing the same pattern of results.

O'Neill et al. (2003) studied a population of shoe cleaners working outdoors in Mexico City and presented a regression model indicating a 0.56 ppb increase in 6-h personal exposure for each 1 ppb increase in ambient concentration. Regression analyses by Sarnat et al. for 24-h data from mixed populations of children and older adults in Baltimore (2001) and Boston (2005) found differing results between the two cities, with Baltimore subjects showing a near-zero slope (0.01) during the summertime while Boston subjects showed a positive slope of 0.27 ppb personal exposure per 1 ppb ambient concentration. In both cities, the winter slope was near zero. The low slope observed in Baltimore may have been due to differences in time spent outdoors, residential ventilation conditions, or other factors. Xue et al. (2005) measured 6-day personal exposure of children in southern California and found that the average ratio of personal exposure to ambient concentration was relatively stable throughout the year at 0.3. These authors also regressed personal exposures on ambient concentration after adjusting for time-activity patterns and housing characteristics and found a slope of 0.54 ppb/ppb, with the regression R^2 value of 0.58. Unadjusted regression slopes were not presented.

Table 4-3 Ratios of Personal to Ambient Ozone Concentration

Study	Location	Years/Season	Population	Sample duration	Ratio	Study Type	Others
Sarnat et al. (2001)	Baltimore	Summer 1998	Older adults, children, and individuals with COPD	24 h	0.01	Longitudinal	
		Winter 1999			0.00		
Brauer and Brook (1997)	Vancouver, Canada	Summers 1992 and 1993	Health clinic workers	24 h	0.35	Pooled	0-25% of time outdoors
			Camp counselors		0.53	Pooled	7.5-45% of time outdoors
			Farm workers		0.96	Pooled	100% of time outdoors
O'Neill et al. (2003)	Mexico City, Mexico	April - July 1996	Shoe cleaners	6 h	0.56 95% CI: 0.43-0.69	Longitudinal	
Sarnat et al. (2005)	Boston	Summer	Older adults and children	24 h	0.27 95% CI: 0.18-0.37	Longitudinal	
		Winter			0.04 95% CI: 0.00-0.07		
Xue et al. (2005)	Southern California	June 1995 - May 1996	Children	6 day	0.3	Longitudinal	Ratio
					0.54		Regression slope (R^2 = 0.58)
Sarnat et al. (2006b)	Steubenville, OH	Summer	Older adults	24 h	0.15 SE: 0.02	Longitudinal	High-ventilation
					0.08 SE: 0.04		Low-ventilation
		Fall			0.27 SE: 0.03		High-ventilation
					0.20 SE: 0.05		Low-ventilation
Ramírez-Aguilar et al. (2008)	Mexico City, Mexico	Dec.1998-Apr. 2000	Asthmatic children	48 h to 72 h	0.17	Pooled	

NR = not reported

A few additional studies have been published since the 2006 O_3 AQCD comparing personal exposures with ambient concentrations, and these findings generally confirm the conclusions of the 2006 O_3 AQCD that ventilation conditions, activity pattern, and season may impact personal-ambient ratios. Sarnat et al. (2006b) measured 24-h personal exposures for a panel of older adults in Steubenville, OH during summer and fall 2000. Subjects were classified as high-ventilation or low-ventilation based on whether they spent time in indoor environments with open windows. Regression of personal exposures on ambient concentration found a higher slope for high-ventilation subjects compared with low-ventilation subjects in both summer (0.15 versus 0.08) and fall (0.27 versus 0.20). Suh and Zanobetti (2010) reported an average 24-h personal exposure of 2.5 ppb as compared to 24-h ambient concentration of 29 ppb for a group of individuals with either recent MI or diagnosed COPD in Atlanta. A similar result was observed in Detroit, where the mean 24-h personal exposure across 137 participants in summer and winter was 2.1 ppb, while the mean ambient concentration on sampling days was 25 ppb (Williams et al., 2009b). Although no personal exposures were measured, McConnell et al. (2006) found that average 24-h home outdoor O_3 concentrations were within 6 ppb of O_3 concentrations measured at central-site monitors in each of three southern California communities, with a combined average home outdoor concentration of 33 ppb compared to the central-site average of 36 ppb. In Mexico City, Ramirez-Aguilar et al. (2008)

regressed 48- to 72-h personal exposures of four groups of asthmatic children aged 6-14 with ambient concentrations and found slope of 0.17 ppb/ppb after adjustment for distance to the fixed-site monitor, time spent outdoors, an interaction term combining these two variables, and an interaction term representing neighborhood and study group.

4.3.4 Co-Exposure to Other Pollutants and Environmental Stressors

Exposure to ambient O_3 occurs in conjunction with exposure to a complex mixture of ambient pollutants that varies over space and time. Multipollutant exposure is an important consideration in evaluating health effects of O_3 since these other pollutants have either known or potential health effects that may impact health outcomes due to O_3. The co-occurrence of high O_3 concentrations with high heat and humidity may also contribute to health effects. This section presents data on relationships between overall personal O_3 exposure and exposure to other ambient pollutants, as well as co-exposure relationships for near-road O_3 exposure.

4.3.4.1 Personal Exposure to Ozone and Co-pollutants

Personal exposure to O_3 shows variable correlation with personal exposure to other pollutants, with differences in correlation depending on factors such as instrument detection limit, season, city-specific characteristics, and spatial variability of the copollutant. Suh and Zanobetti (2010) reported Spearman rank correlation coefficients during spring and fall between 24-h avg O_3 measurements and co-pollutants of 0.14, 0.00, and -0.03 for $PM_{2.5}$, EC, and NO_2, respectively. Titration of O_3 near roadways is likely to contribute to the low or slightly negative correlations with the traffic-related pollutants EC and NO_2. The somewhat higher correlation with $PM_{2.5}$ may reflect the influence of air exchange rate and time spent outdoors on co-exposures to ambient $PM_{2.5}$ and O_3. Overall, the copollutant correlations are quite small, which may be due to the very low personal exposures observed in this study (2-3 ppb), likely to be near or below the detection limit of the passive sampler over a 24-h period. Chang et al. (2000) measured hourly personal exposures to $PM_{2.5}$ and O_3 in summer and winter in Baltimore, Maryland. Correlations between $PM_{2.5}$ and O_3 were 0.05 and -0.28 in summer and winter, respectively. Results indicate personal O_3 exposures were not significantly associated with personal $PM_{2.5}$ exposures in either summer or winter. These non-significant correlations may be attributed in part to the relatively low personal O_3 exposures observed in this study; in both summer and winter, the mean personal O_3 exposure was below the calculated limit of detection.

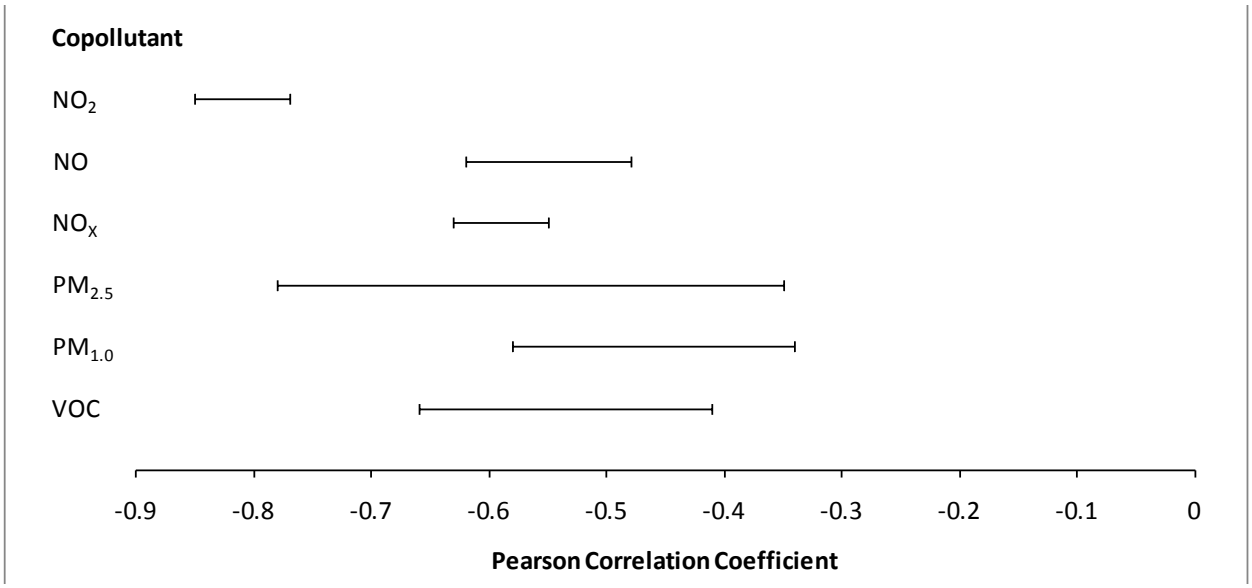
Studies conducted in Baltimore (Sarnat et al., 2001) and Boston (Sarnat et al., 2005) found differing results for the correlation between 24-h avg personal O_3 and personal $PM_{2.5}$ exposures, particularly during the winter season. Sarnat et al. (2001) found a positive slope when regressing personal exposures of both total $PM_{2.5}$ (0.21) and $PM_{2.5}$ of ambient origin (0.22) against personal O_3 exposures during the summer season, but negative slopes (-0.05 and -0.18, respectively) during the winter season. The summertime slope for personal $PM_{2.5}$ exposure versus personal O_3 exposure was much higher for children (0.37) than for adults (0.07), which may be the result of different activity patterns. This team of researchers also found a positive, although higher, summer slope between 24-h avg personal O_3 and personal $PM_{2.5}$ in Boston (0.72) (Sarnat et al., 2005). However, the winter slope was positive (1.25) rather than negative, as in Baltimore. In both cities during both seasons, there was a wide range of subject-specific correlations between personal O_3 and personal $PM_{2.5}$ exposures, with some subjects showing relatively strong positive correlations (>0.75) and others showing strong negative correlations (<-0.50). The median correlation in both cities was slightly positive in the summer and near zero (Boston) or slightly negative (Baltimore) in the winter. These results indicate the potential effects of city-specific characteristics, such as housing stock and building ventilation patterns, on relationships between O_3 and co-pollutants.

4.3.4.2 Near-Road Exposure to Ozone and Co-pollutants

Beckerman et al. (2008) measured both 1-week and continuous concentrations of O_3, NO, NO_2, NO_X, $PM_{2.5}$, $PM_{1.0}$, and several VOCs (the BTEX compounds, MTBE, hexane, and THC) in the vicinity of heavily traveled (annual average daily traffic [AADT] >340,000) roadways in Toronto, Canada. Passive samplers were deployed for one week in August 2004. Ozone concentrations were negatively correlated with all pollutants, with the exception of VOCs at one of the monitoring sites which were suspected of being influenced by small area sources. Site specific correlations are given in Figure 4-2. Correlations were -0.77 to -0.85 for NO_2, -0.48 to -0.62 for NO, and -0.55 to -0.63 for NO_X. Pooled correlations using data from both sites were somewhat lower in magnitude. $PM_{2.5}$ and $PM_{1.0}$ correlations were -0.35 to -0.78 and -0.34 to -0.58, respectively. At the monitoring site not influenced by small area sources, O_3-VOC correlations ranged from -0.41 to -0.66.

Beckerman et al. (2008) also made on-road measurements of multiple pollutants with a instrumented vehicle. Concentrations were not reported, but correlations between O_3 and other pollutants were negative and somewhat greater in magnitude (i.e., more negative) than the near-road correlations. SO_2, CO, and BC were measured in the mobile laboratory, although not at the roadside, and they all showed negative correlations with

O_3 when the data were controlled for site. Correlations for continuous concentrations between O_3 and co-pollutants were somewhat lower than the 1-week correlations, except for O_3-$PM_{2.5}$ correlations. Correlations were -0.90, -0.66, -0.77, and -0.89 for NO_2, NO, NO_X, and $PM_{1.0}$ respectively. The continuous O_3-$PM_{2.5}$ correlation was -0.62, which is in the range of the 1-week correlation.



Source data from: Beckerman et al. (2008)

Figure 4-2 Correlations between 1-week concentrations of O_3 and copollutants measured near roadways.

4.3.4.3 Indoor Exposure to Ozone and Co-pollutants

Ambient O_3 that infiltrates indoors reacts with organic compounds and other chemicals to form oxidized products, as described in Section 3.2.3 as well as the 2006 O_3 AQCD. It is anticipated that individuals are exposed to these reaction products, although no evidence was identified regarding personal exposures. The reactions are similar to those occurring in the ambient air, as summarized in Chapter 3. For example, O_3 can react with terpenes and other compounds from cleaning products, air fresheners, and wood products both in the gas phase and on surfaces to form particulate and gaseous species, such as formaldehyde (Chen et al., 2011; Shu and Morrison, 2011; Aoki and Tanabe, 2007; Reiss et al., 1995a). Ozone has also been shown to react with material trapped on HVAC filters and generate airborne products (Bekö et al., 2007; Hyttinen et al., 2006). Potential oxygenated reaction products have been found to act as irritants (Anderson et al., 2007),

indicating that these reaction products may have health effects separate from those of O_3 itself (Weschler and Shields, 1997). Ozone may also react to form other oxidants, which then go on to participate in additional reactions. White et al. (2010) found evidence that HONO or other oxidants may have been present during experiments to estimate indoor OH concentrations, indicating complex indoor oxidant chemistry. Rates of these reactions are dependent on indoor O_3 concentration, temperature, and air exchange rate, making estimation of exposures to reaction products difficult.

4.4 Exposure-Related Metrics

In this section, parameters are discussed that are relevant to the estimation of exposure, but are not themselves direct measures of exposure. Time-location-activity patterns, including behavioral changes to avoid exposure, have a substantial influence on exposure and dose. Proximity of populations to ambient monitors may influence how well their exposure is represented by measurements at the monitors, although factors other than distance play an important role as well.

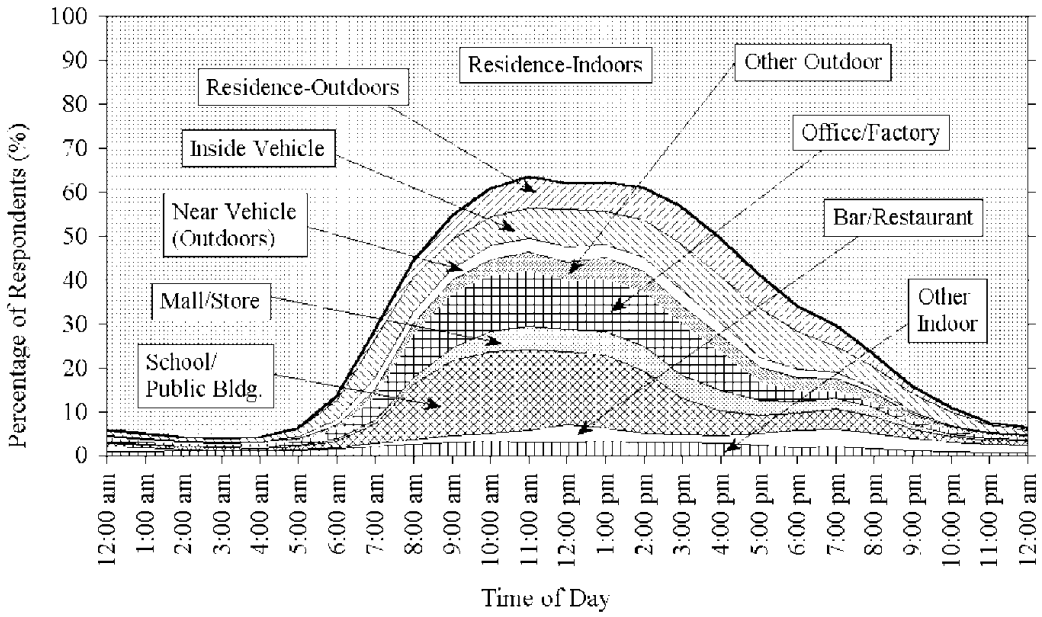
4.4.1 Activity Patterns

The activity pattern of individuals is an important determinant of their exposure. Variation in O_3 concentrations among various microenvironments means that the amount of time spent in each location, as well as the level of activity, will influence an individual's exposure to ambient O_3. The effect of activity pattern on exposure is explicitly accounted for in Equation 4-3 by the fraction of time spent in different microenvironments.

Activity patterns vary both among and within individuals, resulting in corresponding variations in exposure across a population and over time. Large-scale human activity databases, such as those developed for the National Human Activity Pattern Survey (NHAPS) (Klepeis et al., 2001) or the Consolidated Human Activity Database (CHAD) (McCurdy et al., 2000), which includes NHAPS data together with other activity study results, have been designed to characterize exposure patterns among much larger population subsets than can be examined during individual panel studies. The complex human activity patterns across the population (all ages) are illustrated in Figure 4-3 (Klepeis et al., 2001), which is presented to illustrate the diversity of daily activities among the entire population as well as the proportion of time spent in each microenvironment. For example, about 25% of the individuals reported being outdoors or in a vehicle between 2:00 and 3:00 pm, when daily O_3 levels are peaking, although about half

of this time was spent in or near a vehicle, where O_3 concentrations are likely to be lower than ambient concentrations. Different patterns would be anticipated when breaking down activity patterns only for subgroups such as children or the elderly. Population exposures can be estimated using O_3 concentration data in each microenvironment.

Longitudinal activity pattern information is also an important determinant of exposure, as different people may exhibit different patterns of time spent outdoors over time due to age, gender, employment, and lifestyle-dependent factors. These differences may manifest as higher mean exposures or more frequent high-exposure episodes some individuals. The extent to which longitudinal variability in individuals contributes to the population variability in activity and location can be quantified by the ratio of between-person variance to total variance in time spent in different locations and activities (the intraclass correlation coefficient, ICC). Xue et al. (2004) quantified ICC values in time-activity data collected by Harvard University for 160 children aged 7–12 years in Southern California (Geyh et al., 2000). For time spent outdoors, the ICC was approximately 0.15, indicating that 15% of the variance in outdoor time was due to between-person differences. The ICC value might be different for other population groups.



Source: Reprinted with permission of Nature Publishing Group (Klepeis et al., 2001).

Figure 4-3 Distribution of time that NHAPS respondents spent in ten microenvironments based on smoothed 1-min diary data.

The EPA's National Exposure Research Laboratory (NERL) has consolidated the majority of the most significant human activity databases into one comprehensive database called the Consolidated Human Activity Database (CHAD). The current version of CHAD contains data from nineteen human activity pattern studies (including NHAPS), which were evaluated to obtain over 33,000 person-days of 24-h human activities in CHAD (McCurdy et al., 2000). The surveys include probability-based recall studies conducted by EPA and the California Air Resources Board, as well as real-time diary studies conducted in individual U.S. metropolitan areas using both probability-based and volunteer subject panels. All ages of both genders are represented in CHAD. The data for each subject consist of one or more days of sequential activities, in which each activity is defined by start time, duration, activity type, and microenvironment classification (i.e., location). Activities vary from one minute to one hour in duration, with longer activities being subdivided into clock-hour durations to facilitate exposure modeling. CHAD also provides information on the level of exertion associated with each activity, which can be used by exposure models to estimate ventilation rate and pollutant dose.

4.4.2 Ozone Averting Behavior

Individuals can reduce their exposure to O_3 by altering their behaviors, such as reducing their time outdoors. To protect the public from O_3-related health effects, EPA and organizations such as the American Lung Association recommend that people spend more time indoors and engage in less strenuous activities on days with relatively high O_3 concentrations. To assist individuals concerned about O_3 conditions, EPA developed the Air Quality Index (AQI). This index combines information about O_3 (and other pollutant) concentrations to produce five categories of air-quality, ranging from good to very unhealthy. Forecasted and actual conditions typically are reported to the public during high-O_3 months through local media outlets, using various versions of this air-quality categorization scheme. These advisories explicitly state that children in general and children with asthma in particular are potentially sensitive to air pollution. Parents are advised to curtail children's outdoor exertion to varying degrees depending on the predicted pollution levels and whether their children have asthma or other relevant medical conditions.

Evidence of individual averting behaviors in response to advisories has been found in several studies, especially for susceptible populations, such as children, older adults, and asthmatics. Reduced time spent outdoors was reported in an activity diary study in 35 U.S. cities (Mansfield et al., 2006), which found that asthmatic children who spent at least some time outdoors reduced their total time spent outdoors by an average of 30 min on a code red O_3 day relative to a code green, yellow, or orange day; however, the

authors noted that there was appreciable variation in both the overall amount of time spent outdoors and the reduction in outdoor time on high ozone days among asthmatic children. Bresnahan et al. (1997) examined survey data collected during 1985-86 from a panel of adults in the Los Angeles area, many of whom had compromised respiratory function, by an averting behavior model. A regression analysis indicated that individuals with smog-related symptoms spent about 12 minutes less time outdoors over a two-day period for each 10 ppb increase in O_3 concentration above 120 ppb. Considering that the average daily maximum O_3 concentration at the time was approximately 180 ppb on days when the then-current standard (1-h max of 120 ppb) was exceeded, this implies that those individuals spent about 40 minutes less time outside per day on a typical high O_3 day compared to days with O_3 concentrations below the standard. However, the behavior was not specifically linked to exceedances or air quality alerts.

The fraction of individuals who reduce time spent outdoors, or restrict their children's outdoor activity, has been found to vary based on health status. In the Bresnahan et al. study (1997), 40 percent of respondents reported staying indoors on days when air quality was poor. Individuals who reported experiencing smog-related symptoms were more likely to take the averting actions, although the presence of asthma or other chronic respiratory conditions did not significantly affect behavior. A study of parents of asthmatic children (McDermott et al., 2006) suggests that parents are aware of the hazard of outdoor air pollution and the official alerts designed to protect them and their children. It also suggests that a majority of parents (55%) comply with recommendations of the alerts to restrict children's outdoor activity, with more parents of asthmatics reporting awareness and responsiveness to alerts. However, only 7% of all parents complied with more than one-third of the advisories issued (McDermott et al., 2006). Wen et al. (2009) analyzed data from the 2005 Behavioral Risk Factor Surveillance System (BRFSS) and indicated that people with lifetime asthma are about twice as likely as people without asthma to reduce their outdoor activities based on either media alerts of poor air quality (31% vs. 16%) or individual perception of air quality (26% vs. 12%). Respondents who had received advice from a health professional to reduce outdoor activity when air quality is poor were more likely to report a reduction based on media alerts, both for those with and without asthma. In a study of randomly selected individuals in Houston, TX and Portland, OR, Semenza et al. (2008) found that a relatively small fraction of survey respondents (9.7% in Houston, 10.5% in Portland) changed their behaviors during poor air quality episodes. This fraction is appreciably lower than the fraction reported for people with asthma in the Wen et al. (2009) study, although it is similar to the fraction reported in that study for those without asthma. Most of the people in the Semenza et al. (2008) study reported that their behavioral changes were motivated by self-perception of poor air quality rather than an air quality advisory. It should be noted that the McDermott

et al. (2006), Wen et al. (2009), and Semenza et al. (2008) studies evaluated air quality in general and therefore are not necessarily specific to O_3.

Commuting behavior does not seem to change based on air quality alerts. A study in the Atlanta area showed that advisories can raise awareness among commuters but do not necessarily result in a change in an individual's travel behavior (Henry and Gordon, 2003). This finding is consistent with a survey for 1000 commuters in Denver, Colorado, which showed that the majority (76%) of commuters heard and understood the air quality advisories, but did not alter their commuting behavior (Blanken et al., 2001).

Some evidence is available for other behavioral changes in response to air quality alerts. Approximately 40 percent of the respondents in the Los Angeles study by Bresnahan et al. (1997) limited or rearranged leisure activities, and 20 percent increased use of air conditioners. As with changes in time spent outdoors, individuals who reported experiencing smog-related symptoms, but not those with asthma or chronic respiratory conditions, were more likely to take the averting actions. Other factors influencing behavioral changes, such as increased likelihood of averting behavior among high school graduates, are also reported in the study. In a separate Southern California study, attendance at two outdoor facilities (i.e. a zoo and an observatory) was reduced by 6-13% on days when smog alerts were announced, with greater decreases observed among children and older adults (Neidell, 2010, 2009).

The studies discussed in this section indicate that averting behavior is dependent on several factors, including health status and lifestage. People with asthma and those experiencing smog-related symptoms reduce their time spent outdoors and are more likely to change their behavior than those without respiratory conditions. Children and older adults appear more likely to change their behavior than the general population. Commuters, even when aware of air quality advisories, tend not to change their commuting behavior.

4.4.3 Population Proximity to Fixed-Site Ozone Monitors

The distribution of O_3 monitors across urban areas varies between cities (Section 3.6.2.1), and the population living near each monitor varies as well. Monitoring sites in rural areas are generally located in national or state parks and forests, and these monitors may be relevant for exposures of exercising visitors as well as those who live in similar locations. Rural monitors tend to be less affected than urban monitors by strong and highly variable anthropogenic sources of species participating in the formation and destruction of O_3 (e.g., onroad mobile sources) and more highly influenced by regional transport of O_3 or O_3 precursors (Section 3.6.2.2). This may contribute to less diel

variability in O_3 concentration than is observed in urban areas. It is not necessarily true that proximity to a monitor determines the degree to which that monitor represents an individual's ambient exposure, but proximity is one indicator. One way to calculate monitor representativeness is to calculate the fraction of the urban population living within a certain radius of a monitor. Table 4-4 presents the fraction of the population in selected cities living within 1, 5, 10, and 20 km of an O_3 monitor. Values are presented for both total population and for those under 18 years of age, a potentially susceptible population to the effects of O_3. The data indicate that relatively few people live within 1 km of an O_3 monitor, while nearly all of the population in most cities lives within 20 km of a monitor. Many O_3 monitors are sited at "neighborhood scale," intended to represent an area of the city with dimensions in the 0.5-4 km range (Section 3.5.6.1). Looking at the results for a 5-km radius, generally 20-30% of the population lives within this distance from an O_3 monitor. Some cities have a greater population in this buffer, such as Salt Lake City, while others have a lower percentage, such as Minneapolis and Seattle. Percentages for children are generally similar to the total population, with no clear trend.

Another approach is to divide the metropolitan area into sectors surrounding each monitor such that every person in the sector lives closer to that monitor than any other. This facilitates calculation of the fraction of the city's population represented (according to proximity) by each monitor. In Atlanta, for example, the population fraction represented by each of the 11 monitors in the city ranged from 2.9-22%. The two monitors closest to the city center (sites A and B on Figure 3-24) accounted for 16% and 8% of the population, respectively. Site B has two listed monitoring objectives, highest concentration and population exposure. The other monitor in Atlanta with a listed objective of highest concentration is Site C, which represents the largest fraction of the population (22%). The eight monitors with a primary monitoring objective of population exposure account for 2.9-17% of the population per monitor.

Table 4-4 Fraction of the 2009 population living within a specified distance of an ozone monitor in selected U.S. cities

	Population		Within 1 km		Within 5 km		Within 10 km		Within 20 km	
City	Total	<18 yr	Total	<18 yr	Total	<18 yr	Total	<18 yr	Total	<18 yr
Atlanta CSA	5,901,670	1,210,932	0.3%	0.3%	8%	9%	28%	29%	75%	77%
Baltimore CSA	8,421,016	1,916,106	1.3%	1.1%	25%	24%	57%	55%	89%	89%
Birmingham CSA	1,204,399	281,983	1.4%	1.6%	22%	24%	56%	59%	73%	74%
Boston CSA	7,540,533	1,748,918	0.9%	0.9%	17%	16%	49%	47%	85%	85%
Chicago CSA	9,980,113	2,502,454	1.5%	1.5%	28%	29%	63%	65%	89%	91%
Dallas CSA	6,791,942	1,530,877	0.4%	0.4%	13%	13%	45%	44%	87%	87%
Denver CSA	3,103,801	675,380	1.7%	1.6%	35%	36%	66%	68%	92%	93%
Detroit CSA	5,445,448	1,411,875	0.8%	0.9%	15%	17%	42%	44%	77%	78%
Houston CSA	5,993,633	1,387,851	1.5%	1.8%	26%	28%	54%	57%	83%	84%
Los Angeles CSA	18,419,720	4,668,441	1.6%	1.7%	28%	29%	77%	79%	98%	98%
Minneapolis CSA	3,652,490	872,497	0.3%	0.3%	5%	4%	16%	16%	57%	56%
New York CSA	22,223,406	5,284,875	1.5%	1.7%	23%	23%	51%	50%	91%	91%
Philadelphia CSA	6,442,836	1,568,878	0.9%	1.0%	22%	24%	55%	56%	89%	89%
Phoenix CBSA	4,393,462	873,084	2.0%	2.4%	35%	41%	74%	79%	96%	97%
Pittsburgh CSA	2,471,403	563,309	1.5%	1.4%	22%	21%	52%	50%	88%	88%
Salt Lake City CSA	1,717,045	460,747	3.0%	3.0%	41%	38%	79%	79%	95%	95%
San Antonio CBSA	2,061,147	484,473	0.5%	0.5%	12%	12%	42%	43%	78%	80%
San Francisco CSA	7,497,443	1,675,711	2.6%	2.9%	41%	40%	81%	81%	98%	98%
Seattle CSA	4,181,278	918,309	0.3%	0.3%	5%	5%	18%	16%	43%	39%
St. Louis CSA	2,914,754	720,746	1.3%	1.5%	17%	18%	52%	53%	80%	82%

Atlanta population fractions for children (<18 years of age) are similar to those for the general population, but other populations show a different pattern of monitor representativeness. Older adults (age 65 and up) were somewhat differently distributed with respect to the monitors, with most monitors showing a difference of more than a percentage point compared to the general population. Based on 2000 population data, the fraction of older adults closest to the two city center monitors (A and B) was 4% higher and 2% lower, respectively, than the fraction for the population as a whole. Site C showed the highest differential, with 21% of the total population but only 15% of the older adult population. This indicates the potential for monitors to differentially represent potentially susceptible populations.

4.5 Exposure Modeling

In the absence of personal exposure measurements, modeling techniques are used to estimate exposures, particularly for large populations for which individual-level measurements would be impractical. Model estimates may be used as inputs to epidemiologic studies or as stand-alone assessments of the level of exposure likely to be experienced by a population under certain air quality conditions. This section describes approaches used to improve exposure estimates, including concentration surface modeling, which calculates local outdoor concentrations over a geographic area; air exchange rate modeling, which estimates building ventilation based on housing characteristics and meteorological parameters; and microenvironment-based exposure modeling, which combines air quality data with demographic information and activity pattern simulations to estimate time-weighted exposures based on concentrations in multiple microenvironments. These models each have strengths and limitations, as summarized in Table 4-5. The remainder of this section provides more detail on specific modeling approaches, as well as results of applying the models.

Table 4-5 Characteristics of exposure modeling approaches

Model Type	Model	Description	Strengths	Limitations
Concentration Surface	Spatial Interpolation (e.g., Inverse Distance Weighting, Kriging)	Measured concentrations are interpolated across an area to yield local outdoor concentration estimates	High concentration resolution; uses available data; requires low to moderate resources for implementation	Spatial heterogeneity not fully captured; a single high-concentration monitor can skew results; no location-activity information
	Chemistry-transport (e.g., CMAQ)	Grid-based O_3 concentrations are calculated from precursor emissions, meteorology, and atmospheric chemistry and physics	First-principles characterization of physical and chemical processes influencing O_3 formation	Grid cell resolution; resource-intensive; no location-activity information
	Land-use regression (LUR)	Merges concentration data with local-scale variables such as land use factors to yield local concentration surface	High concentration resolution	Reactivity and small-scale spatial variability of O_3; location-specific, limiting generalizability; no location-activity information
Air Exchange Rate	Mechanistic (LBL, LBLX)	Uses database on building leakage tests to predict AER based on building characteristics and meteorological variables (including natural ventilation in LBLX)	Physical characterization of driving forces for air exchange	Moderate resource requirement; no location-activity information
	Empirical	Predicts AER based on factors such as building age and floor area	Low input data requirements	Cannot account for meteorology; no location-activity information
Integrated Microenvironmental Exposure and Dose	Population (APEX, SHEDS)	Stochastic treatment of air quality data, demographic variables, and activity pattern to generate estimates of microenvironmental concentrations, exposures, and doses	Probabilistic estimates of exposure and dose distributions for specific populations; consideration of nonambient sources; small to moderate uncertainty for exercising asthmatic children (APEX)	Resource-intensive; evaluation with measured exposures; underestimation of multiple high-exposure events in an individual (APEX)

4.5.1 Concentration Surface Modeling

One approach to improve exposure estimates in urban areas involves construction of a concentration surface over a geographic area, with the concentration at locations between monitors estimated using a model to compensate for missing data. The calculated O_3 concentration surface can then be used to estimate exposures outside residences, schools, workplaces, roadways, or other locations of interest. This technique does not estimate exposure directly because it does not account for activity patterns or concentrations in different microenvironments. There are three main types of approaches: spatial interpolation of measured concentrations; statistical models using meteorological variables, pollutant concentrations, and other predictors to estimate concentrations at receptors in the domain; and rigorous first-principle models, such as chemistry-transport models or dispersion models incorporating O_3 chemistry. Some researchers have developed models that combine these techniques. The models may be applied over urban, regional, or national spatial scales, and can be used to estimate daily concentrations or longer-term averages. This discussion will focus on short-term concentrations estimated across urban areas.

The 2006 O_3 AQCD discussed concentration surface models, focusing on chemistry-transport models as well as geospatial and spatiotemporal interpolation techniques (e.g., Christakos and Vyas, 1998a, b; Georgopoulos et al., 1997). Recent research has continued to refine and extend the modeling approaches. A few recent papers have compared different approaches for the same urban area.

Marshall et al. (2008) compared four spatial interpolation techniques for estimation of O_3 concentrations in Vancouver, BC. The investigators assigned a daily average O_3 concentration to each of the 51,560 postal-code centroids using one of the following techniques: (1) the concentration from the nearest monitor within 10 km; (2) the average of all monitors within 10 km; (3) the inverse-distance-weighted (IDW) average of all monitors in the area; and (4) the IDW average of the 3 closest monitors within 50 km. Method 1 (the nearest-monitor approach) and Method 4 (IDW-50 km) had similar mean and median estimated annual- and monthly-average concentrations, although the 10th-90th percentile range was smaller for IDW-50. This is consistent with the averaging of extreme values inherent in IDW methods. The Pearson correlation coefficient between the two methods was 0.93 for monthly-average concentrations and 0.78 for annual-average concentrations. Methods 2 and 3 were considered sub-optimal and were excluded from further analysis. In the case of Method 2, a single downtown high-concentration monitor skewed the results in the vicinity, partially as a result of the asymmetric layout of the coastal city of Vancouver. Method 3 was too spatially homogenous because it assigned most locations a concentration near the regional average, except for locations

immediately adjacent to a monitoring site. CMAQ concentration estimates using a 4 km×4 km grid were also compared to the interpolation techniques in this study. Mean and median concentrations from CMAQ were approximately 50% higher than Method 1 and Method 4 estimates for both annual and monthly average concentrations. This may be due in part to the CMAQ grid size, which was too coarse to reveal near-roadway decrements in O_3 concentration due to titration by NO. The IQR for the annual average was similar between CMAQ and the interpolation techniques, but the monthly average CMAQ IQR was approximately twice as large, indicating a seasonal effect.

Bell (2006) compared CMAQ estimates for northern Georgia with nearest-monitor and spatial interpolation techniques, including IDW and kriging. The area-weighted concentration estimates from CMAQ indicated areas of spatial heterogeneity that were not captured by approaches based on the monitoring network. The author concluded that some techniques, such as spatial interpolation, were not suitable for estimation of exposure in certain situations, such as for rural areas. Using the concentration from the nearest monitor resulted in an overestimation of exposure relative to model estimates.

Land use regression (LUR) models have been developed to estimate levels of air pollutants, predominantly NO_2, as a function of several land use factors, such as land use designation, traffic counts, home heating usage, point source strength, and population density (Ryan and LeMasters, 2007; Gilliland et al., 2005; Briggs et al., 1997). LUR, initially termed regression mapping (Briggs et al., 1997), is a regression derived from monitored concentrations as a function of data from a combination of the land use factors. The regression is then used for predicting concentrations at multiple locations based on the independent variables at those particular locations without monitors. Hoek et al. (2008) warn of several limitations of LUR, including distinguishing real associations between pollutants and covariates from those of correlated co-pollutants, limitations in spatial resolution from monitor data, applicability of the LUR model under changing temporal conditions, and introduction of confounding factors when LUR is used in epidemiologic studies. These limitations may partially explain the lack of LUR models that have been developed for O_3 at the urban scale. Brauer et al. (2008) evaluated the use of LUR and IDW-based spatial-interpolation models in epidemiologic analyses for several different pollutants in Vancouver, BC and suggested that LUR is appropriate for directly-emitted pollutants with high spatial variability, such as NO and BC, while IDW is appropriate for secondary pollutants such as NO_2 and $PM_{2.5}$ with less spatial variability. Although O_3 is also a secondary pollutant, its reactivity and high small-scale spatial variability near high-traffic roadways indicates this conclusion may not apply for O_3.

At a much larger spatial scale, EU-wide, Beelen et al. (2009) compared a LUR model for O_3 with ordinary kriging and universal kriging, which incorporated meteorological, topographical, and land use variables to characterize the underlying trend. The LUR model performed reasonably well at rural locations (5-km resolution), explaining a higher percentage of the variability ($R^2 = 0.62$) than for other pollutants. However, at the urban scale (1-km resolution), only one variable was selected into the O_3 LUR model (high-density residential land use), and the R^2 value was very low (0.06). Universal kriging was the best method for the large-scale composite EU concentration map, for O_3 as well as for NO_2 and PM_{10}, with an R^2 value for O_3 of 0.70. The authors noted that these methods were not designed to capture spatial variation in concentrations that are known to occur within tens of meters of roadways (Section 3.6.2.1), which could partially explain poor model performance at the urban scale.

Titration of O_3 with NO emitted by motor vehicles tends to reduce O_3 concentrations near roadways. McConnell et al. (2006) developed a regression model to predict residential O_3 concentrations in southern California using estimates of residential NO_X calculated from traffic data with the CALINE4 line source dispersion model. The authors estimated that local traffic contributes 18% of NO_X concentrations measured in the study communities, with the remainder coming from regional background. Their regression model indicates that residential NO_X reduces residential O_3 concentrations by 0.51 ppb O_3 per 1 ppb NO_X, and that a 10th-90th percentile increase in local NO_X results in a 7.5 ppb decrease in local O_3 concentrations. This intra-urban traffic-related variability in O_3 concentrations suggests that traffic patterns are an important factor in the relationship between central site monitor and residential O_3, and that differences in traffic density between the central site monitor and individual homes could result in either an overestimate or underestimate of residential O_3.

A substantial number of researchers have used geostatistical methods and chemistry-transport models to estimate O_3 concentrations at urban, regional, national, and continental scales, both in the U.S. and in other countries (Section 3.3). In addition to short-term exposure assessment for epidemiologic studies, such models may also be used for long-term exposure assessment, O_3 forecasts, or evaluating emission control strategies. It is difficult to determine the utility of these methods for exposure assessment; while improved local-scale estimates of outdoor concentrations may contribute to better assignment of exposures, information on activity patterns is needed to produce estimates of personal exposure.

4.5.2 Residential Air Exchange Rate Modeling

The residential air exchange rate (AER), which is the airflow into and out of a home, is an important mechanism for entry of ambient O_3. As described in Section 4.3.2, the indoor-outdoor relationship is greatly affected by the AER. Since studies show that people spend approximately 66% of their time indoors at home (Leech et al., 2002; Klepeis et al., 2001), the residential AER is a critical parameter for exposure models, such as APEX, SHEDS, and EMI (discussed in Section 4.5.3) (U.S. EPA, 2011b, 2009b; Burke et al., 2001). Since the appropriate AER measurements may not be available for exposure models, mechanistic and empirical (i.e., regression-based) AER models can be used for exposure assessments. The input data for the AER models can include building characteristics (e.g., age, number of stories, wind sheltering), occupant behavior (e.g., window opening), climatic region, and meteorology (e.g., local temperature and wind speed). Mechanistic AER models use these meteorological parameters to account for the physical driving forces of the airflows due to pressure differences across the building envelope from wind and indoor-outdoor temperature differences (ASHRAE, 2009). Empirical AER models do not consider the driving forces from the wind and indoor-outdoor temperature differences. Instead, a scaling constant can be used based on factors such as building age and floor area (Chan et al., 2005b).

Single-zone mechanistic models represent a whole-building as a single, well-mixed compartment. These AER models, such as the Lawrence Berkeley Laboratory (LBL) model, can predict residential AER using input data from whole-building pressurization tests (Sherman and Grimsrud, 1980), or leakage area models (Breen et al., 2010; Sherman and McWilliams, 2007). Recently, the LBL air infiltration model was linked with a leakage area model using population-level census and residential survey data (Sherman and McWilliams, 2007) and individual-level questionnaire data (Breen et al., 2010). The LBL model, which predicts the AER from air infiltration (i.e., small uncontrollable openings in the building envelope) was also extended to include airflow from natural ventilation (LBLX), and evaluated using window opening data (Breen et al., 2010). The AER predictions from the LBL and LBLX models were compared to daily AER measurements on seven consecutive days during each season from detached homes in central North Carolina (Breen et al., 2010). For the individual model-predicted and measured AER, the median absolute difference was 43% (0.17 h^{-1}) and 40% (0.17 h^{-1}) for the LBL and LBLX models, respectively. Given the uncertainty of the AER measurements (accuracy of 20-25% for occupied homes), these results demonstrate the feasibility of using these AER models for both air infiltration (e.g., uncontrollable openings) and natural ventilation (e.g., window opening) to help reduce the AER uncertainty in exposure models. The capability of AER models could help support the exposure modeling needs, as described in Section 4.5.3, which includes the ability to

predict indoor concentrations of ambient O_3 that may be substantial for conditions of high AER such as open windows.

4.5.3 Microenvironment-Based Models

Population-based methods, such as the Air Pollution Exposure (APEX) and Stochastic Human Exposure and Dose Simulation (SHEDS) integrated microenvironmental exposure and dose models, involve stochastic treatment of the model inputs (U.S. EPA, 2009b; Burke et al., 2001). These are described in detail in the 2008 NO_X ISA (U.S. EPA, 2008b), in AX3.6.1. Stochastic models utilize distributions of pollutant-related and individual-level variables, such as ambient and local O_3 concentration contributions and breathing rate respectively, to compute the distribution of individual exposures across the modeled population. The models also have the capability to estimate received dose through a dosimetry model. Using distributions of input parameters in the model framework rather than point estimates allows the models to incorporate uncertainty and variability explicitly into exposure estimates (Zidek et al., 2007). These models estimate time-weighted exposure for modeled individuals by summing exposure in each microenvironment visited during the exposure period.

The initial set of input data for population exposure models is ambient air quality data, which may come from a monitoring network or model estimates. Estimates of concentrations in a set of microenvironments are generated either by mass balance methods, which can incorporate AER models (Section 4.5.3), or microenvironmental factors. Microenvironments modeled include indoor residences; other indoor locations, such as schools, offices, and public buildings; and vehicles. The sequence of microenvironments and exertion levels during the exposure period is determined from characteristics of each modeled individual. The APEX model does this by generating a profile for each simulated individual by sampling from distributions of demographic variables such as age, gender, and employment; physiological variables such as height and weight; and situational variables such as living in a house with a gas stove or air conditioning. Activity and location (microenvironmental) patterns from a database such as CHAD are assigned to the simulated individual in a longitudinal manner, using age, gender, and biometric characteristics (U.S. EPA, 2009a; Glen et al., 2008). Breathing rates for each individual are calculated for each activity based on predicted energy expenditures, and the corresponding received intake or blood dose may then be computed. APEX has an algorithm to estimate O_3 dose and changes in FEV_1 resulting from O_3 exposure. Summaries of individual- and population-level metrics are produced, such as maximum exposure or dose, number of individuals exceeding a specified exposure/dose, and number of person-days at or above benchmark exposure levels. The

models also consider the nonambient contribution to total exposure. Nonambient source terms are added to the infiltration of ambient pollutants to calculate the total concentration in the microenvironment. Output from model runs with and without nonambient sources can be compared to estimate the ambient contribution to total exposure and dose.

Georgopoulos et al. (2005) used a version of the SHEDS model as the exposure component of a modeling framework known as MENTOR (Modeling Environment for Total Risk Studies) in a simulation of O_3 exposure in Philadelphia over a 2-week period in July 1999. 500 individuals were sampled from CHAD in each of 482 census tracts to match local demographic characteristics from U.S. Census data. Outdoor concentrations over the modeling domain were calculated from interpolation of photochemical modeling results and fixed-site monitor concentrations. These concentrations were then used as input data for SHEDS. Median microenvironmental concentrations predicted by SHEDS for nine simulated microenvironments were strongly correlated with outdoor concentrations, a result consistent with the lack of indoor O_3 sources in the model. A regression of median microenvironmental concentrations against outdoor concentrations indicated that the microenvironmental concentrations were appreciably lower than outdoor concentrations (regression slope = 0.26). 95th percentile microenvironmental concentrations were also well correlated with outdoor concentrations and showed a regression slope of 1.02, although some microenvironmental concentrations were well below the outdoor values. This suggests that in most cases the high-end concentrations were associated with outdoor microenvironments. Although the authors did not report exposure statistics for the population, their dose calculations also indicated that O_3 dose due to time spent outdoors dominated the upper percentiles of the population dose distribution. They found that both the 50th and 95th percentile O_3 concentrations were correlated with census-tract level outdoor concentrations estimated by photochemical modeling combined with spatiotemporal interpolation, and attributed this correlation to the lack of indoor sources of O_3. Relationships between exposure and concentrations at fixed-site monitors were not reported.

As part of the previous NAAQS review completed in 2008, EPA's Office of Air Quality Planning and Standards used APEX-O3 to estimate O_3 exposures in 12 cities during the O_3 monitoring seasons of 2002-04 and reported the results in the 2007 O_3 Staff Paper (U.S. EPA, 2007b). Exposures were modeled for the general population, school-age children (ages 5-18), and asthmatic school-age children. Hourly air quality input data from monitors in each city were adjusted to simulate just meeting various alternative standards, ranging from 65 to 85 ppb (8-h average), to demonstrate the effect of different standards on O_3 exposure metrics. O_3 decay (i.e., reaction) in indoor microenvironments was modeled, but no indoor O_3 sources were included.

Results of the model runs indicated that children and asthmatic children had similar exposures, with the general population experiencing lower exposure. For example, in Boston using 2002 air quality data adjusted to meet the then-current 8-h standard of 0.08 ppm (fourth-highest maximum averaged over 3 yr), approximately 28% of children or asthmatic children were estimated to experience one or more 8-h avg exposures of 70 ppb or greater during an 8-h period in which they engaged in moderate exercise. In comparison, about 10% of the general population (including children) would experience a 70 ppb-8h or greater exposure under the same conditions (Exhibit 2 and Figure 4-7 of the Staff Paper). A similar pattern was observed in other cities, although the magnitude of exposure was different. In most cases, exposures were substantially higher in 2002 than 2004, with 2003 exposures in between the estimates for the other two years (Figure 4-8 of the Staff Paper).

Exposures were quite variable across cities due primarily to differing air quality distributions that resulted in a differential result from the air quality adjustment procedure. For example, the same 74 ppb-8h (fourth maximum) alternative standard scenario for 2002 estimated that 10% of Boston children but very few (<0.5%) of Los Angeles children experience exposures above 70 ppb-8h while engaged in moderate exertion. The relationship between the fourth-highest concentrations (the basis for the air quality adjustment) and the remainder of the air quality distribution is quite different between the two cities, with the result that more of the upper range of the air quality data was rolled back in Los Angeles than in Boston. This substantially reduced the occurrence of modeled high-end exposures.

Simulations indicate that meeting O_3 air quality standards would reduce the fraction of individuals experiencing high-end exposures, as expected. Using unadjusted 2004 air quality data (the lowest of the three years simulated), the estimate of the fraction of children experiencing a 60 ppb-8h exposure while engaging in moderate exertion ranged from 12% (Chicago) to 69% (Los Angeles). Adjusting air quality data to meet fourth-maximum alternative standards of 85, 75, and 65 ppb reduced that range to 1-26%, 0-11%, and 0-1%, respectively (Exhibit 9 of the Staff Paper).

An analysis has been conducted for the APEX model to evaluate the contribution of uncertainty in input parameters and databases to the uncertainty in model outputs (Langstaff, 2007). The Monte Carlo analysis indicates that the uncertainty in model exposure estimates for asthmatic children during moderate exercise is small to moderate, with 95% confidence intervals of at most ± 6 percentage points at exposures above 60, 70, and 80 ppb (8-h avg) However, APEX appears to substantially underestimate the frequency of multiple high-exposure events for a single individual. The two main sources of uncertainty identified were related to the activity pattern database and the spatial

interpolation of fixed-site monitor concentrations to other locations. One area of potential improvement in the activity pattern database is additional information on children's activities, including longitudinal patterns. Improved information on spatial variation of O_3 concentrations, including in near-roadway and indoor microenvironments, would also contribute to reduced uncertainty. Another area of need is for improved personal exposure monitors with shorter averaging times to capture peak exposures and lower detection limits to capture low indoor concentrations. A similar modeling approach is currently being developed which is suitable for panel epidemiologic studies or for controlled human exposure studies, in which activity pattern data specific to the individuals in the study can be collected. Time-activity data is combined with questionnaire data on housing characteristics, presence of indoor or personal sources, and other information to develop a personalized set of model input parameters for each individual. This model, the Exposure Model for Individuals, is under development by EPA's National Exposure Research Laboratory (U.S. EPA, 2011b; Zartarian and Schultz, 2010).

4.6 Implications for Epidemiologic Studies

Exposure measurement error, which refers to the uncertainty associated with using exposure metrics to represent the actual exposure of an individual or population, can be an important contributor to variability in epidemiologic study results. Time-series studies assess the daily health status of a population of thousands or millions of people over the course of multiple years (i.e., thousands of days) across an urban area by estimating their daily exposure using a short monitoring interval (hours to days). In these studies, the community-averaged concentration of an air pollutant measured at central-site monitors is typically used as a surrogate for individual or population ambient exposure. In addition, panel studies, which consist of a relatively small sample (typically tens) of study participants followed over a period of days to months, have been used to examine the health effects associated with short-term exposure to ambient concentrations of air pollutants (Delfino et al., 1996). Panel studies may also apply a microenvironmental model to represent exposure to an air pollutant. A longitudinal cohort epidemiologic study, such as the ACS cohort study, typically involves hundreds or thousands of subjects followed over several years or decades (Jerrett et al., 2009). Concentrations are generally aggregated over time and by community to estimate exposures.

Exposure error can under- or over-estimate epidemiologic associations between ambient pollutant concentrations and health outcomes by biasing effect estimates toward or away from the null. Exposure misclassification can also tend to obscure the presence of thresholds for health effects, as demonstrated by a simulation study of nondifferential

exposure misclassification (Brauer et al., 2002). The importance of exposure misclassification varies with study design and is dependent on the spatial and temporal aspects of the design. For example, the use of a community-averaged O_3 concentration in a time-series epidemiologic study may be adequate to represent the day-to-day temporal concentration variability used to evaluate health effects, but may not capture differences in the magnitude of exposure due to spatial variability. Other factors that could influence exposure estimates include nonambient exposure, topography of the natural and built environment, meteorology, measurement errors, use of ambient O_3 concentration as a surrogate for ambient O_3 exposure, and the presence of O_3 in a mixture of pollutants. The following sections will consider various sources of error and how they affect the interpretation of results from epidemiologic studies of different designs.

4.6.1 Nonambient Ozone Exposure

For other criteria pollutants, nonambient sources can be an important contributor to total personal exposure. There are relatively few indoor sources of O_3; as a result, personal O_3 exposure is expected to be dominated by ambient O_3 in outdoor microenvironments and in indoor microenvironments with high air exchange rates (e.g., with open windows). Even in microenvironments where nonambient exposure is substantial, such as in a room with an O_3 generator, this nonambient exposure is unlikely to be temporally correlated with ambient O_3 exposure (Wilson and Suh, 1997), and therefore would not affect epidemiologic associations between O_3 and a health effect (Sheppard et al., 2005). In simulations of a nonreactive pollutant, Sheppard et al. (2005) concluded that nonambient exposure does not influence the health outcome effect estimate if ambient and nonambient concentrations are independent. Since personal exposure to ambient O_3 is some fraction of the ambient concentration, it should be noted that effect estimates calculated based on personal exposure rather than ambient concentration will be increased in proportion to the ratio of ambient concentration to ambient exposure, and daily fluctuations in this ratio can widen the confidence intervals in the ambient concentration effect estimate, but uncorrelated nonambient exposure will not bias the effect estimate.

4.6.2 Spatiotemporal Variability

Spatial and temporal variability in O_3 concentrations can contribute to exposure error in epidemiologic studies, whether they rely on central-site monitor data or concentration modeling for exposure assessment. Spatial variability in the magnitude of concentrations may affect cross-sectional and large-scale cohort studies by undermining the assumption

that intra-urban concentration and exposure differences are less important than inter-urban differences. This issue may be less important for time-series studies, which rely on day-to-day temporal variability in concentrations to evaluate health effects. Low inter-monitor correlations contribute to exposure error in time-series studies, including bias toward the null and increased confidence intervals.

The averaging time of the daily exposure metrics used to evaluate daily aggregated health data (e.g., 1-h or 8-h daily maximum vs. 24-h avg concentration) may also impact epidemiologic results, since different studies report different daily metrics. Correlations between 1-h daily max, 8-h daily max, and 24-h avg concentrations for U.S. monitoring sites are presented in Section 3.6.1 (Figure 3-18 and accompanying text). The two daily peak values (1-h max and 8-h max) are well correlated, with a median (IQR) correlation of 0.97 (0.96-0.98). The correlation between the 8-h max and 24-h avg are somewhat less well correlated with a median (IQR) correlation of 0.89 (0.86-0.92). While this may complicate quantitative comparisons between epidemiologic studies using different daily metrics, as well as the interpretation of studies using metrics other than the current 8-h standard, the high inter-metric correlations suggest it is a relatively small source of uncertainty in comparing the results of studies using different metrics. This is supported by a study comparing each of these metrics in a time-series study of respiratory ED visits (Darrow et al., 2011b), which found positive associations for all metrics, with the strongest association for the 8-h daily max exposure metric (Section 6.7.3.2).

The ratios of 1-h daily max, 8-h daily max, and 24-h avg concentrations to one another have been found to differ across communities and across time within individual communities (Anderson and Bell, 2010). For example, 8:24 hour ratios ranged from 1.23-1.83, with a median of 1.53. Lower ratios were generally observed in the spring and summer compared to fall and winter. O_3 concentration was identified as the most important predictor of ozone metric ratios, with higher overall O_3 concentrations associated with lower ratios. In communities with higher long-term ozone concentrations, the low 8:24 hour ratio is attributed to high baseline O_3, which results in elevated 24-h average values. Differences in the representativeness of O_3 metrics introduces uncertainty into epidemiologic results and complicates comparison of studies using different metrics. Preferably, studies will report results using multiple metrics. In cases where this does not occur, the results of this study can inform the uncertainty associated with using a standard increment to adjust effect estimates based on different metrics so that they are comparable (Chapter 6).

A study compared measures of spatial and temporal variability for 1-h daily max and 24-h daily avg O_3 concentrations in Brazil (Bravo and Bell, 2011). The 1-h daily max value was found to have higher correlation between monitors (i.e., lower temporal variability)

and lower COD (a measure of spatiotemporal variability which incorporates differences in concentration magnitude, with lower values indicating lower variability; see Chapter 3) than the 24-h avg value. The range of correlation coefficients and COD values was similar between the two metrics, although the variation was lower for the 1-h daily max, as indicated by the R^2 value for the regression of correlation coefficient on inter-monitor distance.

Long-term exposure epidemiologic studies use concentrations averaged over months, years, or decades to evaluate health effects of extended O_3 exposure. A study in Canada comparing exposure assessment methods for long-term O_3 exposure found that the annual average concentration in the census tract of a subject's residence during 1980 and 1994 was well-correlated (0.76 and 0.83, respectively) with a concentration metric accounting for movement among census subdivisions during 1980-2002 (Guay et al., 2011). This may have been due in part to a relatively low rate of movement, with subjects residing on average for 71% of the 22-year period in the same census subdivision they were in during 1980. This suggests that an exposure metric based on a single year can represent exposure over a multi-decade period.

4.6.2.1 Spatial Variability

Spatial variability of O_3 concentrations is highly dependent on spatial scale; in effect, O_3 is a regional pollutant subject to varying degrees of local variability. In the immediate vicinity of roadways, O_3 concentrations are reduced due to reaction with NO and other species (Section 4.3.4.2); over spatial scales of a few kilometers, O_3 may be more homogeneous due to its formation as a secondary pollutant; over scales of tens of kilometers, atmospheric processing can result in higher concentrations downwind of an urban area than in the urban core. Local-scale variations have a large impact on the relative magnitude of concentrations among urban monitors, while conditions favoring high or low rates of O_3 formation (e.g., temperature) vary over large spatial scales. This suggests that neighborhood monitors are likely to track one another temporally, but miss small-scale spatial variability in magnitude. In rural areas, a lower degree of fluctuation in O_3 precursors such as NO and VOCs is likely to make the diel concentration profile less variable than in urban areas, resulting in more sustained ambient levels. Spatial variability contributes to exposure error if the ambient O_3 concentration measured at the central site monitor is used as an ambient exposure surrogate and differs from the actual ambient O_3 concentration outside a subject's residence and/or worksite (in the absence of indoor O_3 sources). Averaging data from a large number of samplers will dampen intersampler variability, and use of multiple monitors over smaller land areas may allow for more variability to be incorporated into an epidemiologic analysis.

Community exposure may not be well represented when monitors cover large areas with several subcommunities having different sources and topographies, such as the Los Angeles CSA (Section 3.6.2.1). Ozone monitors in Los Angeles had a much wider range of intermonitor correlations (-0.06 to 0.97) than Atlanta (0.61 to 0.96) or Boston (0.56 to 0.97) using 2007-2009 data. Although the negative and near-zero correlations in Los Angeles were observed for monitors located some distance apart (>150 km), some closer monitor pairs had low positive correlations, likely due to changes in topography and airflow patterns over short distances. Lower COD values, which indicate less variability among monitors in the magnitude of O_3 concentrations, were observed in Atlanta (0.05-0.13) and Boston (0.05-0.19) than Los Angeles (0.05-0.56), although a single monitor (AM) was responsible for all Los Angeles COD values above 0.40. The spatial and temporal variability in O_3 concentration in 24 MSAs across the U.S. was also examined in the 2006 O_3 AQCD by using Pearson correlation coefficients, values of the 90th percentile of the absolute difference in O_3 concentrations, and CODs. No clear discernible regional differences across the U.S. were found in the ranges of parameters analyzed.

An analysis of the impact of exposure error due to spatial variability and instrument imprecision on time-series epidemiologic study results indicated that O_3 has relatively low exposure error compared to other routinely monitored pollutants, and that the simulated impact on effect estimates is minor. Goldman et al. (2011) computed population-weighted scaled semivariances and Pearson correlation coefficients for daily concentration metrics of twelve pollutants measured at multiple central-site monitors in Atlanta. 8-h daily max O_3 exhibited the lowest semivariance and highest correlation of any of the pollutants. Although this indicates some degree of urban-scale homogeneity for O_3, the analysis did not account for near-road effects on O_3 concentrations.

Studies evaluating the influence of monitor selection on epidemiologic study results have found that O_3 effect estimates are similar across different spatial averaging scales and monitoring sites. A study in Italy compared approaches for using fixed-site monitoring data in a case-crossover epidemiologic study of daily O_3 and mortality (Zauli Sajani et al., 2011). O_3 effect estimates were found to be similar whether the nearest monitor was used, or whether single-city, three-city, or six-city regional averages were used for exposure assessment. In contrast, effect estimates for PM_{10} and NO_2 increased with increasing scale of spatial averaging. Confidence intervals increased with increasing spatial scale for all pollutants. The authors attributed the consistency of O_3 effect estimates to the relative spatial homogeneity of O_3 over multi-km spatial scales, and pointed to the high (0.85-0.95) inter-monitor correlations to support this. The use of background monitors rather than monitors influenced by local sources in this study suggests that local-scale spatial variation in O_3, such as that due to titration by traffic

emissions, was not captured in the analyses. Sarnat et al. (2010) studied the spatial variability of O_3, along with $PM_{2.5}$, NO_2, and CO, in the Atlanta, GA, metropolitan area and evaluated how spatial variability affects interpretation of epidemiologic results, using time-series data for circulatory disease ED visits. The authors found that associations with ambient 8-h daily maximum O_3 concentration were similar among all sites tested, including multiple urban sites and a rural site some 38 miles from the city center. This result was also observed for 24-h $PM_{2.5}$ concentrations. In contrast, hourly CO and NO_2 showed different associations for the rural site than the urban sites, although the urban site associations were similar to one another for CO. This suggests that the choice of monitor may have little impact on the results of O_3 time-series studies, consistent with the moderate to high inter-monitor correlations observed in Atlanta (Chapter 3).

One potential explanation for this finding from the study by Sarnat et al. (2010) is that although spatial variability at different scales contributes to a complicated pattern of variations in the magnitude of O_3 concentrations between near-road, urban core, and urban downwind sites, day-to-day fluctuations in concentrations may be reflected across multiple urban microenvironments. In addition, time-averaging of O_3 and $PM_{2.5}$ concentrations may smooth out some of the intra-day spatial variability observed with the hourly CO and NO_2 concentrations. However, some uncertainty in observed effect estimates due to spatial variability and associated exposure error is expected to remain, including a potential bias towards the null.

4.6.2.2 Seasonality

The relationship between personal exposure and ambient concentration has been found to vary by season, with at least three factors potentially contributing to this variation: differences in building ventilation (e.g., air conditioning or heater use versus open window ventilation), higher O_3 concentrations during the O_3 season contributing to increased exposure and improved detection by personal monitors; and changes in activity pattern resulting in more time spent outside. Evidence has been presented in studies conducted in several cities regarding the effect of ventilation on personal-ambient and indoor-outdoor O_3 relationships (see Sections 4.3.2 and 4.3.3). More limited evidence is available regarding the specific effects of O_3 detection limits and activity pattern changes on O_3 relationships.

Several studies have found increased summertime correlations or ratios between personal exposure and ambient concentration (Sarnat et al., 2005; Sarnat et al., 2000) or between indoor and outdoor O_3 concentrations (Geyh et al., 2000; Avol et al., 1998b). However, others have found higher ratios in fall than in summer (Sarnat et al., 2006b) or equivalent,

near-zero ratios in winter and summer (Sarnat et al., 2001), possibly because summertime use of air conditioners decreases building air exchange rates. It should be noted that O_3 concentrations during winter are generally much lower than summertime concentrations, possibly obscuring wintertime relationships due to detection limit issues. Studies specifically evaluating the effect of ventilation conditions on O_3 relationships have found increased correlations or ratios for individuals or buildings experiencing higher air exchange rates (Sarnat et al., 2006b; Geyh et al., 2000; Sarnat et al., 2000; Romieu et al., 1998b).

Increased correlations or ratios between personal exposure and ambient concentration, or between indoor and outdoor concentration, are likely to reduce error in exposure estimates used in epidemiologic studies. This suggests that studies conducted during the O_3 season or in periods when communities are likely to have high air exchange rates (e.g., during mild weather) may be less prone to exposure error than studies conducted only during winter. Year-round studies that include both the O_3 and non-O_3 seasons may have an intermediate level of exposure error.

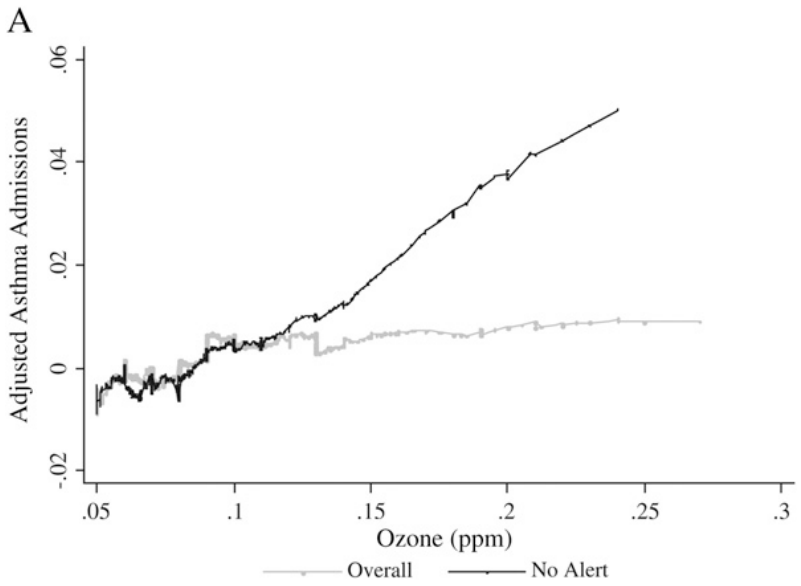
4.6.3 Exposure to Co-pollutants and Ozone Reaction Products

Although indoor O_3 concentrations are usually well below ambient concentrations, the same reactions that reduce O_3 indoors form particulate and gaseous species, including other oxidants, as summarized in Section 4.3.4.3. Exposures to these reaction products would therefore be expected to be correlated with ambient O_3 concentrations, although no evidence was identified regarding personal exposures. Such exposure could potentially contribute to health effects observed in epidemiologic studies.

4.6.4 Averting Behavior

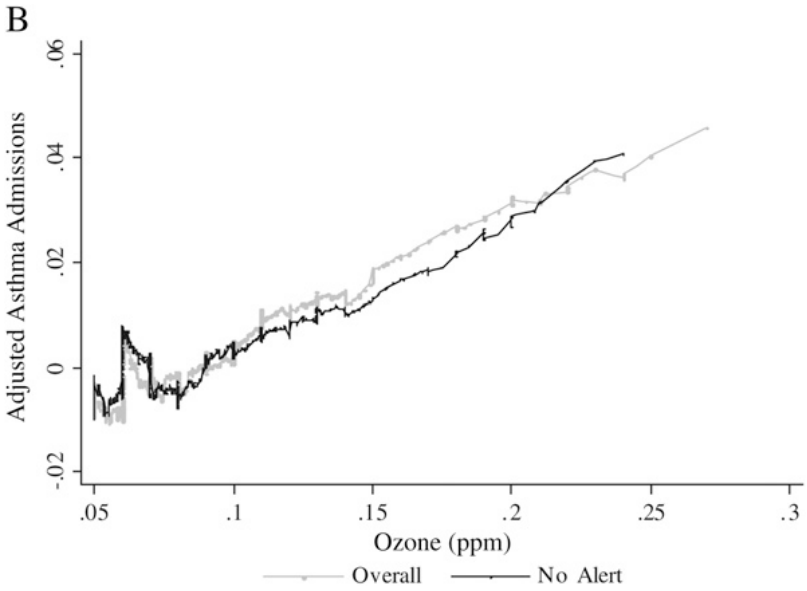
As described in Section 4.4.2, several recent studies indicate that some populations alter their behavior on high ozone days to avoid exposure. Such behavioral responses to information about forecasted air quality may introduce systematic measurement error in air pollution exposure, leading to biased estimates of the impact of air pollution on health. For example, studies have hypothesized that variation in time spent outdoors may be a driving factor behind the considerable heterogeneity in ozone mortality impacts across communities (Bell et al., 2004). If averting behavior in fact results in smaller, in magnitude, effect estimates, then studies that do not account for averting behavior may produce effect estimates that are biased towards the null (Section 6.2.7.5).

This is supported by an epidemiologic study that examined the association between exposure to ambient ozone concentrations and asthma hospitalizations in Southern California during 1989-1997, which indicates that controlling for avoidance behavior increases the effect estimate for both children and older adults, but not for adults aged 20-64 (Neidell and Kinney, 2010; Neidell, 2009). Figure 4-4 and Figure 4-5, reproduced from Neidell (2009), show covariate-adjusted asthma hospital admissions as a function of daily maximum 1-h O_3 concentration for all days (gray line) and days when no O_3 alert was issued (black line). Stage 1 smog alerts were issued by the State of California for days when ambient O_3 concentrations were forecast to be above 0.20 ppm; however, the concentration-response functions are based on measured O_3 concentrations. For children aged 5-19 (Figure 4-4), hospital admissions were higher on high-O_3 days when no alert was issued, especially on days with O_3 concentrations above 0.15 ppm (150 ppb). The concentration-response curves for all days and days with no alert diverge at measured O_3 concentrations between 0.10 and 0.15 ppm because smog alerts begin to be issued more frequently in this range. This suggests that in the absence of information that would enable averting behavior, children experience higher ozone exposure and subsequently a greater number of asthma hospital admissions than on alert days with similar O_3 concentrations. The lower rate of admissions observed when alert days were included in the analysis suggests that averting behavior reduced O_3 exposure and asthma hospital admissions. In both cases, O_3 was found to be associated with asthma hospital admissions, although the strength of the association is underestimated when not accounting for averting behavior. A similar result was not observed when examining associations for adults aged 20-64 (Figure 4-5), who had similar rates of hospital admissions on non-alert days as on all days. The lack of change for adults aged 20-64, which is primary employment age, may reflect lower response to air quality alerts due to the increased opportunity cost of behavior change. The finding that air quality information reduces the daily asthma hospitalization rate in these populations provides additional support for a link between ozone and health effects.



Source: Reprinted with permission of the Board of Regents of the University of Wisconsin System, University of Wisconsin Press (Neidell, 2009)

Figure 4-4 Adjusted asthma hospital admissions by age on lagged ozone by alert status, ages 5-19.



Source: Reprinted with permission of the Board of Regents of the University of Wisconsin System, University of Wisconsin Press; Neidell, (2009)

Figure 4-5 Adjusted asthma hospital admissions by age on lagged ozone by alert status, ages 20-64

4.6.5 Exposure Estimation Methods in Epidemiologic Studies

The use of O_3 measurements from central ambient monitoring sites is the most common method for assigning exposure in epidemiologic studies. However, fixed-site measurements do not account for the effects of spatial variation in O_3 concentration, ambient and non-ambient concentration differences, and varying activity patterns on personal exposures (Brown et al., 2009; Chang et al., 2000; Zeger et al., 2000). The use of fixed-site concentrations results in minimal exposure error when: (1) O_3 concentrations are uniform across the region; (2) personal activity patterns are similar across the population; and (3) housing characteristics, such as air exchange rate and indoor reaction rate, are constant over the study area. Since these factors vary by location and population, there will be errors in the magnitude of total exposure based solely on ambient monitoring data.

Modeling approaches can also be used to estimate exposures for epidemiologic studies, as discussed in Section 4.5. Geostatistical spatial interpolation techniques can provide finer-scale estimates of local concentration over urban areas. A microenvironmental modeling approach simulates exposure using empirical distributions of concentrations in specific microenvironments together with human activity pattern data. The main advantage of the modeling approach is that it can be used to estimate exposures over a wide range of population and scenarios. A main disadvantage of the modeling approach is that the results of modeling exposure assessment must be compared to an independent set of measured exposure levels (Klepeis, 1999). In addition, resource-intensive development of validated and representative model inputs is required, such as human activity patterns, distributions of air exchange rate, and deposition rate. Therefore, modeled exposures are used much less frequently in epidemiologic studies.

4.7 Summary and Conclusions

This section will briefly summarize and synthesize the main points of the chapter, with particular attention to the relevance of the material for the interpretation of epidemiologic studies.

Passive badge samplers are the most widely used technique for measuring personal O_3 exposure (Section 4.3.1). The detection limit of the badges for a 24-h sampling period is approximately 5-10 ppb, with lower detection limits at longer sampling durations. In low-concentration conditions this may result in an appreciable fraction of 24-h samples being below the detection limit. The use of more sensitive portable active monitors, including

some that have recently become available, may help overcome this issue and improve personal monitoring in the future.

Since there are relatively few indoor sources of O_3, indoor O_3 concentrations are often substantially lower than outdoor concentrations due to reactions of O_3 with indoor surfaces and airborne constituents (Section 4.3.2). Air exchange rate is a key determinant of the I/O ratio, which is generally in the range of 0.1-0.4 (Table 4-1), with some evidence for higher ratios during the O_3 season when concentrations are higher.

Personal exposure is moderately correlated with ambient O_3 concentration, as indicated by studies reporting correlations generally in the range of 0.3-0.8 (Table 4-2). Hourly concentration correlations are more variable than those averaged over 24 hours or longer, with correlations in outdoor microenvironments (0.7-0.9) much higher than those in residential indoor (0.1) or other indoor (0.3-0.4) microenvironments. Some studies report substantially lower personal-ambient correlations, a result attributable in part to low air exchange rate and O_3 concentrations below the sampler detection limit, conditions often encountered during wintertime. Low correlations may also occur for individuals or populations spending increased time indoors.

The ratio between personal exposure and ambient concentration varies widely depending on activity patterns, housing characteristics, and season, with higher personal-ambient ratios generally observed with increasing time spent outside, higher air exchange rate, and in seasons other than winter (Table 4-3). Personal-ambient ratios are typically 0.1-0.3, although individuals spending substantial time outdoors (e.g., outdoor workers) may have much higher ratios (0.5-0.9). Thus, applying personal-ambient ratios for outdoor workers to the general population or susceptible populations spending substantial time indoors can result in overestimates of the magnitude of personal exposure for these groups.

Personal exposure to other pollutants shows variable association with personal exposure to O_3, with differences in copollutant relationships depending on factors such as season, city-specific characteristics, activity pattern, and spatial variability of the copollutant (Section 4.3.4). In near-road and on-road microenvironments, correlations between O_3 and traffic-related pollutants are moderately to strongly negative, with the most strongly negative correlations observed for NO_2 (-0.8 to -0.9). This is consistent with the chemistry of NO oxidation, in which O_3 is consumed to form NO_2. The more moderate negative correlations observed for $PM_{2.5}$, $PM_{1.0}$, and VOC may reflect reduced concentrations of O_3 in polluted environments due to other scavenging reactions. A similar process occurs indoors, where infiltrated O_3 reacts with airborne or surface-associated materials to form secondary compounds, such as formaldehyde. Although such

reactions decrease indoor O_3 exposure, they result in increasing exposure to other species which may themselves have health effects.

Variations in ambient O_3 concentrations occur over multiple spatial and temporal scales. Near roadways, O_3 concentrations are reduced due to reaction with NO and other species (Section 4.3.4.2). Over spatial scales of a few kilometers and away from roads, O_3 may be somewhat more homogeneous due to its formation as a secondary pollutant, while over scales of tens of kilometers, additional atmospheric processing can result in higher concentrations downwind of an urban area. Although local-scale variability impacts the magnitude of O_3 concentrations, O_3 formation rates are influenced by factors that vary over larger spatial scales, such as temperature (Section 3.2), suggesting that urban monitors may track one another temporally but miss small-scale variability in magnitude. The resulting uncertainty in exposure contributes to exposure measurement error in epidemiologic studies.

Another factor that may influence epidemiologic results is the tendency for people to avoid O_3 exposure by altering their behavior (e.g., reducing time spent outdoors) on high-O_3 days. Activity pattern has a substantial effect on ambient O_3 exposure, with time spent outdoors contributing to increased exposure (Section 4.4.2). Averting behavior has been predominantly observed among children, older adults, and people with respiratory problems. Such effects are less pronounced in the general population, possibly due to the opportunity cost of behavior modification. Preliminary epidemiologic evidence reports increased asthma hospital admissions among children and older adults when O_3 alert days were excluded from the analysis (presumably thereby eliminating averting behavior based on high O_3 forecasts). The lower rate of admissions observed when alert days were included in the analysis suggests that estimates of health effects based on dose-response functions which do not account for averting behavior may be biased towards the null.

The range of personal-ambient correlations reported by most studies (0.3-0.8) is similar to that for NO_2 (U.S. EPA, 2008b) and somewhat lower than that for $PM_{2.5}$ (U.S. EPA, 2009d). To the extent that relative changes in central-site monitor concentration are associated with relative changes in exposure concentration, this indicates that ambient monitor concentrations are representative of day-to-day changes in average total personal exposure and in personal exposure to ambient O_3. The lack of indoor sources of O_3, in contrast to NO_2 and $PM_{2.5}$, is partly responsible for low indoor-outdoor ratios (generally 0.1-0.4) and low personal-ambient ratios (generally 0.1-0.3), although it contributes to increased personal-ambient correlations. The lack of indoor sources also suggests that fluctuations in ambient O_3 may be primarily responsible for changes in personal exposure, even under low-ventilation, low-concentration conditions. Nevertheless, low personal-ambient correlations are a source of exposure error for epidemiologic studies,

tending to obscure the presence of thresholds, bias effect estimates toward the null, and widen confidence intervals, and this impact may be more pronounced among populations spending substantial time indoors. The impact of this exposure error may tend more toward widening confidence intervals than biasing effect estimates, since epidemiologic studies evaluating the influence of monitor selection indicate that effect estimates are similar across different spatial averaging scales and monitoring sites.

4.8 References

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5 DOSIMETRY AND MODE OF ACTION

5.1 Introduction

This chapter has two main purposes. The first is to describe the principles which underlie the dosimetry of O_3 and to discuss factors which influence it. The second is to describe the modes of action leading to the health effects that will be presented in Chapters 6 and 7. This chapter is not intended to be a comprehensive overview, but rather, it updates the basic concepts derived from O_3 literature presented in previous documents (U.S. EPA, 2006b, 1996a) and introduces the recent relevant literature.

In Section 5.2, particular attention is given to dosimetric factors influencing individual risk of developing effects from O_3 exposure. As there have been few O_3 dosimetry studies published since the last AQCD, the reader is referred to previous documents (U.S. EPA, 2006b, 1996a) for more detailed discussion of the past literature. Evaluation of the progress in the interpretation of past dosimetry studies, as well as studies published since 2005, in the areas of uptake, reactions, and models for O_3 dosimetry, is discussed.

Section 5.3 highlights findings of studies published since the 2006 O_3 AQCD, which provide insight into the biological pathways by which O_3 exerts its actions. Since common mechanisms lead to health effects from both short- and long-term exposure to O_3, these pathways are discussed in Chapter 5 rather than in later chapters. The relevant sections of Chapters 6 and 7 are indicated. Older studies which represent the current state of the science are also discussed. Studies conducted at more environmentally-relevant concentrations of O_3 are of greater interest, since mechanisms responsible for effects at low O_3 concentrations may not be identical to those occurring at high O_3 concentrations. The topics of dosimetry and mode of action are bridged by reactions of O_3 with components of the extracellular lining fluid (ELF), which play a role in both O_3 uptake and biological responses (Figure 5-1).

In addition, this chapter discusses interindividual variability in responses, and issues related to species comparison of doses and responses (Sections 5.4 and 5.5). These topics are included in this chapter because they are influenced by both dosimetric and mechanistic considerations.

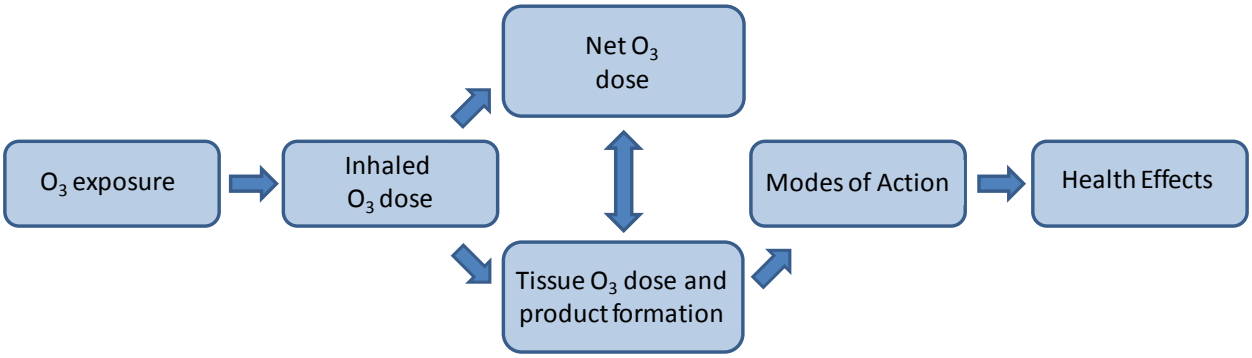


Figure 5-1 Schematic of the O_3 exposure and response pathway. O_3 concentrations can be reported as the exposure concentration, inhaled dose, the net dose, or the local tissue dose. The net dose refers to the total absorption of O_3 and is the sum of all the tissue compartmental doses. Chapter 5 discusses the concepts of dose and modes of action that result in the health effects discussed in Chapters 6 and 7.

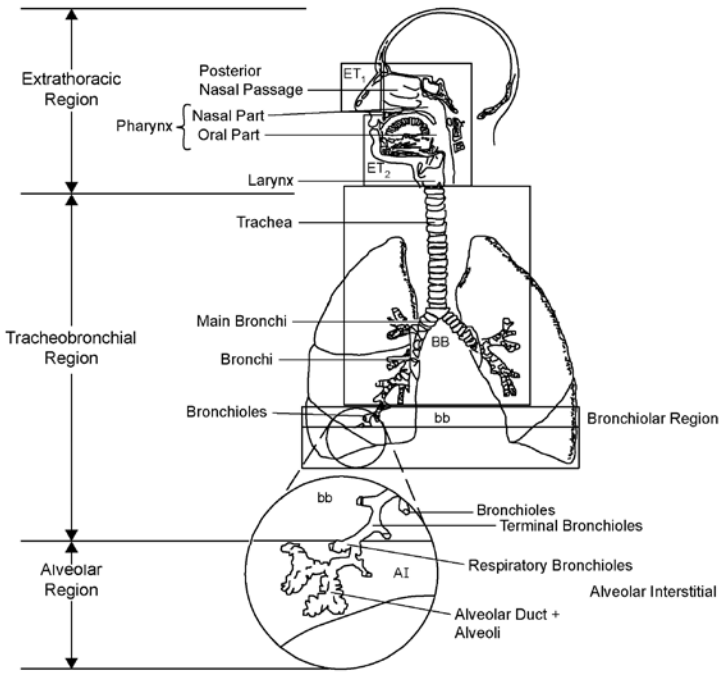
5.2 Human and Animal Ozone Dosimetry

5.2.1 Introduction

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. Dose refers to the amount of O_3 crossing an exposure surface to enter a target area. In the literature, surrogates of dose of reactive gases, such as O_3, can range in refinement from their concentration in the ambient exposure atmosphere to the "effective" dose of the chemical or its reaction products that actively participate in toxic reactions (Dahl, 1990). However, ambient concentrations are not a true measure of dose. Ideally, the units for the expression of the dose of O_3 might range from the quantity of gas inhaled as the product of gas concentration × minute ventilation × time (units of ppm × L × h), to the quantity of gas retained by the whole body, to the concentration of gas molecules that have been absorbed or reacted with the tissue (moles/g tissue weight). In modeling studies, the dose rate is often expressed as a flux per unit of surface area of a region of respiratory epithelium.

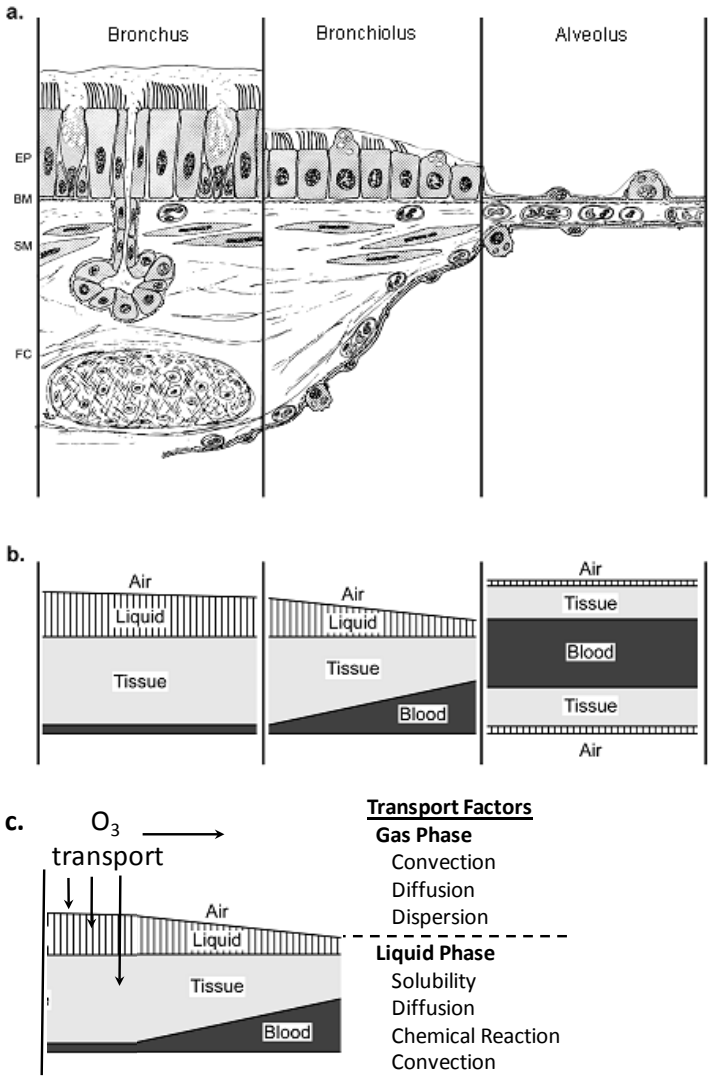
Ozone is a highly reactive, though poorly water soluble, gas at physiological temperature. The latter feature is believed to be the reason why it is able to penetrate into targets in the lower respiratory tract (LRT). Figure 5-2 presents the basic structure of the human respiratory tract (RT). The lung can be divided into three major regions: the extrathoracic

(ET) region or upper respiratory tract (URT, from the nose/mouth to larynx); the tracheobronchial (TB) tree (from trachea to the terminal bronchioles); and the alveolar or pulmonary region (from the respiratory bronchioles to the terminal alveolar sacs). The latter two regions comprise the LRT. Although the structure varies, the illustrated anatomic regions are common to all mammalian species with the exception of the respiratory bronchioles. Respiratory bronchioles, the transition region between ciliated and fully alveolated airways, are found in humans, dogs, ferrets, cats, and monkeys. Respiratory bronchioles are absent in rats and mice and abbreviated in hamsters, guinea pigs, sheep, and pigs. The branching structure of the ciliated bronchi and bronchioles also differs between species from being a rather symmetric and dichotomous branching network of airways in humans to a more monopodial branching network in other mammals.



Source: Based on ICRP (1994)

Figure 5-2 Representation of respiratory tract regions in humans. Structures are anterior nasal passages, ET_1; oral airway and posterior nasal passages, ET_2; bronchial airways, BB; bronchioles, bb; and alveolar interstitial, AI.



Source: Panel (a) reprinted with permission from McGraw-Hill (Weibel, 1980)

Figure 5-3 Structure of lower airways with progression from the large airways to the alveolus. (a) Illustrates basic airway anatomy. Structures are epithelial cells, EP; basement membrane, BM; smooth muscle cells, SM; and fibrocartilaginous coat, FC. (b) Illustrates the relative amounts of liquid, tissue, and blood with distal progression. In the bronchi there is a thick surface lining over a relatively thick layer of tissues. With distal progress, the lining diminishes allowing increased access of compounds crossing the air-liquid interface to the tissues and the blood. (c) Presents the factors acting in the gas and liquid phases of O_3 transport.

Figure 5-3 illustrates the structure of the LRT with progression from the large airways in the TB region to the alveolus in the alveolar region. The fact that O_3 is so chemically reactive has suggested to some that its effective dose at the target sites exists in the form of oxidation products such as aldehydes and peroxides (see Section 5.2.3). Reaction products are formed when O_3 interacts with components of the ELF such as lipids and antioxidants. The ELF varies throughout the length of the RT with the bronchial tree lined with a thin film of mucus and the alveolar region lined with a thinner layer of surfactant. Ozone toxicity is observed to some extent in the nasal cavity, however further toxicity exists in the LRT where the thinness of the ELF layer allows O_3 to react directly with cells protruding from the ELF (Figure 5-3b). Ozone uptake relates directly to these ELF substrate reactions and is termed "reactive absorption." Thus, the uptake of O_3 is related to both the concentration of O_3 as well as the availability of substrates within the ELF.

Chemical reactions are not the only processes controlling the uptake of O_3 from the airstream into compartments of the RT (Figure 5-3c). Ozone uptake is affected by complex interactions between a number of major factors including RT morphology, breathing route, frequency, and volume, physicochemical properties of the gas, physical processes of gas transport, as well as the physical and chemical properties of the ELF and tissue layers. The role of these processes varies throughout the length of the RT and as O_3 moves from the gas to liquid compartments of the RT.

Two types of measurements have been used to arrive at the O_3 dose to target sites during breathing: (1) measurement of removal of O_3 from the air stream (termed "uptake"); and (2) measurement of chemical reactions in tissues or with biomolecules known to be present in tissues (termed "reactants"). The results of the above measurements have been incorporated into mathematical models for the purpose of explaining, predicting, and extrapolating O_3 dose in different exposure scenarios. Few new studies have investigated the uptake of O_3 in the RT since the last O_3 assessment (U.S. EPA, 2006b). The studies that have been conducted generally agree with the results presented in the past and do not change the dosimetry conclusions of the last document.

5.2.2 Ozone Uptake

Past AQCDs provide information on the majority of literature relevant to understanding the state of the science in O_3 dosimetry. One method of quantifying O_3 dosimetry is to measure the amount of O_3 removed from the air stream during breathing (termed "uptake"). The O_3 in the breath that is removed during the breathing period is termed "uptake efficiency" or fractional absorption. Uptake studies have utilized bolus and continuous O_3 breathing techniques as well as modeling to investigate uptake efficiency

and distribution of O_3 uptake between the upper and lower respiratory tract. A number of the studies that have measured the fractional uptake of O_3 in the human RT (F_{RT}), URT (F_{URT}), and LRT (F_{LRT}) are presented in Table 5-1.

Table 5-1 Human respiratory tract uptake efficiency data

Reference	Mouth/Nose[a]	Inspiratory Flow (mL/s)	$V_{T\ (mL)}$	f_B (bpm)[b]	F_{RT}	F_{URT}	F_{LRT}
CONTINUOUS EXPOSURE							
Gerrity et al. (1988)	M	509	832	18		0.40	0.91
	N	456	754	18		0.36	0.91
	M/N	350	832	12		0.41	0.93
	M/N	634	778	24		0.38	0.89
Gerrity et al. (1994)[c]	M	1,360	1,650	25	0.81	0.37	0.43
	M	1,360	1,239	35	0.78	0.41	0.36
Gerrity et al. (1995)	Mouthpiece	330	825	12	0.91	0.27	0.95
Wiester et al. (1996c)	M	539	631	16	0.76		
	N	514	642	16	0.73		
Santiago et al. (2001)	N	50				0.80[d]	
	N	250				0.33	
Rigas et al. (2000)	Face mask	480	1,100	27.6	0.86		
BOLUS EXPOSURE							
Hu et al. (1992)	Mouthpiece	250			0.96	0.46	
Ultman et al. (1994)	Mouthpiece	250	500[e]	15		0.30	
	Mouthpiece	250	500	15		0.47	
Ultman et al. (2004)	M	490	450[e]	32.7	0.87		
	M	517	574	27	0.91		
Nodelman and Ultman (1999)	Nasal Cannula	150	500	18		0.90	
	Nasal Cannula	1,000	500	120		0.45	
	Mouthpiece	150	500	18		0.80	0.95
	Mouthpiece	1,000	500	120		0.25	0.90

[a]M = mouth exposure during spontaneous breathing; N = nasal exposure during spontaneous breathing; M/N = pooled data from mouth and nasal exposure; mouthpiece = exposure by mouthpiece; F_{RT} = total RT uptake; F_{URT} = upper RT uptake; F_{LRT} = lower RT uptake.

[b]f_B is either measured or is computed from flows and V_T.

[c]Total RT uptake reported by Gerrity et al. (1988) and Gerrity et al. (1994) did not include the contribution from URT uptake efficiency during expiration. The data include an expiratory URT contribution, assuming it equals inspiratory URT uptake efficiency.

[d]F_{URT} from Santiago et al. (2001) represents nasal absorption (F_{nose}).

[e]V_T is computed from flow and f_B.

5.2.2.1 Gas Transport Principles

Transport of O_3 in the gas phase is governed by bulk flow or convection, effective axial dispersion, and loss to airway walls (Figure 5-3c) (Miller, 1995). The relative importance of these gas phase transport mechanisms varies among RT regions for a given level of ventilation in any species. For example, bulk airflow is the predominant mechanism for gas transport in the URT and bronchi, while diffusion is the major transport mechanism in the alveolar region of the lung.

Gas transport in the TB region occurs by a combination of bulk flow and mixing (Ultman, 1985). Mixing can occur by diffusion processes associated with the molecular nature of the gas or by dispersion processes which depend on local velocity patterns. The complexity of the airway structure and surface affects the bulk airflow patterns so that not all nasal and lung surfaces receive the same O_3 exposure or dose (Miller and Kimbell, 1995). The principal influence on mixing in the TB region comes from the axial velocity profile and diffusion. When passing through a bifurcation a velocity profile is altered; the inspiratory profile is sharper than the more flattened expiratory profile (Schroter and Sudlow, 1969). The longitudinal dispersion of inspired air depends on the flow regime, laminar flow (i.e., streamlined) or turbulent flow (i.e., possessing random velocity fluctuations), and is influenced by Taylor dispersion forces. In humans, turbulent flow regime persists only a few generations into the RT. Turbulence generation also varies by species and flow rates. For example, airflow is nonturbulent in the rat nose at any physiologic flow rate but may be highly turbulent in the human nose during exercise (Miller, 1995).

Conversely, the principal mechanism of gas mixing in the lung periphery is molecular diffusion (Engel, 1985). While moving into more distal areas of the RT, the cross-sectional area of the airways rapidly increases and linear velocities decrease, leading to a greater role of molecular diffusion of gases. Gas molecules close to the alveolocapillary membrane have almost zero convective velocity with respect to the membrane. Overall, the diffusion of O_3 into the ELF where chemical reactions occur drives alveolar gas uptake.

5.2.2.2 Target Sites for Ozone Dose

A primary uptake site of O_3 delivery to the lung epithelium is believed to be the centriacinar region (CAR). The CAR refers to the zone at the junction of the TB airways and the gas exchange region. This area is also termed the proximal alveolar region (PAR) and is defined as the first generation distal to the terminal bronchioles. Contained within the CAR, the respiratory bronchioles were confirmed as the site receiving the greatest O_3 dose (^{18}O mass/lung weight) in resting O_3 exposed rhesus monkeys, when not considering the nose (Plopper et al., 1998). Furthermore, the greatest cellular injury occurred in the vicinity of the respiratory bronchioles and was dependent on the delivered O_3 dose to these tissues (see also Section 5.4.1). However, ^{18}O label was detected to a lesser extent in other regions of the TB airway tree, showing that O_3 is delivered to these compartments as well, although in a smaller dose. Earlier models predicted that the net O_3 dose (total absorption, O_3 flux to air-liquid interface) gradually decreased with distal progression from the trachea to the end of the TB region and then rapidly decreased in the

alveolar region (Miller et al., 1985). However, the tissue O_3 dose (O_3 flux to liquid-tissue interface) was low in the trachea, increased to a maximum in the terminal bronchioles and the CAR, and then rapidly decreased in the alveolar region. Despite the exclusion of the URT and O_3 reactions with ELF constituents after the 16th generation, the model predicted experimental results showing that the CAR received the greatest O_3 tissue dose (Miller et al., 1985).

Inhomogeneity in the RT structure may affect the dose delivered to this target site. Models have predicted that the farther the PAR is from the trachea, the less the O_3 tissue dose to the region. Ultman and Anjilvel (1990) and Overton et al. (1989) predicted approximately a 50 to 300% greater PAR dose for the shortest path relative to the longest path in humans and rats, respectively. In addition, Mercer et al. (1991) found that both path distance and ventilatory unit size affected dose. The variation of O_3 dose among anatomically equivalent ventilatory units was predicted to vary as much as six-fold, as a function of path length from the trachea. This could have implications in regional damage to the LRT, such that even though the average LRT dose may be at a level that would be considered insignificant, local regions of the RT may receive significantly higher than average doses and therefore be at greater risk of effects.

5.2.2.3 Upper Respiratory Tract Ozone Removal and Dose

The URT provides a defense against O_3 entering the lungs by removing half of the inhaled O_3 from the airstream. In both animals and humans, about 50% of the absorbed O_3 was removed in the head (nose, mouth, and pharynx), about 7% in the larynx/trachea, and about 43% in the lungs (Hu et al., 1992; Hatch et al., 1989; Miller et al., 1979). The fraction of O_3 taken up was inversely related to flow rate and weakly related to inlet O_3 concentration (Yokoyama and Frank, 1972). The limiting factors in nasal O_3 uptake were simultaneous diffusion and chemical reaction of O_3 in the nasal ELF layer (Santiago et al., 2001). The ELF layer in the nose is thicker than in the rest of the RT, and mathematical estimates predicted that O_3 penetrates less than the thickness of the ELF layer; reaction products are likely the agents damaging the nasal tissue and not O_3 itself. It was hypothesized that the nasal nonlinear reaction kinetics could result from the depleting substrates in the nasal ELF becoming the limiting factor of the reaction (Santiago et al., 2001).

Uptake efficiencies have been measured for various segments of the URT (Table 5-1). Gerrity et al. (1995) reported unidirectional uptake efficiencies of O_3 inhaled from a mouthpiece; of 17.6% from the mouth to vocal cords, 9.5% from the vocal cords to the upper trachea (totaling 27.1%), 8.4% from the upper trachea to the main bifurcation

carina (totaling 35.5%), and essentially zero between the carina and the bronchus intermedius (totaling 32.5%). These values are lower than those calculated by Hu et al. (1992) that reported uptake efficiencies of 21, 36, 44, and 46% between the mouth and the vocal cords, the upper trachea, the main bifurcation carina, and the bronchus intermedius, respectively. The lower efficiencies seen in Gerrity et al. (1995) may have resulted from the mouthpiece scrubbing O_3 from the breath during inhalation.

Past studies investigating nasal uptake of O_3 have shown that the nose partially protects the LRT from damage from inspired O_3 (Santiago et al., 2001; Gerrity et al., 1988). Sawyer et al. (2007) further investigated nasal uptake of O_3 in healthy adults during exercise. Fractional O_3 uptake, acoustic rhinometry (AR), and nasal NO measurements were taken on ten adults (8 women, 2 men) exposed to 200 ppb O_3 before and after moderate exercise at two flow rates (10 and 20 L/min). The percent nasal uptake of O_3 was ~50% greater at 10 L/min compared to 20 L/min both pre- and post-exercise. However, the inhaled O_3 delivered dose to the LRT (i.e., flow rate × [O_3 ppm] × nasal O_3 penetration) was 1.6-fold greater at the higher flow than at the lower flow (2.5 compared to 0.9 ppm·L/min). Prior exercise did not affect O_3 uptake at either flow rate, but did significantly increase nasal volume (Vn) and AR measurements of nasal cross-sectional area (minimum cross-sectional area (MCA) which corresponds to the nasal valve, CSA2 which corresponds to the anterior edge of the nasal turbinates, and CSA3 which corresponds to the posterior edge of the nasal turbinates) ($p \leq 0.05$). Conversely, exercise decreased nasal resistance (Rn) ($p < 0.01$) and NO production (nonsignificant, $p > 0.05$). The change in Vn and CSA2:MCA ratio was correlated with the percent change in nasal uptake, however the overall effect was small and sensitive to elimination of outliers and gender segregation.

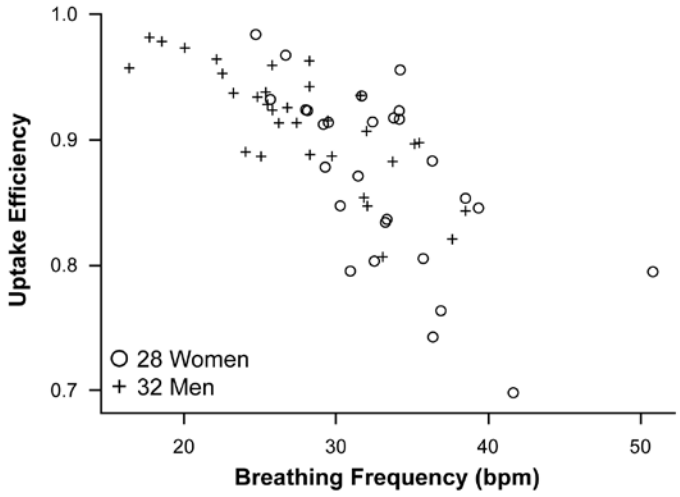
Overall, the URT removes half of the inhaled O_3 by reactions in the nasal ELF. The exact uptake efficiency will change due to variations in flow rate and inhaled concentration.

5.2.2.4 Lower Respiratory Tract Ozone Uptake and Dose

Total O_3 uptake in the entire RT in rats and guinea pigs ranges from 40-54% efficient (Hatch et al., 1989; Wiester et al., 1988; Wiester et al., 1987), while in humans at rest it ranges from 80-95% efficient (Hu et al., 1992). Approximately 43% of inhaled O_3 is absorbed in the LRT of both humans and animals. Models predicted that the net O_3 dose decreases distally from the trachea toward the end of the TB region and then rapidly decreases in the alveolar region (Miller et al., 1985). However, these models predicted low tissue O_3 dose in the trachea and large bronchi. As injury has been seen in these areas, net dose may be a better predictor of local toxic tissue dose.

Uptake efficiency depends on a number of variables, including O_3 exposure concentration, exposure time, and breathing pattern. For breaths of similar waveforms, respiratory patterns are uniquely described by breathing frequency (f_B) and tidal volume (V_T); by minute volume ($MV = f_B \times V_T$) and f_B; or by MV and V_T. Simulations from the Overton et al. (1996) single-path anatomical respiratory tract model, where the upper and lower respiratory tracts were modeled but uptake by the URT was not considered, predicted that fractional uptake and PAR O_3 dose increased with V_T when f_B was held constant. Likewise, experimental studies found that O_3 uptake was positively correlated with changes in V_T (Ultman et al., 2004; Gerrity et al., 1988). Also, O_3 exposure led to a reflex mediated increase in f_B and reduction in V_T, hypothesized to be protective by decreasing the dose delivered to the lung at a particular MV (Gerrity et al., 1994). Nasal O_3 uptake was inversely proportional to flow rate (Santiago et al., 2001), so that an increase in MV will increase O_3 delivery to the lower airways. At a fixed MV, increasing V_T (corresponding to decreasing f_B) drove O_3 deeper into the lungs and increased total respiratory uptake efficiency (Figure 5-4) (Ultman et al., 2004; Wiester et al., 1996c; Gerrity et al., 1988). Modeling also predicted a decrease in fractional uptake with increased f_B when V_T was held constant, but an increase in PAR dose with increased f_B (Overton et al., 1996). Similarly, increased f_B (80 - 160 bpm) and shallow breathing in rats decreased midlevel tracheal ^{18}O content and an increased ^{18}O content in the mainstem bronchi (Alfaro et al., 2004). This dependence may be a result of frequency-induced alterations in contact time that affects the first-order absorption rate for O_3 (Postlethwait et al., 1994). Also, an association of O_3 uptake efficiency was found with MV and exposure time.

Increasing flow leads to deeper penetration of O_3 into the lung, such that a smaller fraction of O_3 is absorbed in the URT and uptake shifts to the TB airways and respiratory airspaces (Nodelman and Ultman, 1999; Hu et al., 1994; Ultman et al., 1994). Hu et al. (1994) and Ultman et al. (1994) found that O_3 absorption increased with volumetric penetration (Vp) of a bolus of O_3 into the RT (Figure 5-5). Ozone uptake efficiency and Vp were not affected by bolus O_3 concentration (Kabel et al., 1994; Hu et al., 1992), indicating that O_3 uptake is a linear absorption process, where the diffusion and chemical reaction rates of O_3 are proportional to the O_3 concentration. This relationship was also true for nasal cavity uptake (Santiago et al., 2001). Rigas et al. (2000) found a weak but significant negative dependence of O_3 concentration on uptake efficiency in exercising individuals; however, only due to large changes in O_3 concentration suggesting that O_3 uptake is likely still essentially linear with respect to O_3 concentration. This study also found that exposure time had a small but significant influence on uptake efficiency; however, this negative dependence may be an artifact of progressive depletion of reactive substrates from the ELF.

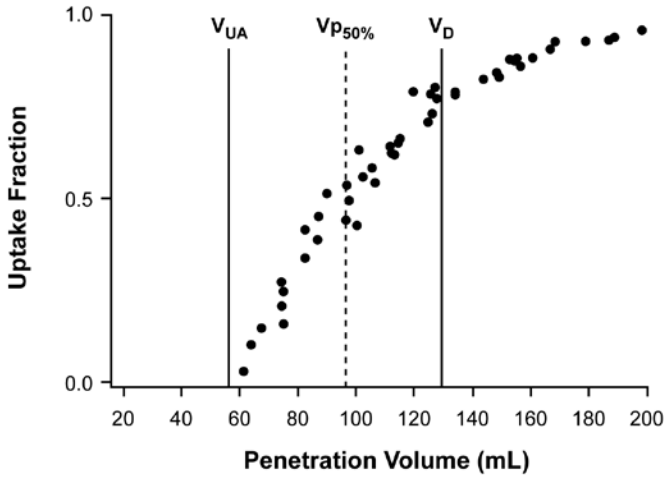


Source: Reprinted with permission of Health Effects Institute (Ultman et al., 2004)

Figure 5-4 Total ozone uptake efficiency as a function of breathing frequency at a constant minute ventilation of 30 L/min. Subjects breathed 0.25 ppm O_3 oronasally via a breathing mask. The uptake efficiency was well correlated with breathing frequency (r = -0.723, p < 0.001) and tidal volume (not illustrated; r = 0.490, p < 0.001).

Past studies have shown that O_3-induced epithelial damage to the lung occurs with a reproducible pattern of severity between daughter branches of individual bifurcations that is dependent on the O_3 concentration-time profile of the inhaled gas. A 3-D computational fluid dynamics model was created to investigate the dose-response relationship leading to the distribution of damage in a single airway bifurcation (Taylor et al., 2007). The model consisted of one parent branch and two symmetrical daughter branches with a branching angle of 90° and a sharp carinal ridge. Various flow scenarios were simulated using Reynolds numbers (Re) ranging from 100 to 500. The Re that corresponds to a certain airway generation is dependent upon both lung size and MV, such that the range in Re from 100-500 would encompass generations 1-5, 3-7, and 6-10 for an adult during quiet breathing, light exertion, and heavy exercise, respectively, whereas the same Re range corresponds to generations 0-4, 1-6, and 4-8 for a 4-year-old child. Consistent with early physical models of Schroter and Sudlow (1969), the model predicted that during inspiration, the velocity and O_3 concentration distribution were axisymmetric throughout the parent branch, but skewed towards the inner wall within the daughter branches. During expiration, the model predicted that the velocity and O_3 concentration distribution was slightly skewed towards the outer walls of the daughter branches. Hot spots of wall flux existed at the carina during inspiration and expiration

with Re >100. Additional hot spots were found during expiration on the parent branch wall downstream of the branching region.



Source: Adapted with permission of Health Effects Institute (Ultman et al., 2004)

Figure 5-5 Ozone uptake fraction as a function of volumetric penetration (V_p) in a representative subject. Each point represents the O_3 uptake of a bolus inspired through a mouthpiece by the subject. The volumes, V_{UA} and V_D, are the volume of the upper airways and anatomical dead space, respectively, and $V_p50\%$ is the V_p at which 50% of the inspired bolus was absorbed. In 47 healthy subjects, Ultman et al. (2004) found that $V_p50\%$ was well correlated with V_D and better correlated with the volume of the conducting airways, i.e., V_D minus V_{UA}.

Overall O_3 inhalation uptake in humans is over 80% efficient, but the exact efficiency that determines how much O_3 is available at longitudinally distributed compartments in the lung is sensitive to changes in V_T, f_B, and to a minor extent, exposure time. Decreased f_B at a fixed penetration volume will shift the O_3 uptake from the upper airways to the central airways and respiratory airspaces.

5.2.2.5 Mode of Breathing

Ozone uptake and distribution is sensitive to the mode of breathing. Variability in TB airways volume had a weaker influence on O_3 absorption during nasal breathing compared to oral breathing. This could be a result of O_3 scrubbing in the nasal

passageways that are bypassed by oral breathing. Studies by Ultman and colleagues using bolus inhalation demonstrated that O_3 uptake fraction was greater during nasal breathing than during oral breathing at each Vp (e.g. 0.90 during nasal breathing and 0.80 during oral breathing at 150 mL/s and 0.45 during nasal breathing and 0.25 during oral breathing at 1,000 mL/s) (Nodelman and Ultman, 1999; Kabel et al., 1994; Ultman et al., 1994). Therefore, oral breathing results in deeper penetration of O_3 into the RT with a higher absorbed fraction in the URT, TB, and alveolar airways (Nodelman and Ultman, 1999). Similar results were obtained from O_3 uptake studies in dogs (Yokoyama and Frank, 1972). Earlier human studies suggesedt that oral or oronasal breathing results in a higher O_3 uptake efficiency than nasal breathing (Wiester et al., 1996c; Gerrity et al., 1988); however the difference observed between inspired O_3 taken up during oral versus nasal breathing may not be biologically significant. These human studies measured total RT absorption after continuous O_3 exposure using a pharyngeal sampling tube, which may decrease sensitivity and lead to measurement errors. Overall, the mode of breathing may have little effect of the RT uptake efficiency, but does play an important role in the distribution of O_3 deposited in the distal airways.

5.2.2.6 Interindividual Variability in Dose

Similarly exposed individuals vary in the amount of actual dose delivered to the LRT (Santiago et al., 2001; Rigas et al., 2000; Bush et al., 1996). Interindividual variability accounted for between 10-50% of the absolute variability in O_3 uptake measurements (Santiago et al., 2001; Rigas et al., 2000). When concentration, time, and MV were held constant, fractional absorption ranged from 0.80 to 0.91 (Rigas et al., 2000). It has been hypothesized that interindividual variation in O_3 induced response such as FEV_1 is the result of interindividual variation in delivered dose or regional O_3 uptake among exposed individuals.

Recent studies have reiterated the importance of intersubject variation in O_3 uptake. The intersubject variability in nasal O_3 uptake determined by Sawyer et al. (2007) ranged from 26.8 to 65.4% (pre- and post-exercise). A second study investigating the use of the CO_2 expirogram to quantify pulmonary responses to O_3 found that intersubject variability accounted for 50% of the overall variance in the study (Taylor et al., 2006).

Variability in local dose may be attributed to differences in the pulmonary physiology, anatomy, and biochemistry. Since the TB airways remove the majority of inhaled O_3 before it reaches the gas exchange region, the volume and surface area of the upper airways will influence O_3 uptake. Models predicted that fractional O_3 uptake and PAR dose (flux of O_3 to the PAR surfaces divided by exposure concentration) increase with

decreasing TB volume and decreasing TB region expansion. On the contrary, alveolar expansion had minimal effect on uptake efficiency as relatively little O_3 reaches the peripheral lung (Bush et al., 2001; Overton et al., 1996). Ozone uptake was virtually complete by the time O_3 reaches the alveolar spaces of the lung (Postlethwait et al., 1994). Experimental studies have found that differences in TB volumes may account for 75% of the variation in absorption between subjects (Ultman et al., 2004). In support of this concept, regression analysis showed that O_3 absorption was positively correlated with anatomical dead space (V_D) and TB volume (i.e., V_D minus V_{URT}), but not total lung capacity (TLC), forced vital capacity (FVC), or functional residual capacity (FRC) (Ultman et al., 2004; Bush et al., 1996; Hu et al., 1994; Postlethwait et al., 1994). Variability in V_D was correlated more with the variability in the TB volume than the URT volume. Similarly, uptake was correlated with changes in individual bronchial cross-sectional area, indicating that changes in cross-sectional area available for gas diffusion are related to overall O_3 retention (Reeser et al., 2005; Ultman et al., 2004). These studies provide support to the pulmonary physiology, especially the TB volume and surface area, playing a key role in variability of O_3 uptake between individuals.

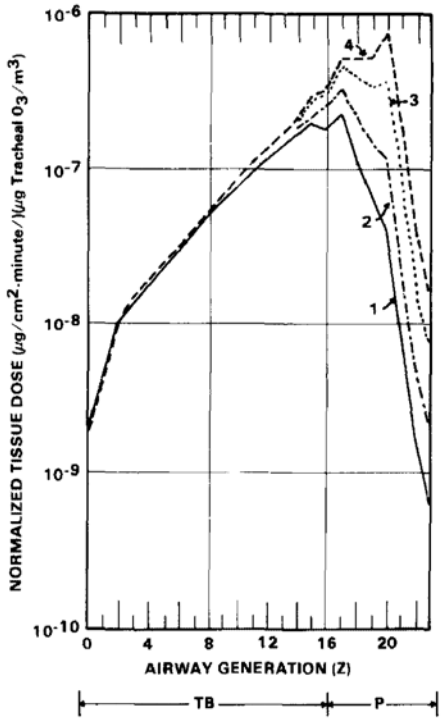
When absorption data were normalized to Vp/V_D, variability attributed to gender differences were not distinguishable (Bush et al., 1996). However, variability due to age has been predicted. Overton and Graham (1989) predicted that the total quantity of O_3 absorbed per minute increased with age from birth to adulthood. This model predicted that the LRT distribution of absorbed O_3 and the CAR O_3 tissue dose were not sensitive to age during quiet breathing. However, during heavy exercise or work O_3 uptake was dependent on age. A physiologically based pharmacokinetic model simulating O_3 uptake predicted that regional extraction of O_3 was relatively insensitive to age, but extraction per unit surface area was two- to eightfold higher in infants compared to adults, due to the fact that children under age 5 have much a much smaller airway surface area in the extrathoracic (nasal) and alveolar regions (Sarangapani et al., 2003).

Smoking history, with its known increase in mucus production, was not found to significantly affect the fractional uptake of a bolus dose of O_3 in apparently healthy smokers with limited smoking history (Bates et al., 2009). Despite similar internal O_3 dose distribution, the smokers exhibited greater pulmonary responses to O_3 bolus exposures, measured as FEV_1 decrements and increases in the normalized slope of the alveolar plateau (S_N). This was contrary to previous studies conducted in smokers with a greater smoking history that found decreased O_3 induced decrements in FEV_1 in smokers during continuous O_3 exposure (Frampton et al., 1997b; Emmons and Foster, 1991).

5.2.2.7 Physical Activity

Exercise increases the overall exposure of the lung to inhaled contaminants due, in most part, to the increased intake of air. As exercise increases from a low to moderate level, V_T increases. This increase in V_T is achieved by encroaching upon both the inspiratory and expiratory reserve volumes of the lung (Dempsey et al., 1990). After V_T reaches about 50% of the vital capacity, generally during heavy exercise, further increases in ventilation are achieved by increasing f_B. Ventilatory demands of heavy exercise require airway flow rates that often exceed 10 times resting levels and V_T that approach 5 times resting levels (Dempsey et al., 2008).

This increase in V_T and flow associated with exercise in humans shifts the O_3 dose further into the periphery of the RT causing a disproportionate increase in distal lung dose. In addition to increasing the bulk transport of O_3 into the lung, exercise also leads to a switch from nasal to oronasal breathing. Higher ventilatory demand necessitates a lower-resistance path through the mouth. Modeling heavy exercise by increasing ventilatory parameters from normal respiration levels predicted a 10-fold increase in total mass uptake of O_3 (Miller et al., 1985). This model also predicted that as exercise and ventilatory demand increased the maximum tissue dose moved distally into the RT (Figure 5-6). By increasing flow to what is common in moderate exercise (respiratory flow = 750 -1,000 mL/s compared to 250 mL/s at rest), the URT absorbed a smaller fraction of the O_3 (~0.50 at rest to 0.10 at exercise); however, the trachea and more distal TB airways received higher doses during exercise than rest (0.65 absorbed in the lower TB airways, and 0.25 absorbed in the alveolar zone with exercise compared to 0.5 in the TB with almost no O_3 reaching the alveolar zone at rest) (Hu et al., 1994). The same shift in the O_3 dose distribution more distally in the lung occurred in other studies mimicking the effects of exercise (Nodelman and Ultman, 1999). Also, LRT uptake efficiency was sensitive to age only under exercise conditions (Overton and Graham, 1989). The total quantity of O_3 absorbed per minute was predicted to increase with age during heavy work or exercise. A recent study by Sawyer et al. (2007) showed that doubling minute ventilation led to only a 1.6-fold higher delivered dose rate of O_3 to the lung. Past models have predicted the increase in uptake during exercise is distributed unevenly in the RT compartments and regions. Tissue and mucus layer dose in the TB region increased ~1.4-fold during heavy exercise compared to resting conditions, whereas the alveolar region surfactant and tissue uptake increased by factors of 5.2 and 13.6, respectively (Miller et al., 1985).



Source: Reprinted with permission. (Miller et al., 1985)

Figure 5-6 Modeled effect of exercise on tissue dose of the LRT. Curve 1: V_T = 500 mL; f_B = 15 breaths/min. Curve 2: V_T = 1,000 mL; f_B = 15 breaths/min. Curve 3: V_T = 1,750 mL; f_B = 20.3 breaths/min. Curve 4: V_T = 2,250 mL; f_B = 30 breaths/min. TB = tracheobronchial region; P = pulmonary region.

5.2.2.8 Summary

In summary, O_3 uptake is affected by complex interactions between a number of factors including RT morphology, breathing route, frequency, and volume, physicochemical properties of the gas, physical processes of gas transport, as well as the physical and chemical properties of the ELF and tissue layers. The role of these processes varies throughout the length of the RT and as O_3 moves from the gas into liquid compartments of the RT. The primary uptake site of O_3 delivery to the lung epithelium is believed to be the CAR, however inhomogeneity in the RT structure may affect the dose delivered to this target site with larger path lengths leading to smaller locally delivered doses. Recent studies have provided evidence for hot spots of O_3 flux around bifurcations in airways. Experimental studies and models have suggested that the net O_3 dose gradually decreases distally from the trachea toward the end of the TB region and then rapidly decreases in the alveolar region. However, the tissue O_3 dose is low in the trachea, increases to a

maximum in the terminal bronchioles and the CAR, and then rapidly decreases distally into the alveolar region.

O_3 uptake efficiency is sensitive to a number of factors. Fractional absorption will decrease with increased flow and increase proportional to V_T, so that at a fixed MV, increasing V_T (or decreasing f_B) drives O_3 deeper into the lungs and increases total respiratory uptake efficiency. Individual total airway O_3 uptake efficiency is also sensitive to large changes in O_3 concentration, exposure time, and MV. Major sources of variability in absorption of O_3 include O_3 concentration, exposure time, f_B, MV, and V_T, but the interindividual variation is the greatest source of variability uptake efficiency. The majority of this interindividual variability is due to differences in TB volume and surface area.

An increase in V_T and f_B are both associated with increased physical activity. These changes and a switch to oronasal breathing during exercise results in deeper penetration of O_3 into the lung with a higher absorbed fraction in the ET, TB, and alveolar airways. For these reasons, increased physical activity acts to move the maximum tissue dose of O_3 distally into the RT and into the alveolar region.

5.2.3 Ozone Reactions and Reaction Products

Ozone dose can be examined by the chemical reactions or the products of these reactions that result from O_3 exposure. Since O_3 is chemically reactive with a wide spectrum of biomolecules, it is not feasible to delineate its many reaction products. Measurements of reaction product formation have included either the loss of a specific molecule and appearance of plausible products, or the addition of O_3-derived oxygen to biomolecules through the use of oxygen-18 labeling. In vitro exposure of ELF showed that O_3 disappearance from the gas phase depends on the characteristics of the ELF substrates (Postlethwait et al., 1998; Hu et al., 1994).

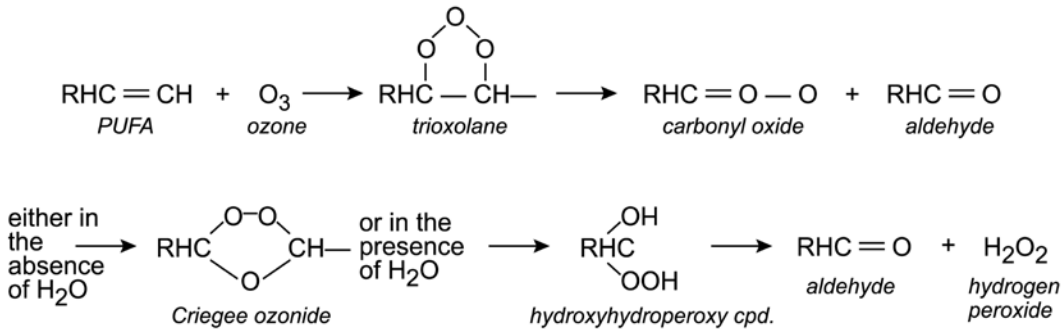
For O_3 to gain access to the underlying cellular compartments, O_3 must dissolve at the air-liquid interface of the airway surface and travel through the ELF layer. The ELF is comprised of the airway surface lining that includes the periciliary sol layer and overlying mucus gel layer, and the alveolar surface lining that includes the subphase of liquid and vesicular surfactant and the continuous surfactant monolayer (Bastacky et al., 1995). There is a progressive decrease in ELF thickness and increase in interfacial surface with progression from the large airways to the alveolus (Mercer et al., 1992). Some cells, such as macrophages, may protrude into the gas phase, allowing for direct contact between O_3 and cell membranes. The progressive thinning of the ELF while moving further down the RT decreases the radial distance O_3 must travel to reach the

cellular tissue layer. A computational fluid dynamics model was able to predict experimentally measured O_3 uptake, but only with nasal mucus layer thickness considered (Cohen-Hubal et al., 1996), reaffirming the importance of the resistance imparted by the ELF layer in dose and lesion patterns in the nasal passage.

Taking into account the high reactivity and low water solubility of O_3, calculations suggest that O_3 will not penetrate ELF layers greater than 0.1 µm without being transformed to other more long-lived reactive species, thus initiating a reaction cascade (Pryor, 1992). However, the surfactant layer in the pulmonary region becomes ultrathin, possibly allowing for direct interaction of O_3 with the underlying epithelial cells. One study measured pulmonary liquid lining thickness over relatively flat portions of the alveolar wall to be 0.14 µm, to be 0.89 µm at the alveolar wall junctions, and 0.09 µm over the protruding features (Bastacky et al., 1995). Still, the ELF should be considered an important target for O_3 and the resulting secondary oxidation products should be considered key mediators of toxicity in the airways (role of reaction products in O_3 induced toxicity is discussed in Section 5.3). Model calculations of the nasal cavity based on diffusion equations and reaction rates of O_3 with model substrates predict an O_3 penetration distance (0.5 µm) less than the thickness of the mucus layer (10 µm) (Santiago et al., 2001). Experimental support for this concept comes from several studies which measured the total oxygen-addition product of O_3 reactions in the airways through the use of oxygen-18 labeled O_3. High concentrations of O_3 reaction products were found in the bronchoalveolar lavage (BAL) mucus and surfactant providing evidence that O_3 reacts at the air-liquid interface. Thus, O_3 may cause injury by direct reaction with constituents of the lining layer, with cells protruding from it and in some cases with cells underlying the lining fluid. The reaction cascade resulting from the interaction of O_3 with ELF substrates acts to carry the oxidative burden deeper into the tissues.

Ozone may interact with many of the components in the ELF including phospholipids, neutral lipids, free fatty acids, proteins, and low molecular weight antioxidants (Perez-Gil, 2008; Uppu et al., 1995). It was estimated that 88% of the O_3 that does not come in contact with antioxidants will react with unsaturated fatty acids in the ELF including those contained within phospholipids or neutral lipids (Uppu et al., 1995). Ozone reacts with the double bond of lipids such as unsaturated fatty acids, a large component of ELF, to form stable and less reactive ozonide, aldehyde, and hydroperoxide reaction products via chemical reactions such as the Criegee ozonolysis mechanism (Figure 5-7) (Pryor et al., 1991). Lipid ozonation products, such as the aldehydes hexanal, heptanal, and nonanal, have been recovered after O_3 exposure in human BAL fluid (BALF), rat BALF, isolated rat lung, and in vitro systems (Frampton et al., 1999; Postlethwait et al., 1998; Pryor et al., 1996). Nonanal has been suggested as a relatively specific biomarker for O_3 exposure since the monounsaturated fatty acid parent compound, oleic acid, does not

undergo autoxidation (Pryor et al., 1996). Adducts of the aldehyde 4-hydroxynonenal were found in human alveolar macrophages after O_3 exposure (Hamilton et al., 1998). Polyunsaturated fatty acid (PUFA) reactions are limited by the availability of O_3 since lipids are so abundant in the ELF. Yields of O_3-induced aldehydes were increased by the decrease in other substrates such as ascorbic acid (AH_2) (Postlethwait et al., 1998). Free radicals are also generated during O_3-mediated oxidation reactions with PUFA (Pryor, 1994). These reactions are reduced by the presence of the lipid-soluble free radical scavenger α-tocopherol (α-TOH) (Pryor, 1994; Fujita et al., 1987; Pryor, 1976). PUFA reactions may not generate sufficient bioactive materials to account for acute cell injury, however only modest amounts of products may be necessary to induce cytotoxicity (Postlethwait and Ultman, 2001; Postlethwait et al., 1998).



Source: U.S. EPA (2006b)

Figure 5-7 Schematic overview of ozone interaction with PUFA in ELF and lung cells. It should be noted that not all secondary reaction products are shown.

Cholesterol is the most abundant neutral lipid in human ELF. Reaction of cholesterol with O_3 results in biologically active cholesterol products such as the oxysterols, β-epoxide and 6-oxo-3,5-diol (Murphy and Johnson, 2008; Pulfer et al., 2005; Pulfer and Murphy, 2004). Product yields will depend on ozonolysis conditions, however cholesterol ozonolysis products were formed in similar abundance to phospholipid-derived ozonolysis products in rat ELF (Pulfer and Murphy, 2004).

The ELF also contains proteins present in blood plasma as well as proteins secreted by surface epithelial cells. Ozone reactions with proteins have been studied by their in vitro reactions as well as reactions of their constituent amino acids (the most reactive of which are cysteine, histidine, methionine, tyrosine, and tryptophan). Ozone has been shown to

preferentially react with biomolecules in the following order: thiosulfate > ascorbate > cysteine ≈ methionine > glutathione (Kanofsky and Sima, 1995). Rate constants for the reaction of amino acids with O_3 vary between investigations due to differing reaction conditions and assumptions; however aliphatic amino acids consistently were very slow to react with O_3 (e.g., alanine: 25-100 moles/L/sec) (Kanofsky and Sima, 1995; Ignatenko and Cherenkevich, 1985; Pryor et al., 1984; Hoigné and Bader, 1983). Uppu et al. (1995) predicted that 12% of inhaled O_3 that does not react with antioxidants will react with proteins in the ELF, whereas 88% will react with PUFAs.

Reactions of ozone with low molecular weight antioxidants have been extensively studied. The consumption of antioxidants such as uric acid (UA), ascorbate (AH_2), and reduced glutathione (GSH) by O_3 was linear with time and positively correlated with initial substrate concentration and chamber O_3 concentration (Mudway and Kelly, 1998; Mudway et al., 1996). Endogenous antioxidants are present in relatively high concentrations in the ELF of the human TB airways and display high intrinsic reactivities toward O_3, but do not possess equal O_3 reactivity. In individual and in limited composite mixtures, UA was the most reactive antioxidant tested, followed by AH_2 (Mudway and Kelly, 1998). GSH was consistently less reactive than UA or AH_2 (Mudway and Kelly, 1998; Mudway et al., 1996; Kanofsky and Sima, 1995). To quantify these reactions, Kermani et al. (2006) recently evaluated the interfacial exposure of aqueous solutions of UA, AH_2, and GSH (50-200 µM) with O_3 (1-5 ppm). Similar to the results of Mudway and Kelly (1998), this study found the hierarchy in reactivity between O_3 and these antioxidants to be UA≥AH_2>>GSH. UA and AH_2 shared a 1:1 stoichiometry with O_3, whereas 2.5 moles of GSH were consumed per mole of O_3. Using these stoichiometries, reaction rate constants were derived (5.8×10^4 M^{-1} sec^{-1}, 5.5×10^4 M^{-1} sec^{-1}, and 57.5 $M^{-0.75}$/sec [20.9 M^{-1} sec^{-1}] for the reaction of O_3 with UA, AH_2, and GSH, respectively). These values are similar to those derived from data presented in Mudway and Kelly (1998). Other studies reported reactive rate constants that are two to three orders of magnitude larger, however these studies used higher concentrations of O_3 and antioxidants under less physiologically relevant experimental conditions (Kanofsky and Sima, 1995; Giamalva et al., 1985; Pryor et al., 1984).

A series of studies used new techniques to investigate the reaction products resulting from initial air-liquid interface interactions of O_3 with ELF components (e.g., antioxidants and proteins) in ~1 millisecond (Enami et al., 2009a, b, c, 2008a, b). Solutions of aqueous UA, AH_2, GSH, α-TOH, and protein cysteines (CyS) were sprayed as microdroplets in O_3/N_2 mixtures at atmospheric pressure and analyzed by electrospray mass spectrometry. These recent studies demonstrated different reactivity toward AH_2, UA, and GSH by O_3 when the large surface to volume ratio of microdroplets promote an interfacial reaction compared to previous studies using bulk liquid phase bioreactors, thus

supporting the relevance of reactions between gas phase O_3 and antioxidants found in the ELF.

As was seen in previous studies (Kermani et al., 2006; Kanofsky and Sima, 1995), the hierarchy of reactivity of these ELF components with O_3 was determined to be $AH_2 \approx$ UA > CyS > GSH. There was some variance between the reaction rates and product formation of UA, AH_2, and GSH with O_3 as investigated by Enami et al. versus O_3 reacting with bulk liquid phase bioreactors as described previously. UA was more reactive than AH_2 toward O_3 in previous studies, but in reactions with O_3 with microdroplets, these antioxidants had equivalent reactivity (Enami et al., 2008b). As O_3 is a kinetically slow one-electron acceptor but very reactive O-atom donor, products of the interaction of O_3 with UA, AH_2, GSH, CyS, and α-TOH result from addition of *n* O-atoms (*n* = 1-4). These products included epoxides (e.g., U-O^-), peroxides (e.g. U-O_2^-), and ozonides (e.g., U-O_3^-). For instance, GSH was oxidized to sulfonates (GSO_3^-/GSO_3^{2-}), not glutathione disulfide (GSSG) by O_3 (Enami et al., 2009b). However, it is possible that other oxidative species are oxidizing GSH in vivo, since sulfonates are not detected in O_3 exposed ELF whereas GSSG is. This is also supported by the fact that O_3 is much less reactive with GSH than other antioxidants, such that < 3% of O_3 will be scavenged by GSH when in equimolar amounts with AH_2 (Enami et al., 2009b).

Ozonolysis product yields and formation were affected by pH. Acidified conditions (pH ≈ 3-4), such as those that may result from acidic particulate exposure or pathological conditions like asthma (pH ≈ 6), decreased the scavenging ability of UA and GSH for O_3; such that at low pH, the scavenging of O_3 must be taken over by other antioxidants, such as AH_2 (Enami et al., 2009b, 2008b). Also, under acidic conditions (pH ≈ 5), the ozonolysis products of AH_2 shifted from the innocuous dehydroascorbic acid to the more persistent products, AH_2 ozonide and threonic acid (Enami et al., 2008a). It is possible that the acidification of the ELF by acidic copollutant exposure will increase the toxicity of O_3 by preventing some antioxidant reactions and shifting the reaction products to more persistent compounds.

In a red blood cell (RBC) based system, AH_2 augmented the in vitro uptake of O_3 by six fold, as computed by the mass balance across the exposure chamber (Ballinger et al., 2005). However, estimated in vitro O_3 uptake was not proportional to the production of O_3-derived aldehydes from exposing O_3 to RBC membranes (Ballinger et al., 2005). In addition, O_3 induced cell membrane oxidation which required interactions with AH_2 and GSH, but not UA or the vitamin E analog Trolox. Further, aqueous phase reactions between O_3 and bovine serum albumin did not result in membrane oxidation (Ballinger et al., 2005). The presence of UA or bovine serum albumin protected against lipid and protein oxidation resulting from the reaction of O_3 and AH_2 (Ballinger et al., 2005). This

study provided evidence that antioxidants may paradoxically facilitate O_3-mediated damage. This apparent contradiction should be viewed in terms of the concentration-dependent role of the ELF antioxidants. Reactions between O_3 and antioxidant species exhibited a biphasic concentration response, with oxidation of protein and lipid occurring at lower, but not higher, concentrations of antioxidant. In this way, endogenous reactants led to the formation of secondary oxidation products which were injurious and also led to quenching reactions which were protective. Moreover, the formation of secondary oxidation products mediated by some antioxidants was opposed by quenching reactions involving other antioxidants.

Alterations in ELF composition can result in alterations in O_3 uptake. Bolus O_3 uptake in human subjects can be decreased by previous continuous O_3 exposure (120-360 ppb), possibly due to depletion of compounds able to react with O_3 (Rigas et al., 1997; Asplund et al., 1996). Conversely, O_3 (360 ppb) bolus uptake was increased with prior NO_2 (360-720 ppb) or SO_2 (360 ppb) exposure (Rigas et al., 1997). It was hypothesized that this increased fractional absorption of O_3 could be due to increased production of reactive substrates in the ELF due to oxidant-induced airway inflammation.

Besides AH_2, GSH and UA, the ELF contains numerous antioxidant substances that appear to be an important cellular defense against O_3 including α-TOH, albumin, ceruloplasmin, lactoferrin, mucins, and transferrin (Mudway et al., 2006; Freed et al., 1999). The level and type of antioxidant present in ELF varies between species, regions of the RT, and can be altered by O_3 exposure. Mechanisms underlying the regional variability are not well-understood. It is thought that both plasma ultrafiltrate and locally secreted substances contribute to the antioxidant content of the ELF (Mudway et al., 2006; Freed et al., 1999). In the case of UA, the major source appears to be the plasma (Peden et al., 1995). Repletion of UA in nasal lavage fluid was demonstrated during sequential nasal lavage in human subjects (Mudway et al., 1999a). When these subjects were exposed to 200 ppb O_3 for 2 hours while exercising, nasal lavage fluid UA was significantly decreased while plasma UA levels were significantly increased (Mudway et al., 1999a). The finding that UA, but not AH_2 or GSH, was depleted in nasal lavage fluid indicated that UA was the predominant antioxidant with respect to O_3 reactivity in the nasal cavity (Mudway et al., 1999a). In addition, concentrations of UA were increased by cholinergic stimulation of the airways in exercising human subjects exposed to 400 ppb O_3 for 2 hours, which suggested that increased mucosal gland secretions were an important source (Peden et al., 1995). Using the O_3-specific antioxidant capacity assay on human nasal lavage samples, Rutkowski et al. (2011) concluded that about 30% of the antioxidant capacity of the nasal liquid lining layer was attributed to UA activity. This assay predicted that more than 50% of the subject-to-subject differences in antioxidant capacity were driven by differences in UA concentration. However, day-to-day within-

subject variations in measured antioxidant capacity were not related to the corresponding variations in UA concentration in the nasal lavage fluid. Efforts to identify the predominant antioxidant(s) in other RT regions besides the nasal cavity have failed to yield definitive results. However, in human BALF samples, the mean consumption of AH_2 was greater than UA (Mudway et al., 1996).

Regulation of AH_2, GSH and α-TOH concentrations within the ELF is less clear than that of UA (Mudway et al., 2006). In a sequential nasal lavage study in humans, wash-out of AH_2 and GSH occurred, indicating the absence of rapidly acting repletion mechanisms (Mudway et al., 1999a). Other studies demonstrated increases in BALF GSH and decreases in BALF and plasma AH_2 levels several hours following O_3 exposure (200 ppb for 2 h, while exercising) (Mudway et al., 2001; Blomberg et al., 1999; Mudway et al., 1999b). Furthermore, high levels of dehydroascorbate, the oxidized form of AH_2, have been reported in human ELF (Mudway et al., 2006). Other investigators have demonstrated cellular uptake of oxidized AH_2 by several cell types leading to intracellular reduction and export of reduced AH_2 (Welch et al., 1995). Studies with rats exposed to 0.4-1.1 ppm O_3 for 1-6 hours have shown consumption of AH_2 that correlates with O_3 exposure (Gunnison and Hatch, 1999; Gunnison et al., 1996; Vincent et al., 1996a).

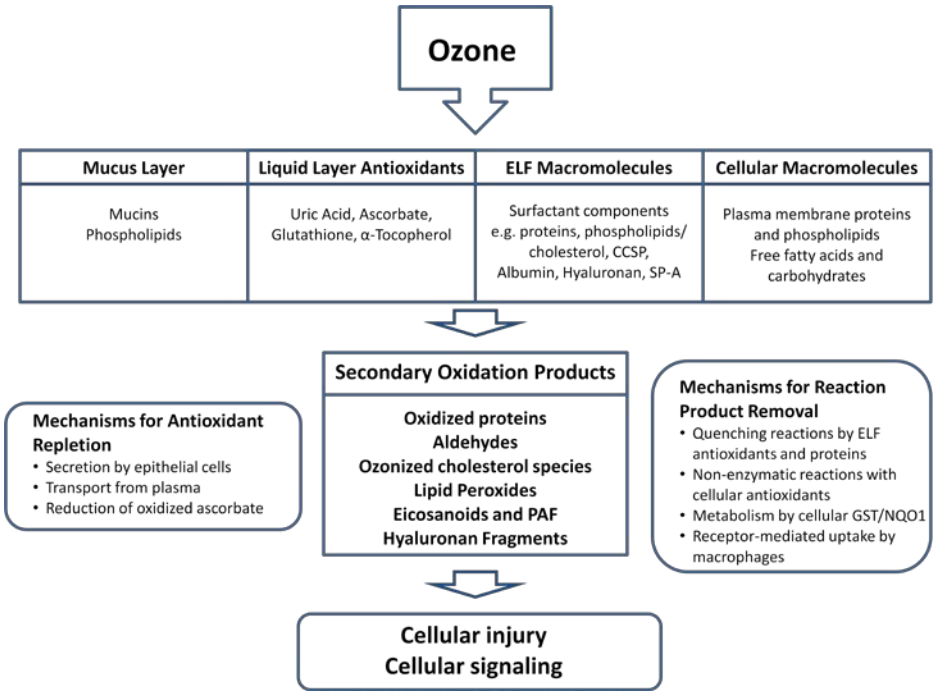
ELF exists as a complex mixture, thus it is important to look at O_3 reactivity in substrate mixtures. Individual antioxidant consumption rates decreased as the substrate mixture complexity increased (e.g., antioxidant mixtures and albumin addition) (Mudway and Kelly, 1998). However, O_3 reactions with AH_2 predominated over the reaction with lipids, when exposed to substrate solution mixtures (Postlethwait et al., 1998). It was suggested that O_3 may react with other substrates once AH_2 concentrations within the reaction plane fall sufficiently. Additionally, once AH_2 was consumed, the absorption efficiency diminished, allowing inhaled O_3 to be distributed to more distal airways (Postlethwait et al., 1998). Multiple studies have concluded O_3 is more reactive with AH_2 and UA than with the weakly reacting GSH (or cysteine or methionine) or with amino acid residues and protein thiols (Kanofsky and Sima, 1995; Cross et al., 1992).

In addition to reactions with components of the ELF, O_3 may react with plasma membranes of cells which reside in the RT. Eicosanoids are an important class of secondary oxidation products which may be formed rapidly by this mechanism. Eicosanoids are metabolites of arachidonic acid, a 20-carbon PUFA, which is released from membrane phospholipids by phospholipase A2-mediated catalysis. Activation of phospholipase A2 occurs by several cell signaling pathways and may be triggered by O_3-mediated lipid peroxidation of cellular membranes (Rashba-Step et al., 1997). Additionally, cellular phospholipases A2, C and D may be activated by lipid ozonation

products (Kafoury et al., 1998). While the conversion of arachidonic acid to prostaglandins, leukotrienes and other eicosanoid products is generally catalyzed by cyclooxygenases and lipoxygenases, non-enzymatic reactions also occur during oxidative stress leading to the generation of a wide variety of eicosanoids and reactive oxygen species. Further, the release of arachidonic acid from phospholipids is accompanied by the formation of lysophospholipids which are precursors for platelet activating factors (PAFs). Thus, formation of eicosanoids, reactive oxygen species and PAFs accompanies O_3-mediated lipid peroxidation.

5.2.3.1 Summary

The ELF is a complex mixture of lipids, proteins, and antioxidants that serve as the first barrier and target for inhaled O_3 (Figure 5-8). The thickness of the lining fluid and mucus layer is an important determinant of the dose of O_3 to the tissues. The antioxidant substances present in the ELF appear in most cases to limit interaction of O_3 with



Contents of this figure not discussed in Section 5.2 will be discussed in Section 5.3. Clara cell secretory protein, CCSP; Surfactant Protein-A, SP-A; Platelet activating factor, PAF.

Figure 5-8 Details of the O_3 interaction with the airway ELF to form secondary oxidation products. Ozone will react with components of the ELF to produce reaction products that may lead to cellular injury and cell signaling as discussed in Section 5.3.

underlying tissues and to prevent penetration of O_3 deeper into the lung. The formation of secondary oxidation products is likely related to the concentration of antioxidants present and the quenching ability of the lining fluid. Mechanisms are present to replenish the antioxidant substrate pools as well as to remove secondary reaction products from tissue interactions. Important differences exist in the reaction rates for O_3 and these ELF biomolecules and the reactivity of the resulting products. Overall, studies suggest that UA and AH_2 are more reactive with O_3 than GSH, proteins, or lipids. In addition to contributing to the driving force for O_3 uptake, formation of secondary oxidation products may lead to increased cellular injury and cell signaling (discussed in Section 5.3). Studies indicate that the antioxidants might be participating in reactions where the resulting secondary oxidation products might penetrate into the tissue layer and cause injury.

5.3 Possible Pathways/Modes of Action

5.3.1 Introduction

Mode of action refers to a sequence of key events and processes which result in a given toxic effect (U.S. EPA, 2005). Elucidation of mechanisms provides a more detailed understanding of these key events and processes (U.S. EPA, 2005). Moreover, toxicity pathways describe the processes by which perturbation of normal biological processes produce changes sufficient to lead to cell injury and subsequent events such as adverse health effects (U.S. EPA, 2009f). The purpose of this section of Chapter 5 is to describe the key events and toxicity pathways which contribute to health effects resulting from short-term and long-term exposures to O_3. The extensive research carried out over several decades in humans and in laboratory animals has yielded numerous studies on mechanisms by which O_3 exerts its effects. This section will discuss some of the representative studies with particular emphasis on studies published since the 2006 O_3 AQCD and on studies in humans which inform biological mechanisms underlying responses to O_3.

It is well-appreciated that secondary oxidation products, which are formed as a result of O_3 exposure, initiate numerous responses at the cellular, tissue and whole organ level of the respiratory system. These responses include the activation of neural reflexes, initiation of inflammation, alteration of epithelial barrier function, sensitization of bronchial smooth muscle, modification of innate/adaptive immunity and airways remodeling, as will be discussed below. Exposure to O_3 also may result in effects on other organ systems such as the cardiovascular, central nervous, hepatic and reproductive systems. It is unlikely that lipid ozonides and other secondary oxidation products, which are bioactive and cytotoxic in the respiratory system, gain access to the vascular space (Chuang et al., 2009). However the inhalation of O_3 may result in systemic oxidative stress. The following subsections describe the current understanding of potential pathways and modes of action responsible for the pulmonary and extrapulmonary effects of O_3 exposure.

5.3.2 Activation of Neural Reflexes

Acute O_3 exposure results in reversible effects on lung function parameters through activation of neural reflexes. The involvement of bronchial C-fibers, a type of nociceptive sensory nerve, has been demonstrated in dogs exposed through an endotracheal tube to 2-3 ppm O_3 for 20-70 minutes (Coleridge et al., 1993; Schelegle et al., 1993). This vagal

afferent pathway was found to be responsible for O_3-mediated rapid shallow breathing and other changes in respiratory mechanics in O_3-exposed dogs (Schelegle et al., 1993). Ozone also triggers neural reflexes which stimulate the autonomic nervous system and alter electrophysiologic responses of the heart. For example, bradycardia, altered HRV and arrhythmia have been demonstrated in rodents exposed to 0.1-0.6 ppm O_3 (Hamade and Tankersley, 2009; Watkinson et al., 2001; Arito et al., 1990). Another effect is hypothermia, which in rodents occurred subsequent to the activation of neural reflexes involoving the parasympathetic nervous system (Watkinson et al., 2001). Vagal afferent pathways originating in the respiratory tract may also be responsible for O_3-mediated activation of nucleus tractus solitarius neurons which resulted in neuronal activation in stress-responsive regions of the central nervous system (CNS) (rats, 0.5-2.0 ppm O_3 for 1.5-120 hours) (Gackière et al., 2011).

Recent studies in animals provide new information regarding the effects of O_3 on reflex responses mediated by bronchopulmonary C-fibers. In ex vivo mouse lungs, O_3 exposure selectively activated a subset of C-fiber receptors which are TRPA1 ion channels (Taylor-Clark and Undem, 2010). TRPA1 ion channels are members of the TRP family of ion channels, which are known to mediate the responses of sensory neurons to inflammatory mediators (Caceres et al., 2009). In addition to TRPA1 ion channels possibly playing a key role in O_3-induced decrements in pulmonary function, they may mediate allergic asthma (Caceres et al., 2009). Activation of TRPA1 ion channels following O_3 exposure is likely initiated by secondary oxidation products such as aldehydes and prostaglandins (Taylor-Clark and Undem, 2010) through covalent modification of cysteine and lysine residues (Trevisani et al., 2007). Ozonation of unsaturated fatty acids in the ELF was found to result in the generation of aldehydes (Frampton et al., 1999) such as 4-hydroxynonenal and 4-oxononenal (Taylor-Clark et al., 2008; Trevisani et al., 2007). 4-oxononenal is a stronger electrophile than 4-hydroxynonenal and exhibits greater potency towards the TRPA1 channels (Taylor-Clark et al., 2008). (Trevisani et al., 2007). In addition, PGE_2 is known to sensitize TRPA1 channels (Bang et al., 2007).

In exercising humans, the response to O_3 (500 ppb for 2 h) was characterized by substernal discomfort, especially on deep inspiration, accompanied by involuntary truncation of inspiration (Hazucha et al., 1989). This led to decreased inspiratory capacity and to decreased forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), as measured by spirometry. These changes, which occurred during O_3 exposure, were accompanied by decreased V_T and increased respiratory frequency in human subjects. Spirometric changes in FEV_1 and FVC were not due to changes in respiratory muscle strength (Hazucha et al., 1989). In addition, parasympathetic involvement in the O_3-mediated decreases in lung volume was minimal (Mudway and Kelly, 2000), since changes in FVC or symptoms were not modified by treatment with bronchodilators such

as atropine in exercising human subjects exposed to 400 ppb O_3 for 0.5 hour (Beckett et al., 1985). However, the loss of vital capacity was reversible with intravenous administration of the rapid-acting opioid agonist, sufentanyl, in exercising human subjects exposed to 420 ppb O_3 for 2 hours, which indicated the involvement of opioid receptor-containing nerve fibers and/or more central neurons (Passannante et al., 1998). The effects of sufentanyl may be attributed to blocking C-fiber stimulation by O_3 since activation of opioid receptors downregulated C-fiber function (Belvisi et al., 1992). Thus, nociceptive sensory nerves, presumably bronchial C-fibers, are responsible for O_3-mediated responses in humans (Passannante et al., 1998). This vagal afferent pathway is responsible for pain-related symptoms and inhibition of maximal inspiration in humans (Hazucha et al., 1989).

There is some evidence that eicosanoids (see Section 5.3.3) play a role in the neural reflex since cyclooxygenase inhibition with indomethacin (Alexis et al., 2000; Schelegle et al., 1987) or ibuprofen, which also blocks some lipoxygenase activity (Hazucha et al., 1996), before exposure to O_3 significantly blunted the spirometric responses. These studies involved exposures of 1-2 hours to 350-400 ppb O_3 in exercising human subjects. In the latter study, ibuprofen treatment resulted in measurable decreases in BALF levels of PGE_2 and TXB_2 at 1-hour postexposure (Hazucha et al., 1996). Although an earlier study demonstrated that PGE_2 stimulated bronchial C-fibers (Coleridge et al., 1993; Coleridge et al., 1976) and suggested that PGE_2 mediated O_3-induced decreases in pulmonary function, no correlation was observed between the degree of ibuprofen-induced inhibition of BALF PGE_2 levels and blunting of the spirometric response to O_3 (Hazucha et al., 1996). These results point to the involvement of a lipoxygenase product. Further, as noted above, PGE_2 may play a role in the neural reflex by sensitizing TRPA1 channels. A recent study in exercising human subjects exposed for 1 hour to 350 ppb O_3 also provided evidence that arachidonic acid metabolites, as well as oxidative stress, contribute to human responsiveness to O_3 (Alfaro et al., 2007).

In addition to the spirometric changes, mild airways obstruction occurred in exercising humans during O_3 exposure (500 ppb for 2 hours) (Hazucha et al., 1989). This pulmonary function decrement is generally measured as specific airway resistance (sRaw) which is the product of airway resistance and thoracic gas volume. In several studies involving exercising human subjects exposed for 1-4 hours to 200-300 ppb O_3, changes in sRaw correlated with changes in inflammatory and injury endpoints measured 18-hours postexposure, but did not follow the same time course or change to the same degree as spirometric changes (i.e. FEV_1, FVC) measured during exposure (Balmes et al., 1996; Aris et al., 1993; Schelegle et al., 1991). In addition, a small but persistent increase in airway resistance associated with narrowing of small peripheral airways (measured as changes in isovolumetric FEF_{25-75}) was demonstrated in O_3-exposed human subjects (350

ppb for 130 minutes with exercise) (Weinmann et al., 1995a; Weinmann et al., 1995b). A similar study (400 ppb O_3 for 2 hours in exercising human subjects) found decreases in FEF_{25-75} concomitant with increases in residual volume, which is suggestive of small airways dysfunction (Kreit et al., 1989). In separate studies, a statistically significant increase in residual volume (500 ppb for 2 hours) (Hazucha et al., 1989) and a statistically significant decrease in FEF_{25-75} (160 ppb for 7.6 hours) (Horstman et al., 1995) were observed following O_3 exposure in exercising human subjects, providing further support for an O_3-induced effect on small airways.

Mechanisms underlying this rapid increase in airway resistance following O_3 exposure are incompletely understood. Pretreatment with atropine decreased baseline sRaw and prevented O_3-induced increases in sRaw in exercising human subjects (400 ppb for 0.5 hours) (Beckett et al., 1985), indicating the involvement of muscarinic cholinergic receptors of the parasympathetic nervous system. Interestingly, atropine pretreatment partially blocked the decrease in FEV_1, but had no effect on the decrease in FVC, breathing rate, tidal volume or respiratory symptoms (Beckett et al., 1985). Using a β-adrenergic agonist, it was shown that smooth muscle contraction, not increased airway mucus secretion, was responsible for O_3-induced increases in airway resistance (Beckett et al., 1985). Thus, pulmonary function decrements measured as FEV_1 may reflect both restrictive (such as decreased inspiratory capacity) and obstructive (such as bronchoconstriction) type changes in airway responses. This is consistent with McDonnell et al. (1983) who observed a relatively strong correlation between sRaw and FEV_1 (r=-0.31, p=0.001) and a far weaker correlation between sRaw and FVC (r=-0.16, p=0.10) in exercising human subjects exposed for 2.5 hours to 120-400 ppb O_3.

Furthermore, tachykinins may contribute to O_3-mediated increases in airway resistance. In addition to stimulating CNS reflexes, bronchopulmonary C-fibers mediate local axon responses by releasing neuropeptides such as substance P (SP), neurokinin (NK) A and calcitonin gene-related peptide (CGRP). Tachykinins bind to NK receptors resulting in responses such as bronchoconstriction. Recent studies in animals demonstrated that NK-1 receptor blockade had no effect on O_3-stimulated physiologic responses such as V_T and f_B in rats over the 8 hour exposure to 1 ppm O_3 (Oslund et al., 2008). However, SP and NK receptors contributed to vagally-mediated bronchoconstriction in guinea pigs 3 days after a single 4-hour exposure to 2 ppm O_3 (Verhein et al., 2011). In one human study in which bronchial biopsies were performed and studied by immunohistochemistry, SP was substantially diminished in submucosal sensory nerves 6 hours following O_3 exposure (200 ppb for 2 hours with exercise) (Krishna et al., 1997). A statistically significant correlation was observed between loss of SP immunoreactivity from neurons in the bronchial mucosa and changes in FEV_1 measured 1-hour postexposure (Krishna et al., 1997). Another study found that SP was increased in lavage fluid of human subjects

immediately after O_3 challenge (250 ppb for 1 hour with exercise) (Hazbun et al., 1993). These results provide evidence that the increased airway resistance observed following O_3 exposure is due to vagally-mediated responses and possibly by local axon reflex responses through bronchopulmonary C-fiber-mediated release of SP.

5.3.3 Initiation of inflammation

As described previously (5.2.3), O_3 reacts with components of the ELF and cellular membranes resulting in the generation of secondary oxidation products. Higher concentrations of these products may directly injure respiratory tract epithelium. Lower concentrations may initiate cellular responses including cytokine generation, adhesion molecule expression and modification of tight junctions leading to inflammation and increased permeability across airway epithelium (Section 5.3.4) (Dahl et al., 2007; Mudway and Kelly, 2000). Subsequent airways remodeling may also occur (Section 5.3.7) (Mudway and Kelly, 2000).

An important hallmark of acute O_3 exposure in humans and animals is neutrophilic airways inflammation. Although neutrophil influx into nasal airways has been demonstrated in exercising human subjects (400 ppb O_3, 2 hours) (Graham and Koren, 1990), most studies of neutrophil influx have focused on the lower airways (Hazucha et al., 1996; Aris et al., 1993). The time course of this response in the lower airways and its resolution was slower than that of the decrements in pulmonary function in exercising human subjects exposed for 2 hours to 500 ppb O_3 (Hazucha et al., 1996). In several studies, airways neutrophilia was observable within 1-2 hours, peaked at 4-6 hours and was returning to baseline levels at 24 hours following exposure of 1-2 hours to 300-400 ppb O_3 in exercising humans (Devlin et al., 1991; Schelegle et al., 1991). Since the influx and persistence of neutrophils in airways following O_3 exposure correlated with the temporal profile of epithelial injury (guinea pigs, 0.26-1 ppm O_3, 72 hours) (Hu et al., 1982), neutrophils were probably injurious. However, neutrophils have also been shown to contribute to repair of O_3-injured epithelium in rats exposed for 8 hours to 1 ppm O_3, possibly by removing necrotic epithelial cells (Mudway and Kelly, 2000; Vesely et al., 1999). Nonetheless, the degree of airways inflammation due to O_3 is thought to have more important long-term consequences than the more quickly resolving changes in pulmonary function since airways inflammation is often accompanied by tissue injury (Balmes et al., 1996).

Ozone exposure results in alterations in other airways inflammatory cells besides neutrophils, including lymphocytes, macrophages, monocytes and mast cells. Influx of some of these cells accounts for the later (i.e. 18-20 hours) phase of inflammation

following O_3 exposure. Numbers of lymphocytes and total cells in BALF were decreased early after O_3 exposure in exercising humans exposed for 2 hours to 200 ppb O_3, which preceded the neutrophil influx (Mudway and Kelly, 2000; Blomberg et al., 1999; Krishna et al., 1997). The decrease in total cells was thought to reflect decreases in macrophages, although it was not clear whether the cells were necrotic or whether membrane adhesive properties were altered making them more difficult to obtain by lavage (Mudway and Kelly, 2000; Blomberg et al., 1999; Mudway et al., 1999b; Frampton et al., 1997a; Pearson and Bhalla, 1997). A recent study in exercising human subjects exposed for 6.6 hours to 80 ppb O_3 demonstrated an increase in numbers of sputum monocytes and dendritic-like cells with increased expression of innate immune surface proteins and antigen presentation markers (Peden, 2011; Alexis et al., 2010) (see Section 6.2.3.1). An increase in submucosal mast cells was observed 1.5 hours after a 2 hour-exposure to 200 ppb O_3 (Blomberg et al., 1999) and an increase in BAL mast cell number was observed 18 hours after a 4-hour exposure to 220 ppb O_3 exposure in exercising human subjects (Frampton et al., 1997a). Mast cells may play an important role in mediating neutrophil influx since they are an important source of several pro-inflammatory cytokines and since their influx preceded that of neutrophils in exercising human subjects exposed for 2 hours to 200 ppb O_3 (Stenfors et al., 2002; Blomberg et al., 1999). Further, a study using mast cell-deficient mice demonstrated decreased neutrophilic inflammation in response to O_3 (1.75 ppm, 3 hours) compared with wild type mice (Kleeberger et al., 1993). Influx of these inflammatory cell types in the lung is indicative of O_3-mediated activation of innate immunity as will be discussed in Section 5.3.6.

Much is known about the cellular and molecular signals involved in inflammatory responses to O_3 exposure (U.S. EPA, 2006b). Eicosanoids are one class of secondary oxidation products which may be formed rapidly following O_3 exposure and which may mediate inflammation. In addition, secondary reaction products may stimulate macrophages to produce cytokines such as IL-1, IL-6 and TNF-α which in turn activate IL-8 production by epithelial cells. Although IL-8 has been proposed to play a role in neutrophil chemotaxis, measurements of IL-8 in BALF from humans exposed to O_3 found increases that were too late to account for this effect (Mudway and Kelly, 2000). The time-course profiles of PGE_2 and IL-6 responses suggest that they may play a role in neutrophil chemotaxis in humans (Mudway and Kelly, 2000). However, pretreatment with ibuprofen attenuated O_3-induced increases in BALF PGE_2 levels, but had no effect on neutrophilia in exercising human subjects exposed for 2 hour to 400 ppb O_3 (Hazucha et al., 1996).

One set of studies in humans focused on the earliest phase of airways inflammation (1-2 hours following exposure). Exercising subjects were exposed to 200 ppb O_3 for 2 hours and bronchial biopsy tissues were obtained 1.5 and 6 hours after exposure (Bosson et al.,

2009; Bosson et al., 2003; Stenfors et al., 2002; Blomberg et al., 1999). Results demonstrated upregulation of vascular endothelial adhesion molecules P-selectin and ICAM-1 at both 1.5 and 6 hours (Stenfors et al., 2002; Blomberg et al., 1999). Submucosal mast cell numbers were increased at 1.5 hours in the biopsy samples without an accompanying increase in neutrophil number (Blomberg et al., 1999). Pronounced neutrophil infiltration was observed at 6 hours in the bronchial mucosa (Stenfors et al., 2002). Surprisingly, suppression of the NF-κB and AP-1 pathways at 1.5 hours and a lack of increased IL-8 at 1.5 or 6 hours in bronchial epithelium was observed (Bosson et al., 2009). The authors suggested that vascular endothelial adhesion molecules, rather than redox sensitive transcription factors, play key roles in early neutrophil recruitment in response to O_3.

Increases in markers of inflammation occurred to a comparable degree in exercising human subjects with mild (least sensitive) and more remarkable (more sensitive) spirometric responses to O_3 (200 ppb, 4 hours) (Balmes et al., 1996). Two other studies using similar protocols (200 ppb for 4 hours and 300 ppb for 1 hour) found that acute spirometric changes were not positively correlated with cellular and biochemical indicators of inflammation (Aris et al., 1993; Schelegle et al., 1991). However inflammation was correlated with changes in sRaw (Balmes et al., 1996). In another study, pretreatment with ibuprofen had no effect on neutrophilia although it blunted the spirometric response in exercising human subjects exposed for 2 hours to 400 ppb O_3 (Hazucha et al., 1996). Taken together, results from these studies indicate different mechanisms underlying the spirometric and inflammatory responses to O_3.

A common mechanism underlying both inflammation and impaired pulmonary function was suggested by Krishna et al. (1997). This study, conducted in exercising humans exposed to 200 ppb O_3 for 2 hours, demonstrated a correlation between loss of SP immunoreactivity from neurons in the bronchial mucosa and numbers of neutrophils and epithelial cells (shed epithelial cells are an index of injury) in the BALF 6-hours postexposure. Furthermore, the loss of SP immunoreactivity was correlated with the observed changes in FEV_1. Another study found that SP was increased in lavage fluid of exercising human subjects immediately after O_3 challenge (250 ppb, 1 hour) (Hazbun et al., 1993). SP is a neuropeptide released by sensory nerves which mediates neurogenic edema and bronchoconstriction (Krishna et al., 1997). Taken together, these findings suggest that O_3-mediated stimulation of sensory nerves which leads to activation of central and local axon reflexes is s a common effector pathway leading to impaired pulmonary function and inflammation.

Studies in animal models have confirmed many of these findings and provided evidence for additional mechanisms involved in O_3-induced inflammation. A study in mice (2 ppm

O_3, 3 hours) demonstrated that PAF may be important in neutrophil chemotaxis (Longphre et al., 1999), while ICAM-1 and macrophage inflammatory protein-2 (MIP-2), the rodent IL-8 homologue, have been implicated in a rat model (1 ppm O_3, 3 hours) (Bhalla and Gupta, 2000). Key roles for CXCR2, a receptor for keratinocyte-derived chemokine (KC) and MIP-2, and for IL-6 in O_3-mediated neutrophil influx were demonstrated in mice (1 ppm O_3, 3 hours) (Johnston et al., 2005a; Johnston et al., 2005b). Activation of JNK and p38 pathways and cathepsin-S were also found to be important in this response (3 ppm O_3, 3 hours) (Williams et al., 2009a; Williams et al., 2008b; Williams et al., 2007a). Matrix metalloproteinase-9 (MMP-9) protected against O_3-induced airways inflammation and injury in mice (0.3 ppm O_3, 6-72 hours) (Yoon et al., 2007). Interleukin-10 (IL-10) was also found to be protective since IL-10 deficient mice responded to O_3 exposure (0.3 ppm, 24-72 hours) with enhanced numbers of BAL neutrophils, enhanced NF-κB activation and MIP-2 levels compared with IL-10 sufficient mice (Backus et al., 2010).

In addition, lung epithelial cells may release ATP in response to O_3 exposure (Ahmad et al., 2005). ATP and its metabolites (catalyzed by ecto-enzymes) can bind to cellular purinergic receptors resulting in activation of cell signaling pathways (Picher et al., 2004). One such metabolite, adenine, is capable of undergoing oxidation leading to the formation of UA which, if present in high concentrations, could activate inflammasomes and result in caspase 1 activation and the maturation and secretion of IL-1β and IL-18 (Dostert et al., 2008). A recent study in exercising human subjects exposed for 2 hours to 400 ppb O_3 demonstrated a correlation between ATP metabolites and inflammatory markers (Esther et al., 2011), which provides some support for this mechanism.

Several recent studies have focused on the role of toll-like receptor (TLR) and its related adaptor protein MyD88 in mediating O_3-induced neutrophilia. While Hollingsworth et al. (2004) demonstrated airways neutrophilia which was TLR4-independent following acute (2 ppm, 3 hours) and subchronic (0.3 ppm, 72 hours) O_3 exposure in a mouse model, Williams et al. (2007b) found that MyD88 was important in mediating O_3-induced neutrophilia in mice (3 ppm, 3 hours), with TLR4 and TLR2 contributing to the speed of the response. Moreover, MyD88, TLR2 and TLR4 contributed to inflammatory gene expression in this model and O_3 upregulated MyD88, TLR4 and TLR4 gene expression (Williams et al., 2007a)

Hyaluronan was found to mediate a later phase (24 hours) of O_3-induced inflammation in mice (Garantziotis et al., 2010; Garantziotis et al., 2009). Hyaluronan is an extracellular matrix component which is normally found in the ELF as a large polymer. Exposure to 2 ppm O_3 for 3 hours resulted in elevated levels of soluble low molecular weight hyaluronan in the BALF 24-hours postexposure (Garantziotis et al., 2010; Garantziotis et

al., 2009). Ozone may have caused the depolymerization of hyaluronan to soluble fragments which are known to be endogenous ligands of the CD44 receptor and TLR4 in the macrophage (Jiang et al., 2005). Binding of hyaluronan fragments to the CD44 receptor activates hyaluronan clearance, while binding to TLR4 results in signaling through MyD88 to produce chemokines that stimulate the influx of inflammatory cells (Jiang et al., 2005). Activation of NF-κB occurred in both airway epithelia and alveolar macrophages 24-hours postexposure to O_3. Increases in BALF pro-inflammatory factors KC, IL-1β, MCP-1, TNF-α and IL-6 observed 24 hours following O_3 exposure were found to be partially dependent on TLR4 (Garantziotis et al., 2010) while increases in BAL inflammatory cells, which consisted mainly of macrophages, were dependent on CD44 (Garantziotis et al., 2009). BAL inflammatory cells number and injury markers following O_3 exposure were similar in wild-type and TLR4-deficient animals (Garantziotis et al., 2010).

Since exposure to O_3 leads to airways inflammation characterized by neutrophilia, and since neutrophil-derived oxidants often scavenge ELF antioxidants, concentrations of ELF antioxidants have been examined during airways neutrophilia (Long et al., 2001; Gunnison and Hatch, 1999; Mudway et al., 1999b). In exercising humans exposed to 200 ppb O_3 for 2 hours, UA, GSH and α-TOH levels remained unchanged in BALF 6-hours postexposure while AH2 was decreased significantly in both BALF and plasma (Mudway et al., 1999b). A second study involving the same protocol reported a loss of AH2 from bronchial wash fluid and BALF, representing proximal and distal airway ELF respectively, as well as an increase in oxidized GSH in both compartments (Mudway et al., 2001). No change was observed in ELF UA levels in response to O_3 (Mudway et al., 2001). Further, O_3 exposure (0.8 ppm, 4 hours) in female rats resulted in a 50% decrease in BALF AH2 immediately postexposure (Gunnison and Hatch, 1999). These studies suggested a role for AH2 and GSH in protecting against the oxidative stress associated with inflammation.

5.3.4 Alteration of epithelial barrier function

Following O_3 exposure, injury and inflammation can lead to altered airway barrier function. Histologic analysis has demonstrated damage to tight junctions between epithelial cells, suggesting an increase in epithelial permeability. In addition, the presence of shed epithelial cells in the BALF and increased epithelial permeability, which is measured as the flux of small solutes, have been observed and are indicative of epithelial injury. Increases in vascular permeability, as measured by BALF protein and albumin, have also been demonstrated (Costa et al., 1985; Hu et al., 1982).

An early study in sheep measured changes in airway permeability as the flux of inhaled radiolabeled histamine into the plasma (Abraham et al., 1984). Exposure of sheep to 0.5 ppm O_3 for 2 hours via an endotracheal tube resulted in an increased rate of histamine appearance in the plasma at 1 day postexposure. Subsequently, numerous studies have measured epithelial permeability as the flux of the small solute ^{99m}TcDTPA which was introduced into the air spaces in different regions of the respiratory tract. Increased pulmonary epithelial permeability, measured as the clearance of ^{99m}Tc-DTPA, was demonstrated in humans 1-2 hours following a 2-hour exposure to 400 ppb O_3 while exercising moderately (Kehrl et al., 1987). Another study in human subjects found increased epithelial permeability 19-hours postexposure to 240 ppb O_3 for 130 minutes while exercising (Foster and Stetkiewicz, 1996). Increased bronchial permeability was also observed in dogs 1-day postexposure (0.4 ppm O_3 by endotracheal tube for 6 hours) and did not resolve for several days (Foster and Freed, 1999).

A role for tachykinins in mediating airway epithelial injury and decreased barrier function has been suggested. Nishiyama et al. (1998) demonstrated that capsaicin, which depletes nerve fibers of substance P, blocked the O_3-induced increase in permeability of guinea pig tracheal mucosa (0.5-3 ppm O_3, 0.5 hours). Pretreatment with propranolol or atropine failed to inhibit this response, suggesting that adrenergic and cholinergic pathways were not involved. In another study, tachykinins working through NK-1 and CGRP receptors were found to contribute to airway epithelial injury in O_3-exposed rats (1 ppm, 8 hours) (Oslund et al., 2009, 2008).

Kleeberger et al. (2000) evaluated genetic susceptibility to O_3-induced altered barrier function in recombinant inbred strains of mice. Lung hyperpermeability, measured as BALF protein, was evaluated 72 hours after exposure to 0.3 ppm O_3 and found to be associated with a functioning TLR4 gene. This study concluded that Tlr4 was a strong candidate gene for susceptibility to hyperpermeability in response to O_3 (Kleeberger et al., 2000). A subsequent study by these same investigators found that Tlr4 modulated Nos2 mRNA levels and suggested that the gene product of Nos2, iNOS, plays an important role in O_2-induced lung hyperpermeability (0.3 ppm, 72 hours) (Kleeberger et al., 2001). More recently, HSP70 was identified as part of the TLR4 signaling pathway (0.3 ppm, 6-72 hours) (Bauer et al., 2011).

Antioxidants have been shown to confer resistance to O_3-induced injury. In a recent study, lung hyperpermeability in response to O_3 (0.3 ppm, 48 hours) was unexpectedly reduced in mice deficient in the glutamate-cysteine ligase modifier subunit gene compared with sufficient mice (Johansson et al., 2010). Since the lungs of these mice exhibited 70% glutathione depletion, protection against O_3-induced injury was unexpected (Johansson et al., 2010). However it was found that several other antioxidant

defenses, including metallothionein, were upregulated in response to O_3 to a greater degree in the glutathione-deficient mice compared with sufficient mice (Johansson et al., 2010). The authors suggested that resistance to O_3-induced lung injury was due to compensatory augmentation of antioxidant defenses (Johansson et al., 2010). Antioxidant effects have also been attributed to Clara cell secretory protein (CCSP) and surfactant protein A (SP-A). CCSP was found to modulate the susceptibility of airway epithelium to injury in mice exposed to O_3 (0.2 or 1 ppm for 8 hours) by an unknown mechanism (Plopper et al., 2006). SP-A protected against O_3-induced airways inflammation and injury in mice (2 ppm, 3 hours), possibly by acting as a sacrificial substrate (Haque et al., 2007).

Increased epithelial permeability has been proposed to play a role in allergic sensitization (Matsumura, 1970), in activation of neural reflexes and in stimulation of smooth muscle receptors (Dimeo et al., 1981). Abraham et al. (1984) reported a correlation between airway permeability and airways hyperresponsiveness (AHR) in O_3-exposed sheep. However a recent study in human subjects exposed to 220 ppb O_3 for 135 minutes while exercising did not find a relationship between O_3-induced changes in airway permeability and AHR (Que et al.).

5.3.5 Sensitization of bronchial smooth muscle

Bronchial reactivity is generally determined in terms of a response to a challenge agent. Non-specific bronchial reactivity in humans is assessed by measuring the effect of inhaling increasing concentrations of a bronchoconstrictive drug on lung mechanics (sRaw or FEV_1). Methacholine is most commonly employed but histamine and other agents are also used. Specific bronchial reactivity is assessed by measuring effects in response to an inhaled allergen in individuals (or animals) already sensitized to that allergen. An increase in sRaw in response to non-specific or specific challenge agents indicates AHR.

In addition to causing mild airway obstruction as discussed above, acute O_3 exposure results in reversible increases in bronchial reactivity by mechanisms which are not well understood. In one study, bronchial reactivity of healthy subjects was significantly increased 19-hours postexposure to O_3 (120-240 ppb O_3 for 2 hours with intermittent exercise) (Foster et al., 2000). These effects may be more significant in human subjects with already compromised airways (Section 5.4.2.2).

Ozone may sensitize bronchial smooth muscle to stimulation through a direct effect on smooth muscle or through effects on the sensory nerves in the epithelium or on the motor nerves innervating the smooth muscle (O'Byrne et al., 1984; O'Byrne et al., 1983;

Holtzman et al., 1979). It is also recognized that increased bronchial reactivity can be both a rapidly occurring and a persistent response to O_3 (Foster and Freed, 1999). Tachykinins and secondary oxidation products of O_3 have been proposed as mediators of the early response and inflammation-derived products have been proposed as mediators of the later response (Foster and Freed, 1999).

Ozone-induced increases in epithelial permeability, which could improve access of agonist to smooth muscle receptors, may be one mechanism of sensitization through a direct effect on bronchial smooth muscle (Holtzman et al., 1979). As noted above, a correlation between airway permeability and AHR has been reported in O_3-exposed sheep (Abraham et al., 1984) but not in O_3-exposed human subjects (Que et al.).

Neurally-mediated sensitization has been demonstrated. In human subjects exposed for 2 hours to 600 ppb O_3 while exercising, pretreatment with atropine inhibited O_3-induced AHR, suggesting the involvement of cholinergic postganglionic pathways (Holtzman et al., 1979). Animal studies have demonstrated that O_3-induced AHR involved vagally-mediated responses (rabbits, 0.2 ppm O_3, 72 hours) (Freed et al., 1996) and local axon reflex responses through bronchopulmonary C-fiber-mediated release of SP (guinea pigs, 0.8 ppm O_3, 2 hours) (Joad et al., 1996). Further, pretreatment with capsaicin to deplete nerve fibers of SP blocked O_3-mediated AHR (guinea pigs, 1-2 ppm O_3, 2-2.25 hours) (Tepper et al., 1993). Other investigators demonstrated that SP released from airway nociceptive neurons in ferrets contributed to O_3-induced AHR (2 ppm O_3, 3 hours) (Wu et al., 2008b; Wu et al., 2003).

Some evidence suggests the involvement of arachidonic acid metabolites and neutrophils in mediating O_3-induced AHR (Seltzer et al., 1986; Fabbri et al., 1985). Increased BAL neutrophils and cyclooxygenase products were found in one study demonstrating AHR in exercising humans (600 ppb for 2 hours) immediately postexposure to (Seltzer et al., 1986). Another study found that ibuprofen pretreatment had no effect on AHR in exercising humans following exposure to 400 ppb O_3 for 2 hours, although spirometric responses were blunted (Hazucha et al., 1996). This study indicated that the arachidonic acid metabolites whose generation was blocked by ibuprofen, (i.e. prostaglandins, thromboxanes and some leukotrienes) did not play a role in AHR. Experiments in dogs exposed for 2 hours to 2.1 ppm O_3 demonstrated a close correlation between O_3-induced AHR and airways neutrophilic inflammation measured in tissue biopsies (Holtzman et al., 1983). Furthermore, the increased AHR observed in dogs following O_3 exposure (3 ppm, 2 hours) was inhibited by neutrophil depletion (O'Byrne et al., 1983) and by pre-treatment with inhibitors of arachidonic acid metabolism. In one of these studies, indomethacin pre-treatment did not prevent airways neutrophilia in response to O_3 (3 ppm, 2 hours) providing evidence that the subset of arachidonic acid metabolites whose

generation was inhibitable by the cyclooxygenase inhibitor indomethacin (i.e., prostaglandins and thromboxanes) was not responsible for neutrophil influx (O'Byrne et al., 1984). Taken together, these findings suggest that arachidonic acid metabolites, but probably not prostaglandins or thromboxanes, may be involved in the AHR response following O_3 exposure in dogs. Studies probing the role of neutrophils in mediating the AHR response have provided inconsistent results (Al-Hegelan et al., 2011).

Evidence for cytokine and chemokine involvement in the AHR response to O_3 has been described. Some studies have suggested a role for TNF-α (mice, 0.5 and 2 ppm O_3, 3 hours) (Cho et al., 2001; Shore et al., 2001) and IL-1 (mice and ferrets, 2 ppm O_3, 3 hours) (Wu et al., 2008b; Park et al., 2004). The latter study found that SP expression in airway neurons was upregulated by IL-1 which was released in response to O_3. Other studies in mice have demonstrated a key role for CXCR2, the chemokine receptor for the neutrophil chemokines KC and MIP-2, but not for IL-6 in O_3-mediated AHR (1 ppm O_3, 3 hours) (Johnston et al., 2005a; Johnston et al., 2005b). In contrast, CXCR2 and IL-6 were both required for neutrophil influx in this model (Johnston et al., 2005a; Johnston et al., 2005b), as discussed above. Williams et al. (2008a) demonstrated that the Th2 cytokine IL-13 contributed to AHR, as well as to airways neutrophilia, in mice (3 ppm O_3, 3 hours).

Other studies have focused on the role of TLR4. Hollingsworth et al. (2004) measured AHR, as well as airways neutrophilia, in mice 6 and 24 hours following acute (2 ppm O_3 for 3 hours) and subchronic (0.3 ppm for 3 days) exposure to O_3. TLR4 is a key component of the innate immune system and is responsible for the immediate inflammatory response seen following challenge with endotoxin and other pathogen-associated substances. In this study, a functioning TLR4 was required for the full AHR response following O_3 exposure but not for airways neutrophilia (Hollingsworth et al., 2004). These findings are complemented by an older study demonstrating that O_3 effects on lung hyperpermeability required a functioning TLR4 (mice, 0.3 ppm O_3, 72 hours) (Kleeberger et al., 2000). Williams et al. (2007b) found that TLR2, TLR4 and the TLR adaptor protein MyD88 contributed to AHR in mice (3 ppm O_3, 3 hours). Ozone was also found to upregulate MyD88, TLR4 and TLR4 gene expression in this model (Williams et al., 2007b).

A newly recognized mechanistic basis for O_3-induced AHR is provided by studies focusing on the role of hyaluronan following O_3 exposure in mice (Garantziotis et al., 2010; Garantziotis et al., 2009). Hyaluronan is an extracellular matrix component which is normally found in the ELF as a large polymer. Briefly, TLR4 and CD44 were found to mediate AHR in response to O_3 and hyaluronan. Exposure to 2 ppm O_3 for 3 hours resulted in enhanced AHR and elevated levels of soluble low molecular weight

hyaluronan in the BALF 24-hours postexposure (Garantziotis et al., 2010; Garantziotis et al., 2009). Ozone may have caused the depolymerization of hyaluronan to soluble fragments which are known to be endogenous ligands of the CD44 receptor and TLR4 in the macrophage (Jiang et al., 2005). In the two recent studies, O_3-induced AHR was attenuated in CD44 and TLR4-deficient mice (Garantziotis et al., 2010; Garantziotis et al., 2009). Hyaluronan fragment-mediated stimulation of AHR was found to require functioning CD44 receptor and TLR4 (Garantziotis et al., 2010; Garantziotis et al., 2009). In contrast, high-molecular-weight hyaluronan blocked AHR in response to O_3 (Garantziotis et al., 2009). In another study high-molecular-weight hyaluronan enhanced repair of epithelial injury (Jiang et al., 2005). These studies provide a link between innate immunity and the development of AHR following O_3 exposure, and indicate a role for TLR4 in increasing airways responsiveness. While TLR4-dependent responses usually involve activation of NF-κB and the upregulation of proinflammatory factors, the precise mechanisms leading to AHR are unknown (Al-Hegelan et al., 2011).

In guinea pigs, AHR was found to be mediated by different pathways at 1- and 3-days postexposure to a single dose of O_3 (2 ppm for 4 hours) (Verhein et al., 2011; Yost et al., 2005). At 1 day, AHR was due to activation of airway parasympathetic nerves rather than to a direct effect on smooth muscle (Yost et al., 2005). This effect occurred as a result of O_3-stimulated release of major basic protein from eosinophils (Yost et al., 2005). Major basic protein is known to block inhibitory M2 muscarinic receptors which normally dampen acetylcholine release from parasympathetic nerves (Yost et al., 2005). The resulting increase in acetylcholine release caused an increase in smooth muscle contraction following O_3 exposure (Yost et al., 2005). Eosinophils played a different role 3-days postexposure to O_3 in guinea pigs (Yost et al., 2005). Ozone-mediated influx of eosinophils into lung airways resulted in a different population of cells present 3-days postexposure compared to those present at 1 day (Yost et al., 2005). At this time point, eosinophil-derived major basic protein increased smooth muscle responsiveness to acetylcholine which also contributed to AHR (Yost et al., 2005). However, the major effect of eosinophils was to protect against vagal hyperreactivity (Yost et al., 2005). The authors suggested that these beneficial effects were due to the production of nerve growth factor (Yost et al., 2005). Further work by these investigators demonstrated a key role for IL-1β in mediating AHR 3-days postexposure to O_3 (Verhein et al., 2011). In this study, IL-1β increased nerve growth factor and SP which acted through the NK1 receptor to cause vagally-mediated bronchoconstriction (Verhein et al., 2011). The mechanism by which SP caused acetylcholine release from parasympathetic nerves following O_3 exposure was not determined (Verhein et al., 2011). Taken together, the above study results indicate that mechanisms involved in O_3-mediated AHR can vary over time postexposure and that eosinophils and SP can play a role. Results of this animal model

may provide some insight into allergic airways disease in humans which is characterized by eosinophilia (Section 5.4.2.2).

5.3.6 Modification of innate/adaptive immune system responses

Host defense depends on effective barrier function and on innate immunity and adaptive immunity (Al-Hegelan et al., 2011). Ozone's effect on barrier function in the airways was discussed above (Section 5.3.4). This section focuses on the mechanisms by which O_3 impacts innate and adaptive immunity. Both tissue damage and foreign pathogens are triggers for the activation of the innate immune system. This results in the influx of inflammatory cells such as neutrophils, mast cells, basophils, eosinophils, monocytes and dendritic cells and the generation of cytokines such as TNF-α, IL-1, IL-6, KC and IL-17 . Further, innate immunity encompasses the actions of complement and collectins and the phagocytic functions of macrophages, neutrophils and dendritic cells. Airway epithelium also contributes to innate immune responses. Innate immunity is highly dependent on cell signaling networks involving TLR4. Adaptive immunity provides immunologic memory through the actions of B and T cells. Important links between the two systems are provided by dendritic cells and antigen presentation. Recent studies demonstrate that exposure to O_3 modifies cells and processes which are required for innate immunity, contributes to innate-adaptive immune system interaction and primes pulmonary immune responses to endotoxin.

Ozone exposure of human subjects resulted in recruitment of activated innate immune cells to the airways. Healthy individuals were exposed to 80 ppb O_3 for 6.6 hours with intermittent exercise and airways inflammation was characterized in induced sputum 18-hours postexposure (Alexis et al., 2010). Previous studies demonstrated that induced sputum contains liquid and cellular constituents of the ELF from central conducting airways (Alexis et al., 2001b) and also identified these airways as a site of preferential O_3 absorption during exercise (Hu et al., 1994). Ozone exposure resulted in increased numbers of neutrophils, airway monocytes and dendritic-like cells in sputum (Alexis et al., 2010). In addition, increased expression of cell surface markers characteristic of innate immunity and antigen presentation (i.e. CD-14 and HLA-DR) was demonstrated on airway monocytes (Alexis et al., 2010). Enhanced antigen presentation contributes to exaggerated T cell responses and promotes Th2 inflammation and an allergic phenotype (Lay et al., 2007). Upregulation of pro-inflammatory cytokines was also demonstrated in sputum of O_3-exposed subjects (Alexis et al., 2010). One of these cytokines, IL-12p70, correlated with numbers of dendritic-like cells in the sputum, and is an indicator of dendritic cell activation (Alexis et al., 2010). These authors have previously reported that exposure of exercising human subjects to 400 ppb O_3 for 2 hours resulted in activation of

monocytes and macrophages (Lay et al., 2007), which could play a role in exacerbating existing asthma by activating allergen-specific memory T cells. The current study confirms these findings and extends them by suggesting a potential mechanism whereby O_3-activated dendritic cells could stimulate naïve T-cells to promote the development of asthma (Alexis et al., 2010). A companion study by these same investigators (described in detail in Section 5.4.2.1) provides evidence of dendritic cell activation, measured as increased expression of HLA-DR, in a subset of the human subjects (GSTM1 null) exposed to 400 ppb O_3 for 2 hours with intermittent exercise (Alexis et al., 2009). Since dendritic cells are a link between innate and adaptive immunity, these studies provide evidence for an O_3-mediated interaction between the innate and adaptive immune systems.

Another recent study linked O_3-mediated activation of the innate immune system to the development of non-specific AHR in a mouse model (Pichavant et al., 2008). Repeated exposure to 1 ppm O_3 for 3 hours (3 days over a 5 day period) induced non-specific AHR measured 24 hours following the last exposure (Pichavant et al., 2008). This response was found to require NKT cells, which are effector lymphocytes of innate immunity, as well as IL-17 and airways neutrophilia (Pichavant et al., 2008). Since glycolipids such as galactosyl ceramide are ligands for the invariant CD1 receptor on NKT cells and serve as endogenous activators of NKT cells, a role for O_3-oxidized lipids in activating NKT cells was proposed (Pichavant et al., 2008). The authors contrasted this innate immunity pathway with that of allergen-provoked specific AHR which involves adaptive immunity, the cytokines IL-4, IL -13, IL-17, and airways eosinophilia (Pichavant et al., 2008). Interestingly, NKT cells were required for both the specific AHR provoked by allergen and the non-specific AHR provoked by O_3 (Pichavant et al., 2008). Different cytokine profiles of the NKT cells from allergen and O_3-exposed mice was proposed to account for the different pathways (Pichavant et al., 2008). More recently, NKT cells have been found to function in both innate and adaptive immunity (Vivier et al., 2011).

An interaction between allergen and O_3 in the induction of nonspecific AHR was shown in another animal study (Larsen et al., 2010). Mice were sensitized with the aerosolized allergen OVA on 10 consecutive days followed by exposure to O_3 (0.1-0.5 ppm for 3 hours) (Larsen et al., 2010). While allergen sensitization alone did not alter airways responsiveness to a nonspecific challenge, O_3 exposure of sensitized mice resulted in nonspecific AHR at 6- and 24-hours postexposure (Larsen et al., 2010). The effects of O_3 on AHR were independent of airways eosinophilia and neutrophilia (Larsen et al., 2010). However, OVA pretreatment led to goblet cell metaplasia which was enhanced by O_3 exposure (Larsen et al., 2010). It should be noted that OVA sensitization using only aerosolized antigen in this study is less common than the usual procedure for OVA sensitization achieved by one or more initial systemic injections of OVA and adjuvant

followed by repeated inhalation exposure to OVA. This study also points to an interaction between innate and adaptive immune systems in the development of the AHR response.

Furthermore, O_3 was found to act as an adjuvant for allergic sensitization (Hollingsworth et al., 2010). Oropharyngeal aspiration of OVA on day 0 and day 6 failed to lead to allergic sensitization unless mice were first exposed to 1 ppm O_3 for 2 hours (Hollingsworth et al., 2010). The O_3-mediated response involved Th2 (IL-4, IL-5 and IL-9) and Th17 cytokines (IL-17) and was dependent on a functioning TLR4 (Hollingsworth et al., 2010). Ozone exposure also activated OVA-bearing dendritic cells in the thoracic lymph nodes, as measured by the presence of the CD86 surface marker, which suggests naïve T cell stimulation and the involvement of Th2 pathways (Hollingsworth et al., 2010). Thus the adjuvant effects of O_3 may be due to activation of both innate and adaptive immunity.

Priming of the innate immune system by O_3 was reported by Hollingsworth et al. (2007). In this study, exposure of mice to 2 ppm O_3 for 3 hours led to nonspecific AHR at 24- and 48-hours postexposure, an effect which subsided by 72 hours (Hollingsworth et al., 2007). However, in mice treated with aerosolized endotoxin immediately following O_3 exposure, AHR was greatly enhanced at 48-and 72-hours postexposure (Hollingsworth et al., 2007). In addition, O_3 pre-exposure was found to reduce the number of inflammatory cells in the BALF, to increase cytokine production and total protein in the BALF and to increase systemic IL-6 following exposure to endotoxin (Hollingsworth et al., 2007). Furthermore, O_3 stimulated the apoptosis of alveolar macrophages 24-hours postexposure, an effect which was greatly enhanced by endotoxin treatment. Apoptosis of circulating blood monocytes was also observed in response to the combined exposures (Hollingsworth et al., 2007). Ozone pre-exposure enhanced the response of lung macrophages to endotoxin (Hollingsworth et al., 2007). Taken together, these findings demonstrated that O_3 exposure increased innate immune responsiveness to endotoxin. The authors attributed these effects to the increased surface expression of TLR4 and increased signaling in macrophages observed in the study (Hollingsworth et al., 2007). It was proposed that the resulting decrease in airway inflammatory cells could account for O_3-mediated decreased clearance of bacterial pathogens observed in numerous animal models (Hollingsworth et al., 2007).

More recently, these authors demonstrated that hyaluronan contributed to the O_3-primed response to endotoxin (Li et al., 2010). In this study, exposure of mice to 1 ppm O_3 for 3 hours resulted in enhanced responses to endotoxin, which was mimicked by intratracheal instillation of hyaluronan fragments (Li et al., 2010). Hyaluronan, like O_3, was also found to induce TLR4 receptor peripheralization in the macrophage membrane (Li et al., 2010; Hollingsworth et al., 2007), an effect which is associated with enhanced responses to

endotoxin. This study and previous ones by the same investigators showed elevation of BALF hyaluronan in response to O_3 exposure (Garantziotis et al., 2010; Li et al., 2010; Garantziotis et al., 2009), providing evidence that the effects of O_3 on innate immunity are at least in part mediated by hyaluronan fragments. The authors note that excessive TLR4 signaling can lead to lung injury and suggest that O_3 may be responsible for an exaggerated innate immune response which may underlie lung injury and decreased host defense (Li et al., 2010).

Activation or upregulation of the immune system has not been reported in all studies. Impaired antigen-specific immunity was demonstrated following subacute O_3 exposure (0.6 ppm, 10 h/day for 15 days) in mice (Feng et al., 2006). Specifically, O_3 exposure altered the lymphocyte subset and cytokine profile and impacted thymocyte early development leading to immune dysfunction. Further, recent studies demonstrated SP-A oxidation in mice exposed for 3-6 hours to 2 ppm O_3. SP-A is an important innate immune protein which plays a number of roles in host defense including acting as opsonin for the recognition of some pathogens (Haque et al., 2009). These investigations found that O_3-mediated carbonylation of SP-A was associated with impaired macrophage phagocytosis in vitro (Mikerov et al., 2008b). Furthermore, O_3 exposure (2 ppm for 3 hours) in mice was found to increase susceptibility to pneumonia infection in mice through an impairment of SP-A dependent phagocytosis (Mikerov et al., 2008a; Mikerov et al., 2008c).

Taken together, results of recent studies provide evidence that O_3 alters host immunologic response and leads to immune system dysfunction through its effects on innate and adaptive immunity.

5.3.7 Airways remodeling

As noted above, the degree of airways inflammation due to O_3 may have important long-term consequences since airways inflammation is often accompanied by tissue injury (Balmes et al., 1996). The nasal airways, conducting airways and distal airways (i.e. respiratory bronchioles or centriacinar region depending on the species) have all been identified as sites of O_3-mediated injury and inflammation (Mudway and Kelly, 2000). At all levels of the respiratory tract, loss of sensitive epithelial cells, degranulation of secretory cells, proliferation of resistant epithelial cells and neutrophilic influx have been observed as a result of O_3 exposure (Mudway and Kelly, 2000; Cho et al., 1999). An important study (Plopper et al., 1998) conducted in adult rhesus monkeys (0.4 and 1.0 ppm O_3 for 2 hours) found that 1 ppm O_3 resulted in the greatest epithelial injury in the respiratory bronchioles immediately postexposure although injury was observed at all

of the RT sites studied except for the lung parenchyma. Exposure to 0.4 ppm O_3 resulted in epithelial injury only in the respiratory bronchioles.

Persistent inflammation and injury, observed in animal models of chronic and intermittent exposure to O_3, are associated with airways remodeling, including mucous cell metaplasia of nasal transitional epithelium (Harkema et al., 1999; Hotchkiss et al., 1991) and bronchiolar metaplasia of alveolar ducts (Mudway and Kelly, 2000). Fibrotic changes such as deposition of collagen in the airways and sustained lung function decrements especially in small airways have also been demonstrated as a response to chronic O_3 exposure (Mudway and Kelly, 2000; Chang et al., 1992). These effects, described in detail in Section 7.2.3.1, have been demonstrated in rats exposed to levels of O_3 as low as 0.25 ppm. Mechanisms responsible for the resolution of inflammation and the repair of injury remain to be clarified and there is only a limited understanding of the biological processes underlying long-term morphological changes. However, a recent study in mice demonstrated a key role for the TGF-β signaling pathway in the deposition of collagen in the airways wall following chronic intermittent exposure to 0.5 ppm O_3 (Katre et al., 2011).

It should be noted that repeated exposure to O_3 results in attenuation of some O_3-induced responses, including those associated with the activation of neural reflexes (e.g. decrements in pulmonary function), as discussed in Section 5.3.2. However, numerous studies demonstrate that some markers of injury and inflammation remain increased during multi-day exposures to O_3. Mechanisms responsible for attenuation, or the lack thereof, are incompletely understood.

5.3.8 Systemic inflammation and oxidative/nitrosative stress

Extrapulmonary effects of O_3 have been noted for decades (U.S. EPA, 2006b). It has been proposed that lipid oxidation products resulting from reaction of O_3 with lipids and/or cellular membranes in the ELF are responsible for systemic effects, however it is not known whether they gain access to the vascular space (Chuang et al., 2009). Alternatively, extrapulmonary release of diffusible mediators may initiate or propagate inflammatory responses in the vascular or in systemic compartments (Cole and Freeman, 2009). A role for O_3 in modulating endothelin, a potent vasoconstrictor, has also been proposed. Studies in rats found that exposure to 0.4 and 0.8 ppm O_3 induced endothelin system genes in the lung and increased circulating levels of endothelin (Thomson et al., 2006; Thomson et al., 2005). Systemic oxidative stress is suggested by studies in humans which reported associations between O_3 exposure and levels of plasma 8-isoprostanes

and the presence of peripheral blood lymphocyte micronuclei (Chen et al., 2007; Chen et al., 2006a).

Ozone-induced perturbations of the cardiovascular system were recently investigated in young mice and monkeys (Chuang et al., 2009) and in rats (Kodavanti et al., 2011; Perepu et al., 2010) (see Sections 6.3.3.2 and 7.3.1.2). These are the first studies to suggest that systemic oxidative stress and inflammation play a mechanistic role in O_3-induced effects on the systemic vascular and heart. Exposure to 0.5 ppm O_3 for 5 days resulted in oxidative/nitrosative stress, vascular dysfunction and mitochondrial DNA damage in the aorta (Chuang et al., 2009). Chronic exposure to 0.8 ppm O_3 resulted in an enhancement of inflammation and lipid peroxidation in the heart following an ischemia-reperfusion challenge (Perepu et al., 2010). In addition, chronic intermittent exposure to 0.4 ppm O_3 increased aortic levels of mRNA for biomarkers of oxidative stress, thrombosis, vasoconstriction and proteolysis and aortic lectin-like oxidized-low density lipoprotein receptor-1(LOX-1) mRNA and protein levels (Kodavanti et al., 2011). The latter study suggests a role for circulating oxidized lipids in mediating the effects of O_3.

Systemic inflammation and oxidative/nitrosative stress may similarly affect other organ systems as well as the plasma compartment. Circulating cytokines have the potential to enter the brain through diffusion and active transport and to contribute to neuroinflammation, neurotoxicity, cerbrovascular damage and a break-down of the blood brain barrier (Block and Calderón-Garcidueñas, 2009) (see Sections 6.4 and 7.5). They can also activate neuronal afferents (Block and Calderón-Garcidueñas, 2009). Vagal afferent pathways originating in the respiratory tract may also be responsible for O_3-mediated activation of nucleus tractus solitarius neurons which resulted in neuronal activation in stress-responsive regions of the CNS in rats (0.5 or 2 ppm O_3 for 1.5-120 hours) (Gackière et al., 2011). Recent studies have demonstrated O_3-induced brain lipid peroxidation, cytokine production in the brain and upregulated expression of VEGF in rats (0.5 ppm O_3 , 3 hours or 0.25-0.5 ppm O_3, 4 h/day, 15-60 days) (Guevara-Guzmán et al., 2009; Araneda et al., 2008; Pereyra-Muñoz et al., 2006). Further, O_3-induced oxidative stress resulted in increased plasma lipid peroxides (0.25 ppm, 4h/day, 15-60 days) (Santiago-López et al., 2010), which was correlated with damage to specific brain regions (Pereyra-Muñoz et al., 2006).

Oxidative stress is one mechanism by which testicular and sperm function is disrupted (see Section 7.4.1). Oxidative stress may inhibit testicular steroidogenesis leading to decreased testosterone levels (Diemer et al., 2003). It may decrease sperm quality by lipid peroxidation of sperm plasma membrane which leads to impaired sperm mobility (Agarwal et al., 2003). Further, it may damage DNA in the sperm nucleus leading to apoptosis and a decline in sperm counts (Agarwal et al., 2003). Since oxidative stress is a

key event underlying many of the health effects of O_3, it is possible that sperm quality and quantity may be impacted by this mechanism (Sokol et al., 2006).

A role for plasma antioxidants in modulating O_3-induced respiratory effects was suggested by a recent study (Aibo et al., 2010). In this study, pretreatment of rats with a high dose of acetaminophen resulted in increased levels of plasma cytokines and the influx of inflammatory cells into the lung following O_3 exposure (0.25-0.5 ppm, 6 hours) (Aibo et al., 2010). These effects were not observed in response to O_3 alone. Furthermore, acetaminophen-induced liver injury was exacerbated by O_3 exposure. A greater increase in hepatic neutrophil accumulation and greater alteration in gene expression profiles was observed in mice exposed to O_3 and acetaminophen compared with either exposure alone (Aibo et al., 2010). Although not measured in this study, glutathione depletion in the liver is known to occur in acetaminophen toxicity. Since liver glutathione is the source of plasma glutathione, acetaminophen treatment may have lowered plasma glutathione levels and altered the redox balance in the vascular compartment. These findings indicate interdependence between respiratory tract, plasma and liver responses to O_3, possibly related to glutathione status.

5.3.9 Impaired alveolar-arterial O_2 transfer

O_3 may impair alveolar-arterial oxygen transfer and reduce the supply of arterial oxygen to the myocardium. This may have a greater impact in individuals with compromised cardiopulmonary systems. Gong et al. (1998) provided evidence of a small decrease in arterial oxygen saturation in human subjects exposed for 3 hours to 300 ppb O_3 while exercising. In addition, Delaunois et al. (1998) demonstrated pulmonary vasoconstriction in O_3-exposed rabbits (0.4 ppm, 4 hours). Although of interest, the contribution of this pathway to O_3-induced cardiovascular effects remains uncertain.

5.3.10 Summary

This section summarizes the modes of action and toxicity pathways resulting from O_3 inhalation (Figure 5-9). These pathways provide a mechanistic basis for the health effects which are described in detail in Chapters 6 and 7. Three distinct short-term responses have been well-characterized in humans challenged with O_3: decreased pulmonary function, airways inflammation, and increased bronchial reactivity. In addition, O_3 exposure exacerbates, and possibly also causes, asthma and allergic airways disease in humans. Animal studies have demonstrated airways remodeling and fibrosis in response to chronic and intermittent O_3 exposures and a wide range of other responses. While the

respiratory tract is the primary target tissue, cardiovascular and other organ effects occur following short- and long-term exposures of animals to O_3.

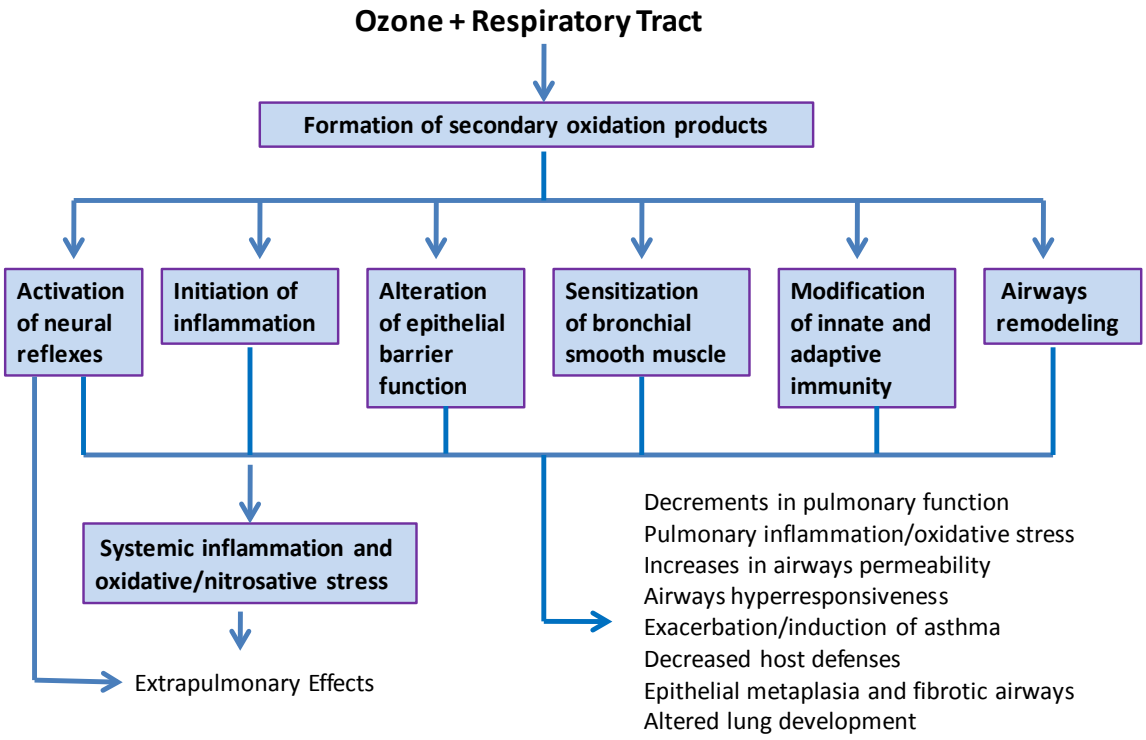


Figure 5-9 The modes of action/possible pathways underlying the health effects resulting from inhalation exposure to O_3.

The initial key event in the toxicity pathway of O_3 is the formation of secondary oxidation products in the respiratory tract. This involves direct reactions with components of the ELF and/or plasma membranes of cells residing in the respiratory tract. The resulting secondary oxidation products transmit signals to the epithelium, nociceptive sensory nerve fibers and, if present, dendritic cells, mast cells and eosinophils. Thus, O_3 effects are mediated by components of ELF and by the multiple cell types found in the respiratory tract. Further, oxidative stress is an implicit part of this initial key event.

Another key event in the toxicity pathway of O_3 is the activation of neural reflexes which lead to decrements in pulmonary function (see Section 6.2.1). Evidence is accumulating that secondary oxidation products are responsible for this effect. Eicosanoids have been implicated in humans, while both eicosanoids and aldehydes are effective in animal models. Different receptors on bronchial C-fibers have been shown to mediate separate

effects of O_3 on pulmonary function. Nociceptive sensory nerves are involved in the involuntary truncation of respiration which results in decreases in FVC, FEV_1, tidal volume and pain upon deep inspiration. Opioids block these responses while atropine has only a minimal effect. New evidence in an animal model suggests that TRPA1 receptors on bronchial C-fibers mediate this pathway. Ozone exposure also results in activation of vagal sensory nerves and a mild increase in airway obstruction measured as increased sRaw. Atropine and β-adrenergic agonists greatly inhibit this response in humans indicating that the airway obstruction is due to bronchoconstriction. Other studies in humans implicated SP release from bronchial C-fibers resulting in airway narrowing due to either neurogenic edema or bronchoconstriction. New evidence in an animal model suggests that the SP-NK receptor pathway caused bronchoconstriction following O_3 exposure.

Initiation of inflammation is also a key event in the toxicity pathway of O_3. Secondary oxidation products, as well as chemokines and cytokines elaborated by airway epithelial cells and macrophages, have been implicated in the initiation of inflammation. Vascular endothelial adhesion molecules may also play a role. Work from several laboratories in using human subjects and animal models suggest that O_3 triggers the release of tachykinins such as SP from airway sensory nerves which could contribute to downstream effects including inflammation (see Sections 6.2.3 and 7.2.4). Airways neutrophilia has been demonstrated in BALF, mucosal biopsy and induced sputum samples. Influx of mast cells, monocytes and macrophages also occur. Inflammation further contributes to O_3-mediated oxidative stress. Recent investigations show that O_3 exposure leads to the generation of hyaluronan fragments from high molecular weight polymers of hyaluronan normally found in the ELF in mice. Hyaluronan activates TLR4 and CD44-dependent signaling pathways in macrophages, and results in an increased number of macrophages in the BALF. Activation of these pathways occurs later than the acute neutrophilic response suggesting that they may contribute to longer-term effects of O_3. The mechanisms involved in clearing O_3-provoked inflammation remain to be clarified. It should be noted that inflammation, as measured by airways neutrophilia, is not correlated with decrements in pulmonary function as measured by spirometry.

A fourth key event in the toxicity pathway of O_3 is alteration of epithelial barrier function. Increased permeability occurs as a result of damage to tight junctions between epithelial cells subsequent to O_3-induced injury and inflammation. It may play a role in allergic sensitization and in AHR (see Sections 6.2.2, 6.2.6, and 7.2.5). Tachykinins mediate this response while antioxidants confer protection. Genetic susceptibility has been associated with a functioning TLR4 gene and with iNOS.

A fifth key event in the toxicity pathway of O_3 is the sensitization of bronchial smooth muscle.

Increased bronchial reactivity can be both a rapidly occurring and a persistent response. The mechanisms responsible for early and later AHR are not well-understood (see Section 6.2.2). One proposed mechanism of sensitization, O_3-induced increases in epithelial permeability, would improve access of agonist to smooth muscle receptors. The evidence for this mechanism is not consistent. Another proposed mechanism, for which there is greater evidence, is neurally-mediated sensitization. In humans exposed to O_3, atropine blocked the early AHR response indicating the involvement of cholinergic postganglionic pathways. Animal studies demonstrated that O_3-induced AHR involved vagally-mediated responses and local axon reflex responses through bronchopulmonary C-fiber-mediated release of SP. Later phases of increased bronchial reactivity may involve the induction of IL-1β which in turn upregulates SP production. In guinea pigs, eosinophil-derived major basic protein contributed to the stimulation of cholinergic postganglionic pathways. A novel role for hyaluronan in mediating the later phase effects O_3-induced AHR has recently been demonstrated. Hyaluronan fragments stimulated AHR in a TLR4- and CD44 receptor-dependent manner. Tachykinins and secondary oxidation products of O_3 have been proposed as mediators of the early response and inflammation-derived products have been proposed as mediators of the later response. Inhibition of arachidonic acid metabolism was ineffective in blocking O_3-induced AHR in humans while in animal models mixed results were found. Other cytokines and chemokines have been implicated in the AHR response to O_3 in animal models.

A sixth key event in the toxicity pathway of O_3 is the modification of innate/adaptive immunity. While the majority of evidence for this key event comes from animal studies, there are several studies suggesting that this pathway may also be relevant in humans. O_3 exposure of human subjects resulted in recruitment of activated innate immune cells to the airways. This included macrophages and monocytes with increased expression of cell surface markers characteristic of innate immunity and antigen presentation, the latter of which could contribute to exaggerated T cell responses and the promotion of an allergic phenotype. Evidence of dendritic cell activation was observed in GSTM1 null human subjects exposed to O_3, suggesting O_3-mediated interaction between the innate and immune systems. Animal studies further linked O_3-mediated activation of the innate immune system to the development of nonspecific AHR, demonstrated an interaction between allergen and O_3 in the induction of nonspecific AHR, and found that O_3 acted as an adjuvant for allergic sensitization through the activation of both innate and adaptive immunity. Priming of the innate immune system by O_3 was reported in mice. This resulted in an exaggerated response to endotoxin which included enhanced TLR4 signaling in macrophages. Ozone-mediated impairment of the function of SP-A, an innate

immune protein, has also been demonstrated. Taken together these studies provide evidence that O_3 can alter host immunologic response and lead to immune system dysfunction. These mechanisms may underlie the exacerbation and induction of asthma (see Sections 6.2.6 and 7.2.1), as well as decreases in host defense (see Sections 6.2.5 and 7.2.6).

Another key event in the toxicity pathway of O_3 is airways remodeling. Persistent inflammation and injury, which are observed in animal models of chronic and intermittent exposure to O_3, are associated with morphologic changes such as mucous cell metaplasia of nasal epithelium, bronchiolar metaplasia of alveolar ducts and fibrotic changes in small airways (see Section 7.2.3). Mechanisms responsible for these responses are not well-understood. However a recent study in mice demonstrated a key role for the TGF-β signaling pathway in the deposition of collagen in the airway wall following chronic intermittent exposure to O_3.

Systemic inflammation and vascular oxidative/nitrosative stress are also key events in the toxicity pathway of O_3. Extrapulmonary effects of O_3 occur in numerous organ systems, including the cardiovascular, central nervous, reproductive and hepatic systems (see Sections 6.3 to 6.5 and 7.3 to 7.5). It has been proposed that lipid oxidation products resulting from reaction of O_3 with lipids and/or cellular membranes in the ELF are responsible for systemic responses, however it is not known whether they gain access to the vascular space. Alternatively, release of diffusible mediators from the lung into the circulation may initiate or propagate inflammatory responses in the vascular or in systemic compartments. Systemic oxidative stress is suggested by studies in humans which reported associations between O_3 exposure and levels of plasma 8-isoprostanes and the presence of peripheral blood lymphocyte micronuclei.

5.4 Interindividual Variability in Response

Responses to O_3 exposure are variable within the population and the basis for this variability is not clear (Mudway and Kelly, 2000). Both dosimetric and mechanistic factors are likely to contribute to this variability and are discussed below.

5.4.1 Dosimetric Considerations

Two studies have investigated the correlation of O_3 uptake with the pulmonary function responses to O_3 exposure (Reeser et al., 2005; Gerrity et al., 1994). These studies found that the large subject-to-subject variability in $\%\Delta FEV_1$ response to O_3 does not appear to

have a dosimetric explanation. Reeser et al. (2005) found no significant relationship between $\%\Delta FEV_1$ and fractional absorption of O_3 using the bolus method. Contrary to previous findings, the percent change in dead space volume of the respiratory tract ($\%\Delta V_D$) did not correlate with O_3 uptake, possibly due to the contraction of dead space caused by airway closure. Gerrity et al. (1994) found that intersubject variability in FEV_1 and airway resistance was not related to differences in the O_3 dose delivered to the lower airways, whereas minute ventilation was predictive of FEV_1 decrement. No study has yet demonstrated that subjects show a consistent pattern of O_3 retention when re-exposed over weeks of time, as has been shown to be the case for the FEV_1 response, or that within-subject variation in FEV_1 response is related to fluctuations in O_3 uptake.

A delay in onset of O_3-induced pulmonary function responses has been noted in numerous studies. Recently the delay was characterized in terms of changes in f_B (Schelegle et al., 2007). In humans exposed for 1-2 hours to 120-350 ppb O_3 while exercising, no change in f_B was observed until a certain cumulative inhaled dose of O_3 had been reached. Subsequently, the magnitude of the change in f_B was correlated with the inhaled dose rate (Schelegle et al., 2007). These investigators proposed that initial reactions of O_3 with ELF resulted in a time-dependent depletion of ELF antioxidants, and that activation of neural reflexes occurred only after the antioxidant defenses were overwhelmed (Schelegle et al., 2007).

Other studies investigated the relationship between O_3 dose and cellular injury. In two studies, the initial cellular injury was found to correlate with the site-specific O_3 dose. Contained within the CAR, the respiratory bronchioles were confirmed as the site receiving the greatest O_3 dose (^{18}O mass/lung weight) and sustained the greatest initial cellular injury in O_3 (0.4 and 1.0 ppm for 2 hours) exposed resting rhesus monkeys (Plopper et al., 1998). The respiratory bronchioles, having the highest concentration of local O_3 dose, were also the site of significant GSH reduction. In addition, a study in isolated perfused rat lungs found greater injury in conducting airways downstream of bifurcations where local doses of O_3 were higher (Postlethwait et al., 2000).

Further, the degree of inflammation in rats has been correlated with ^{18}O-labeled O_3 dose markers in the lower lung. In female rats exposed to 0.8 ppm O_3 for 4 hours, BAL neutrophil number and ^{18}O reaction product were directly proportional (Gunnison and Hatch, 1999). Kari et al. (1997) observed that a 3-week caloric restriction (75%) in rats abrogated the toxicity of O_3 (2 ppm, 2 hours), measured as BALF increases in protein, fibronectin and neutrophils, which was seen in normally fed rats. Accompanying this resistance to O_3 toxicity was a reduction (30%) in the accumulation of ^{18}O reaction product in the lungs. These investigations also demonstrated an inverse relationship between AH2 levels and O_3 dose and provided evidence for AH2 playing a protective

role following O_3 exposure in these studies. Pregnant and lactating rats had lower AH2 content in BALF and exhibited a greater increase in accumulation of ^{18}O reaction products compared with pre-pregnant rats in response to O_3 exposure (Gunnison and Hatch, 1999). In the calorie restricted model, a 30% higher basal BALF AH2 concentration and a rapid accumulation of AH2 into the lungs to levels 60% above normal occurred as result of O_3 exposure (Kari et al., 1997). However, this relationship between AH2 levels and O_3 dose did not hold up in every study. Aging rats (9 and 24 months old) had 49% and 64% lower AH2 in lung tissue compared with month-old rats but the aging-induced AH2 loss did not increase the accumulation of ^{18}O reaction products following O_3 exposure (0.4-0.8 ppm, 2-6 hours) (Vincent et al., 1996a).

Interindividual variability in the neutrophilic response has been noted in human subjects (Holz et al., 1999; Devlin et al., 1991; Schelegle et al., 1991). One study demonstrated a threefold difference in airways neutrophilia, measured as percent of total cells in proximal BALF, among human subjects exposed to 300 ppb O_3 for 1 hour while exercising (Schelegle et al., 1991). Another study reported a 20-fold difference in BAL neutrophils following exposure to 80-100 ppb O_3 for 6.6 hours in exercising human subjects (Devlin et al., 1991). Reproducibility of intra-individual responses to 1-hour exposure to 250 ppb O_3, measured as sputum neutrophilia, was demonstrated by Holz (1999). Few studies have examined the dose- or concentration-responsiveness of airways neutrophilia in O_3-exposed humans (Holz et al., 1999; Devlin et al., 1991). No concentration-responsiveness was observed in healthy human subjects exposed for 1 hour to 125-250 ppb O_3 and a statistically significant increase in sputum neutrophilia was observed only at the higher dose (Holz et al., 1999). However, concentration-dependent and statistically significant increases in BAL neutrophils and the inflammatory mediator IL-6 were reported following exposure to 80 and 100 ppb O_3 for 6.6 hours in exercising humans (Devlin et al., 1991). Additional evidence is provided by a meta-analysis of the O_3 dose-inflammatory response in controlled human exposure studies involving exposure to 80-600 ppb O_3 for 60-396 minutes (Mudway and Kelly, 2004b). Results demonstrated a linear relationship between inhaled O_3 dose (determined as the product of concentration, ventilation and time) and BAL neutrophils at 0-6 hours and 18-24 hours following O_3 exposure (Mudway and Kelly, 2004b).

Collectively these studies demonstrate a correlation between dose and response for some O_3-induced effects and suggest a role for ELF antioxidants in modulating the dose to tissue. The lack of correlation between O_3-induced effects and calculated O_3 dose may be a result of interindividual differences in TB volume.

5.4.2 Mechanistic Considerations

There was a large range of pulmonary function responses to O_3 among healthy young adults exposed for 4 hours to 200 ppb O_3 or for 1.5 hours to 420 ppb O_3 while exercising (Hazucha et al., 2003; Balmes et al., 1996). Since individual responses were relatively consistent across time, it was thought that responsiveness reflected an intrinsic characteristic of the subject (Mudway and Kelly, 2000). Older adults were generally not responsive to O_3 (Hazucha et al., 2003), while obese young women may have been more responsive than lean young women (420 ppb, 1.5 hours, while exercising) (Bennett et al., 2007). The lack of spirometric responsiveness was not attributable to the presence of endogenous endorphins, which could potentially block C-fiber stimulation by O_3, as demonstrated in a study involving intravenous administration of naloxone immediately following the O_3 exposure (420 ppb, 2 hours, while exercising) to weak responders (Passannante et al., 1998). Inflammation and other responses to O_3 were also characterized by a large degree of interindividual variability. Currently, the mechanisms underlying this variability are not known. It has been proposed that some of the variation in responses may be genetically determined (Yang et al., 2005a). The role of gene-environment interactions, pre-existing diseases and conditions, nutritional status, lifestage, attenuation, and co-exposures in modulating responses to O_3 are discussed below.

5.4.2.1 Gene-Environment Interactions

The significant interindividual variation in responses to O_3 infers that genetic background is an important determinant of susceptibility to O_3 (Cho and Kleeberger, 2007; Kleeberger et al., 1997) (see also Section 8.4). Strains of mice which are prone or resistant to O_3-induced effects have been used to systematically identify candidate susceptibility genes. Genome wide linkage analyses (also known as positional cloning) demonstrated quantitative trait loci for O_3-induced lung inflammation and hyperpermeability on chromosome 17 (Kleeberger et al., 1997) and chromosome 4 (Kleeberger et al., 2000), respectively, using these recombinant inbred strains of mice and exposures to 0.3 ppm O_3 for up to 72 hours. More specifically, these studies found that Tnf, whose protein product is the inflammatory cytokine TNF-α, and Tlr4, whose protein product is TLR4, were candidate susceptibility genes (Kleeberger et al., 2000; Kleeberger et al., 1997). Other studies, which used targeted deletion, identified genes encoding iNOS and heat shock proteins as TLR4 effector genes (Bauer et al., 2011; Kleeberger et al., 2001) and found that IL-10 protects against O_3-induced pulmonary inflammation (Backus et al., 2010). Investigations in inbred mouse strains found that differences in expression of certain proteins, such as CCSP (1.8 ppm O_3 for 3 hours) (Broeckaert et al.,

2003) and MARCO (0.3 ppm O_3 for up to 48 hours) (Dahl et al., 2007), were responsible for phenotypic characteristics, such as epithelial permeability and scavenging of oxidized lipids, respectively, which confer sensitivity to O_3.

Genetic polymorphisms have received increasing attention as modulators of O_3-mediated effects. Functionally relevant polymorphisms in candidate susceptibility genes have been studied at the individual and population level in humans, and also in animal models. Genes whose protein products are involved in antioxidant defense/oxidative stress and xenobiotic metabolism, such as glutathione-S-transferase M1 (GSTM1) and NADPH:quinone oxidoreductase 1 (NQO1), have also been a major focuses of these efforts. This is because oxidative stress resulting from O_3 exposure is thought to contribute to the pathogenesis of asthma, and because xenobiotic metabolism detoxifies secondary oxidation products formed by O_3 which contribute to oxidative stress (Islam et al., 2008). TNF-α is of interest since it is linked to a candidate O_3 susceptibility gene and since it plays a key role in initiating airways inflammation (Li et al., 2006d). Polymorphisms of genes coding for GSTM1, NQO1 and TNF-α have been associated with altered susceptibility to O_3-mediated effects (Li et al., 2006d; Yang et al., 2005a; Romieu et al., 2004a; Corradi et al., 2002; Bergamaschi et al., 2001). Additional studies have focused on functional variants in other genes involved in antioxidant defense such as catalase (CAT), myeloperoxidase, heme oxygenase (HMOX-1) and manganese superoxide dismutase (MnSOD) (Wenten et al., 2009; Islam et al., 2008). These studies are discussed below.

GSTM1 is a phase II antioxidant enzyme which is transcriptionally regulated by NF-E2-related factor 2-antioxidant response element (Nrf2-ARE) pathway. A large proportion (40-50%) of the general public (across ethnic populations) has the GSTM1-null genotype, which has been linked to an increased risk of health effects due to exposure to air pollutants (London, 2007). A role for GSTs in metabolizing electrophiles such as 4-hydroxynonenal, which is a secondary oxidation product formed following O_3 exposure, has been demonstrated (Awasthi et al., 2004). A recent study found that the GSTM1 genotype modulated the time course of the neutrophilic inflammatory response following acute O_3 exposure (400 ppb for 2 hours with intermittent exercise) in healthy adults (Alexis et al., 2009). In GSTM1-null and -sufficient subjects, O_3-induced sputum neutrophilia was similar at 4 hours. However, neutrophilia resolved by 24 hours in sufficient subjects but not in GSTM1-null subjects. In contrast, no differences in 24 hour sputum neutrophilia were observed between GSTM1-null and -sufficient human subjects exposed to 60 ppb O_3 for 2 hours with intermittent exercise (Kim et al., 2011). It is not known whether the effect seen at the higher exposure level (Alexis et al., 2009) was due to the persistence of pro-inflammatory stimuli, impaired production of downregulators or impaired neutrophil apoptosis and clearance. However, a subsequent in vitro study by

these same investigators found that GSTM1 deficiency in airway epithelial cells enhanced IL-8 production in response to 0.4 ppm O_3 for 4 hours (Wu et al., 2011). Furthermore, NF-κB activation was required for O_3-induced IL-8 production (Wu et al., 2011). Since IL-8 is a potent neutrophil activator and chemotaxin, this study provides additional evidence for the role of GSTM1 as a modulator of inflammatory responses due to O_3 exposure.

In addition, O_3 exposure increased the expression of the surface marker CD14 in airway neutrophils of GSTM1-null subjects compared with sufficient subjects (Alexis et al., 2009). Furthermore, differences in airway macrophages were noted between the GSTM1-sufficient and -null subjects. Nnumbers of airway macrophages were decreased at 4 and 24 hours following O_3 exposure in GSTM1-sufficient subjects (Alexis et al., 2009). Airway macrophages in GSTM1-null subjects were greater in number and found to have greater oxidative burst and phagocytic capability than those of sufficient subjects. Airway macrophages and dendritic cells from GSTM1-null subjects exposed to O_3 expressed higher levels of the surface marker HLA-DR, suggesting activation of the innate immune system (Alexis et al., 2009). These differences in inflammatory responses between the GSTM1-null and -sufficient subjects may provide biological plausibility for the differences in O_3-mediated effects reported in controlled human exposure studies (Corradi et al., 2002; Bergamaschi et al., 2001). It should also be noted that GSTM1 genotype did not affect the acute pulmonary function (i.e. spirometric) response to O_3 which provides additional evidence for separate mechanisms underlying O_3's effects on pulmonary function and inflammation in adults (Alexis et al., 2009). However, GSTM1-null asthmatic children were previously found to be more at risk of O_3-induced effects on pulmonary function than GSTM1-sufficient asthmatic children (Romieu et al., 2004a).

Another enzyme involved in the metabolism of secondary oxidation products is NQO1. NQO1 catalyzes the 2-electron reduction by NADPH of quinones to hydroquinones. Depending on the substrate, it is capable of both protective detoxification reactions and redox cycling reactions resulting in the generation of reactive oxygen species. A recent study using NQO1-null mice demonstrated that NQO1 contributes to O_3-induced oxidative stress, AHR and inflammation following a 3-hour exposure to 1 ppm O_3 (Voynow et al., 2009). These experimental results may provide biological plausibility for the increased biomarkers of oxidative stress and increased pulmonary function decrements observed in O_3-exposed individuals bearing both the wild-type NQO1 gene and the null GSTM1 gene (Corradi et al., 2002; Bergamaschi et al., 2001).

Besides enzymes, other mechanisms participate in the removal of secondary oxidation products formed as a result of O_3 inhalation. One involves scavenging of oxidized lipids via the macrophage receptor with collagenous structure (MARCO) expressed on the cell

surface of alveolar macrophages. A recent study demonstrated increased gene expression of MARCO in the lungs of an O_3-resistant C3H mouse strain (HeJ) but not in an O_3-sensitive, genetically similar strain (OuJ) (Dahl et al., 2007). Upregulation of MARCO occurred in mice exposed to 0.3 ppm O_3 for 24-48 hours; inhalation exposure for 6 hours at this concentration was insufficient for this response. Animals lacking the MARCO receptor exhibited greater inflammation and injury, as measured by BAL neutrophils, protein and isoprostanes, following exposure to 0.3 ppm O_3 (Dahl et al., 2007). MARCO also protected against the inflammatory effects of oxidized surfactant lipids (Dahl et al., 2007). Scavenging of oxidized lipids may limit O_3-induced injury since ozonized cholesterol species formed in the ELF (mice, 0.5-3 ppm O_3, 3 hours) (Pulfer et al., 2005; Pulfer and Murphy, 2004) stimulated apoptosis and cytotoxicity in vitro (Gao et al., 2009b; Sathishkumar et al., 2009; Sathishkumar et al., 2007a; Sathishkumar et al., 2007b).

Two studies reported relationships between TNF promoter variants and O_3-induced effects in humans. In one study, O_3-induced change in lung function was significantly lower in adult subjects with TNF promoter variants -308A/A and -308G/A compared with adult subjects with the variant -308G/G (Yang et al., 2005a). This response was modulated by a specific polymorphism of LTA (Yang et al., 2005a), a previously identified candidate susceptibility gene whose protein product is lymphotoxin-α (Kleeberger et al., 1997). In the second study, an association between the TNF promoter variant -308G/G and decreased risk of asthma and lifetime wheezing in children was found (Li et al., 2006d). The protective effect on wheezing was modulated by ambient O_3 levels and by GSTM1 and GSTP1 polymorphisms. The authors suggested that the TNF-308 G/G genotype may have a protective role in the development of childhood asthma (Li et al., 2006d).

Similarly, a promoter variant of the gene HMOX-1, consisting of a smaller number of (GT)n repeats, was associated with a reduced risk for new-onset asthma in non-Hispanic white children (Islam et al., 2008). The number of $(GT)_n$ repeats in this promoter has been shown to be inversely related to the inducibility of HMOX-1. A modulatory effect of O_3 was demonstrated since the beneficial effects of this polymorphism were seen only in children living in low O_3 communities (Islam et al., 2008). This study also identified an association between a polymorphism of the CAT gene and increased risk of new-onset asthma in Hispanic children; however no modulation by O_3 was seen (Islam et al., 2008). No association was observed in this study between a MnSOD polymorphism and asthma (Islam et al., 2008).

Studies to date indicate that some variability in individual responsiveness to O_3 may be accounted for by functional genetic polymorphisms. Further, the effects of gene-environment interactions may be different in children and adults.

5.4.2.2 Pre-existing Diseases and Conditions

Pre-existing diseases and conditions can alter the response to O_3 exposure. For example, responsiveness to O_3, as measured by spirometry, is decreased in smokers and individuals with COPD (U.S. EPA, 2006b). Asthma and allergic diseases are of major importance in this discussion. In individuals with asthma, there is increased responsiveness to bronchoconstrictor challenge. This results from a combination of structural and physiological factors including increased airway inner-wall thickness, smooth muscle responsiveness and mucus secretion. Although inflammation is likely to contribute, its relationship to AHR is not clear (U.S. EPA, 2006b). However, some asthmatics have higher baseline levels of neutrophils, lymphocytes, eosinophils and mast cells in bronchial washes and bronchial biopsy tissue (Stenfors et al., 2002). It has been proposed that enhanced sensitivity to O_3 is conferred by the presence of greater numbers of resident airway inflammatory cells in disease states such as asthma (Mudway and Kelly, 2000).

In order to determine whether asthmatics exhibit greater responses to O_3, several older studies compared pulmonary function in asthmatic and non-asthmatic subjects following O_3 exposure. Some also probed mechanisms which could account for enhanced sensitivity. While the majority focused on measurements of FEV_1 and FVC and found no differences between the two groups following exposures of 2-4 hours to 125-250 ppb O_3 or to a 30-minute exposure to 120-180 ppb O_3 by mouthpiece while exercising (Stenfors et al., 2002; Mudway et al., 2001; Holz et al., 1999; Scannell et al., 1996; Koenig et al., 1987; Linn et al., 1978), there were notable exceptions. In one study, greater airway obstruction in asthmatics compared with non-asthmatic subjects was observed immediately following a 2-hour exposure to 400 ppb O_3 with intermittent exercise (Kreit et al., 1989). These changes were measured as statistically significant greater decreases in FEV_1 and in FEF_{25-75} (but not in FVC) in the absence of a bronchoconstrictor challenge (Kreit et al., 1989). These results suggest that this group of asthmatics responded to O_3-exposure with a greater degree of vagally-mediated bronchoconstriction compared with the non-asthmatics. A second study demonstrated a statistically significant greater decrease in FEV_1 and in FEV_1/FVC (but not in FVC) in asthmatics compared with non-asthmatics exposed to 160 ppb O_3 for 7.6 hours with light exercise (Horstman et al., 1995). These responses were accompanied by wheezing and inhaler use in the asthmatics (Horstman et al., 1995). Aerosol bolus dispersion measurements demonstrated a

statistically significant greater change in asthmatics compared with non-asthmatics, which was suggestive of O_3-induced small airway dysfunction (Horstman et al., 1995). Furthermore, a statistically significant correlation was observed between the degree of baseline airway status and the FEV_1 response to O_3 in the asthmatic subjects (Horstman et al., 1995). A third study found similar decreases in FVC and FEV_1 in both asthmatics and non-asthmatics exposed to 400 ppb O_3 for 2 hours with mild exercise (Alexis et al., 2000). However, a statistically significant decrease in FEF_{75}, a measure of small airway function, was observed in asthmatics but not in non-asthmatics (Alexis et al., 2000). Taken together, these latter studies indicate that while the magnitude of restrictive type spirometric decline was similar in asthmatics and non-asthmatics, that obstructive type changes (i.e. bronchoconstriction) were greater in asthmatics. Further, asthmatics exhibited greater sensitivity to O_3 in terms of small airways function.

Since asthma exacerbations occur in response to allergens and/or other triggers, some studies have focused on O_3-induced changes in AHR following a bronchoconstrictor challenge. No difference in sensitivity to methacholine bronchoprovocation was observed between asthmatics and non-asthmatics exposed to 400 ppb O_3 for 2 hours with moderate exercise (Kreit et al., 1989). However, increased bronchial reactivity to inhaled allergens was demonstrated in mild allergic asthmatics exposed to 160 ppb for 7.6 hours, 250 ppb for 3 hours and 120 ppb for 1 hour while exercising (Kehrl et al., 1999; Jorres et al., 1996; Molfino et al., 1991) and in allergen-sensitized guinea pigs following O_3 exposure (1 ppm, 1 hour) (Sun et al., 1997). Similar, but modest, responses were reported for individuals with allergic rhinitis (Jorres et al., 1996). Further, the contractile response of isolated airways from human donor lung tissue, which were sensitized and challenged with allergen, was increased by pre-exposure to 1 ppm O_3 for 20 (Roux et al., 1999). These studies provide support for O_3-mediated enhancement of responses to allergens in allergic subjects.

In terms of airways neutrophilia, larger responses were observed in asthmatics compared to non-asthmatics subjects exposed to O_3 in some (Balmes et al., 1997; Scannell et al., 1996; Basha et al., 1994) but not all (Mudway et al., 2001) of the older studies. While each of these studies involved exposure of exercising human subjects to 200 ppb O_3, the duration of exposure was longer (i.e. 4-6 hours) in the former studies than in the latter study (2 hours). Further, statistically significantly increases in myeloperoxidase levels (an indicator of neutrophil activation) in bronchial washes was observed in mild asthmatics compared with non-asthmatics, despite no difference in O_3-stimulated neutrophil influx between the 2 groups following exposure to 200 ppb O_3 for 2 hours with mild exercise (Stenfors et al., 2002). A more recent study found that atopic asthmatic subjects exhibited an enhanced inflammatory response to O_3 (400 ppb, 4 hours, with exercise) (Hernandez et al., 2010). This response was characterized by greater numbers of neutrophils, higher

levels of IL-6, IL-8 and IL-1β and greater macrophage cell-surface expression of TLR4 and IgE receptors in induced sputum compared with healthy subjects. This study also reported a greater increase in hyaluronan in atopic subjects and atopic asthmatics compared with healthy subjects following O_3 exposure. Animal studies have previously reported that hyaluronic acid activates TLR4 signaling and results in AHR (see Section 5.3.5). Furthermore, levels of IL-10, a potent anti-inflammatory cytokine, were greatly reduced in atopic asthmatics compared to healthy subjects. These results provide evidence that innate immune and adaptive responses are different in asthmatics and healthy subjects exposed to O_3.

Eosinophils may be an important modulator of responses to O_3 in asthma and allergic airways disease. Eosinophils and associated proteins are thought to affect muscarinic cholinergic receptors which are involved in vagally-mediated bronchoconstriction (Mudway and Kelly, 2000). Studies described in Section 5.3.5 which demonstrated a key role of eosinophils in O_3-mediated AHR may be relevant to human allergic airways disease which is characterized by airways eosinophilia (Yost et al., 2005). Furthermore, O_3 exposure sometimes results in airways eosinophilia in allergic subjects or animal models. For example, eosinophilia of the nasal and other airways was observed in individuals with pre-existing allergic disease following O_3 inhalation (270 and 400 ppb O_3, 2 hours, with exercise) (Vagaggini et al., 2002; Peden et al., 1995). Further, O_3 exposure (0.5 ppm, 8 hours/day for 1-3 days) increased allergic responses, such as eosinophilia and augmented intraepithelial mucosubstances, in the nasal airways of ovalbumin (OVA)-sensitized rats (Wagner et al., 2002). In contrast, Stenfors (2002) found no stimulation of eosinophil influx measured in bronchial washes and BALF of mild asthmatics following exposure to a lower concentration (200 ppb, 2 hours, with exercise) of O_3.

The role of mast cells in O_3-mediated asthma exacerbations has been investigated. Mast cells are thought to play a key role in O_3-induced airways inflammation, since airways neutrophilia was decreased in mast cell-deficient mice exposed to O_3 (Kleeberger et al., 1993). However, another study found that mast cells were not involved in the development of increased bronchial reactivity in O_3-exposed mice (Noviski et al., 1999). Nonetheless, mast cells release a wide variety of important inflammatory mediators which may lead to asthma exacerbations (Stenfors et al., 2002). A large increase in mast cell number in bronchial submucosa was observed in non-asthmatics and a significant decrease in mast cell number in bronchial epithelium was observed in mild asthmatics 6 hours following exposure to 200 ppb O_3 for 2 hours during mild exercise (Stenfors et al., 2002). While these results point to an O_3-mediated flux in bronchial mast cell populations which differed between the non-asthmatics and mild asthmatics,

interpretation of these findings is difficult. Furthermore, mast cell number did not change in airway lavages in either group in response to O_3 (Stenfors et al., 2002)

Cytokine profiles in the airways have been investigated as an indicator of O_3 sensitivity. Differences in epithelial cytokine expression were observed in bronchial biopsy samples in non-asthmatic and asthmatic subjects both at baseline and 6-hours postexposure to 200 ppb O_3 for 2 hours (Bosson et al., 2003). The asthmatic subjects had a higher baseline expression of IL-4 and IL-5 compared to non-asthmatics. In addition, expression of IL-5, IL-8, GM-CSF, and ENA-78 in asthmatics was increased significantly following O_3 exposure compared to non-asthmatics (Bosson et al., 2003). Some of these (IL-4, IL-5 and GM-CSF) are Th2-related cytokines or neutrophil chemoattractants, and play a role in IgE production, airways eosinophilia and suppression of Th1-cytokine production (Bosson et al., 2003). These findings suggest a link between adaptive immunity and enhanced responses of asthmatics to O_3.

A further consideration is the compromised status of ELF antioxidants in disease states such as asthma (Mudway and Kelly, 2000). This could possibly be due to ongoing inflammation which causes antioxidant depletion or to abnormal antioxidant transport or synthesis (Mudway and Kelly, 2000). For example, basal levels of AH2 were significantly lower and basal levels of oxidized GSH and UA were significantly higher in bronchial wash fluid and BALF of mild asthmatics compared with healthy control subjects (Mudway et al., 2001). Differences in ELF antioxidant content have also been noted between species. These observations have led to the suggestion that the amount and composition of ELF antioxidants, the capacity to replenish antioxidants in the ELF or the balance between beneficial and injurious interactions between antioxidants and O_3 may contribute to O_3 sensitivity, which varies between individuals and species (Mudway et al., 2006; Mudway and Kelly, 2000; Mudway et al., 1999a). The complexity of these interactions was demonstrated by a study in which a 2-hour exposure to 200 ppb O_3, while exercising, resulted in similar increases in airway neutrophils and decreases in pulmonary function in both mild asthmatics and healthy controls, despite differences in ELF antioxidant concentrations prior to O_3 exposure (Mudway et al., 2001). Further, the O_3-induced increase in oxidized GSH and decrease in AH2 observed in ELF of healthy controls was not observed in mild asthmatics (Mudway et al., 2001). While the authors concluded that basal AH2 and oxidized GSH concentrations were not predictive of responsiveness to O_3, they also suggested that the increased basal UA concentrations in the mild asthmatics may have played a protective role (Mudway et al., 2001). Thus compensatory mechanisms resulting in enhanced total antioxidant capacity may play a role in modulating responses to O_3.

Collectively these older and more recent studies provide insight into mechanisms which may contribute to enhanced responses of asthmatic and atopic individuals following O_3 exposure. Greater airways inflammation and/or greater bronchial reactivity have been demonstrated in asthmatics compared to non-asthmatics. This pre-existing inflammation and altered baseline bronchial reactivity may contribute to the enhanced bronchoconstriction seen in asthmatics exposed to O_3. Furthermore, O_3-induced inflammation may contribute to O_3-mediated AHR. An enhanced neutrophilic response has been demonstrated in some asthmatics. A recent study in humans provided evidence for differences in innate immune responses related to TLR4 signaling between asthmatics and healthy subjects. Animal studies have demonstrated a role for eosinophil-derived proteins in mediating the effects of O_3. Since airways eosinophilia occurs in both allergic humans and allergic animal models, this pathway may underlie the exacerbation of allergic asthma by O_3. In addition, differences have been noted in epithelial cytokine expression in bronchial biopsy samples of healthy and asthmatic subjects. A Th2 phenotype, indicative of adaptive immune system activation and enhanced allergic responses, was observed before O_3 exposure and was increased by O_3 exposure in asthmatics. These findings support links between innate and adaptive immunity and sensitivity to O_3-mediated effects in asthmatics and allergic airways disease.

In addition to asthma and allergic diseases, obesity may alter responses to O_3. While O_3 is a trigger for asthma, obesity is a known risk factor for asthma (Shore, 2007). The relationship between obesity and asthma is not well understood but recent investigations have focused on alterations in endocrine function of adipose tissue in obesity. It is thought that the increases in serum levels of factors produced by adipocytes (i.e. adipokines) such as cytokines, chemokines, soluble cytokine receptors and energy regulating hormones, may contribute to the relationship between obesity and asthma. Some of these same mechanisms may be relevant to insulin resistant states such as metabolic syndrome.

In a reanalysis of the data of Hazucha (2003), increasing body mass index in young women was associated with increased O_3 responsiveness, as measured by spirometry following a 2-hour exposure to 500 ppb O_3 while exercising (Bennett et al., 2007). In several mouse models of obesity, airways were found to be innately more hyperresponsive and responded more vigorously to acute O_3 exposure than lean controls (Shore, 2007). Pulmonary inflammatory and injury in response to O_3 were also enhanced (Shore, 2007). It was postulated that oxidative stress resulting from obesity-related hyperglycemia could account for these effects (Shore, 2007). However, responses to O_3 in the different mouse models are somewhat variable and depend on whether exposures are acute or subacute. For example, diet-induced obesity augmented inflammation and injury, as measured by BALF markers, and enhanced AHR in mice exposed acutely to O_3

(2 ppm, 3 hours) (Johnston et al., 2008). In contrast, the inflammatory response following sub-acute exposure to O_3 was dampened by obesity in a different mouse model (0.3 ppm, 72 hours) (Shore et al., 2009).

5.4.2.3 Nutritional Status

Many investigations have focused on antioxidant deficiency and supplementation as modulators of O_3-mediated effects. One study in mice found that vitamin A deficiency enhanced lung injury induced by exposure to 0.3 ppm O_3 for 72 hours (Paquette et al., 1996). Ascorbate deficiency was shown to increase the effects of acute (0.5-1 ppm for 4 hours), but not subacute (0.2-0.8 ppm for 7 days), O_3 exposure in guinea pigs (Kodavanti et al., 1995; Slade et al., 1989). Supplementation with AH2 and α-TOH was protective in healthy adults who were on an AH2-deficient diet and exposed to 400 ppb O_3 for 2 hours while exercising (Samet et al., 2001). In this study, the protective effect consisted of a smaller reduction in FEV_1 following O_3 exposure (Samet et al., 2001). However the inflammatory response (influx of neutrophils and levels of IL-6) measured in BALF 1 hour after O_3 exposure was not different between supplemented and non-supplemented subjects (Samet et al., 2001). Other investigators found that AH2 and α-TOH supplementation failed to ameliorate the pulmonary function decrements or airways neutrophilia observed in humans exposed to 200 ppb O_3 for 2 hours (Mudway et al., 2006). It was suggested that supplementation may be ineffective in the absence of antioxidant deficiency (Mudway et al., 2006).

In asthmatic adults, these same dietary antioxidants reduced O_3-induced bronchial hyperresponsiveness (120 ppb, 45 min, with exercise) (Trenga et al., 2001). Furthermore, supplementation with AH2 and α-tocopherol protected against pulmonary function decrements and nasal inflammatory responses which were associated with high levels of ambient O_3 in asthmatic children living in Mexico City (Sienra-Monge et al., 2004; Romieu et al., 2002). Similarly, supplementation with ascorbate, α-tocopherol and β-carotene improved pulmonary function in Mexico City street workers (Romieu et al., 1998a).

Protective effects of supplementation with α-tocopherol alone have not been observed in humans experimentally exposed to O_3 (Mudway and Kelly, 2000). Alpha-TOH supplementation also failed to protect against O_3-induced effects in animal models of allergic rhinosinusitis and lower airways allergic inflammation (rats, 1 ppm O_3 for 2 days) (Wagner et al., 2007). However, protection in these same animal models was reported using γ-TOH supplementation (Wagner et al., 2009; Wagner et al., 2007). Other investigators found that α-TOH deficiency led to an increase in liver lipid peroxidation

(rats, 0.3 ppm 3 hours/day for 7 months) (Sato et al., 1980) and a drop in liver α-TOH levels following O_3 exposure (mice, 0.5 ppm, 6 hours/day for 3 days) (Vasu et al., 2010). A recent study used α-TOH transfer protein null mice as a model of α-TOH deficiency and demonstrated an altered adaptive response of the lung genome to O_3 exposure (Vasu et al., 2010). Taken together, these studies provide evidence that the tocopherol system modulates O_3-induced responses.

5.4.2.4 Lifestage

Responses to O_3 are modulated by factors associated with lifestage. On one end of the lifestage spectrum is aging. The spirometric response to O_3 appears to be lost in humans as they age, as was demonstrated in two studies involving exposures of exercising human subjects to 420-450 ppb O_3 for 1.5-2 hours (Hazucha et al., 2003; Drechsler-Parks, 1995). In mice, physiological responses to O_3 (600 ppb, 2 hours) were diminished with age (Hamade et al., 2010). Mechanisms accounting for this effect have not been well-studied but could include altered number and sensitivity of receptors or altered signaling pathways involved in neural reflexes.

On the other side of the lifestage spectrum is pre/postnatal development. Critical windows of development during the pre/postnatal period are associated with an enhanced sensitivity to environmental toxicants. Adverse birth outcomes and developmental disorders may occur as a result.

Adverse birth outcomes may result from stressors which impact transplacental oxygen and nutrient transport by a variety of mechanisms including oxidative stress, placental inflammation and placental vascular dysfunction (Kannan et al., 2006). These mechanisms may be linked since oxidative/ nitrosative stress is reported to cause vascular dysfunction in the placenta (Myatt et al., 2000). As described in Section 7.4, systemic inflammation and oxidative/nitrosative stress and modification of innate and adaptive immunity are key events underlying the health effects of O_3 and as such they may contribute to adverse birth outcomes. An animal toxicology study showing that exposure to 2 ppm O_3 led to anorexia (Kavlock et al., 1979) (see Section 7.4.2) in exposed rat dams provide an additional mechanism by which O_3 exposure could lead to diminished transplacental nutrient transport. Disturbances of the pituitary-adrenocortico-placental system (Ritz et al., 2000) may also impact normal intrauterine growth and development. Further, restricted fetal growth may result from pro-inflammatory cytokines which limit trophoblast invasion during the early stages of pregnancy (Hansen et al., 2008). Direct effects on maternal health, such as susceptibility to infection, and on fetal health, such as DNA damage, have also been proposed as mechanisms underlying adverse birth

outcomes (Ritz et al., 2000). In addition to restricted fetal growth, preterm birth may contribute to adverse birth outcomes. Preterm birth may result from the development of premature contractions and/or premature rupture of membranes as well as from disrupted implantation and placentation which results in suboptimal placental function (Darrow et al., 2009; Ritz et al., 2000). Genetic mutations are thought to be an important cause of placental abnormalities in the first trimester, while vascular alterations may be the main cause of placental abnormalities in later trimesters (Jalaludin et al., 2007). Ozone-mediated systemic inflammation and oxidative stress/nitrosative stress may possibly be related to these effects although there is no firm evidence.

Enhanced sensitivity to environmental toxicants during critical windows of development may also result in developmental disorders. For example, normal migration and differentiation of neural crest cells are important for heart development and are particularly sensitive to toxic insults (Ritz et al., 2002). Further, immune dysregulation and related pathologies are known to be associated with pre/postnatal environmental exposures (Dietert et al., 2010). Ozone exposure is associated with developmental effects in several organ systems. These include neurobehavioral changes which could reflect O_3's effects on CNS plasticity or the hypothalamic-pituitary axis (Auten and Foster, In Press) (see Section 7.4.9).

The majority of developmental effects due to O_3 have been described for the respiratory system (see Section 7.2.3 and 7.4.8). Since its growth and development take place during both the prenatal and early postnatal periods, both prenatal and postnatal exposures to O_3 have been studied. Maternal exposure to 0.4-1.2 ppm O_3 during gestation resulted in developmental health effects in the RT of mice (Sharkhuu et al., 2011). Recent studies involving postnatal exposure to O_3 have focused on differences between developing and adult animals in antioxidant defenses, respiratory physiology and sensitivity to cellular injury (Auten and Foster, In Press). In particular, one set of studies in infant rhesus monkeys exposed to 0.5 ppm O_3 intermittently over 5 months has identified numerous O_3-mediated perturbations in the developing lung and immune system (Plopper et al., 2007). These investigations were prompted by the dramatic rise in the incidence of childhood asthma and focused on the possible role of O_3 and allergens in promoting remodeling of the epithelial-mesenchymal trophic unit during postnatal development of the tracheobronchial airway wall. These and other studies have focused on mechanisms, such as lung structural changes, antigen sensitization, interaction with nitric oxide signaling, altered airway afferent innervation and loss of alveolar repair capacity, by which early O_3 exposure could lead to asthma pathogenesis or exacerbations in later life (Auten and Foster, In Press). Further, a recent study demonstrated that maternal exposure to particulate matter (PM) resulted in augmented lung inflammation, airway epithelial mucous metaplasia and AHR in young mice exposed chronically and intermittently to 1

ppm O_3 (Auten et al., 2009). Early life exposure to O_3 has also been found to modulate pulmonary and systemic innate immunity later in life in the infant rhesus monkey model (Maniar-Hew et al., 2011).

5.4.2.5 Attenuation of Responses

In responsive individuals, a striking degree of response attenuation occurred following repeated daily exposures to O_3. Generally, the young O_3 responder was no longer responsive on the fourth or fifth day of consecutive daily O_3 exposure (200-500 ppb O_3 for 2-4 hours) and required days to weeks of non-exposure in order for the subject to regain O_3 responsiveness (Christian et al., 1998; Devlin et al., 1997; Linn et al., 1982a; Horvath et al., 1981; Hackney et al., 1977). This phenomena has been reported for both lung function and symptoms such as upper airway irritation, nonproductive cough, substernal discomfort and pain upon deep inspiration (Linn et al., 1982a; Horvath et al., 1981; Hackney et al., 1977). Repeated daily exposures also led to an attenuation of the sRaw response in exercising human subjects exposed for 4 hours to 200 ppb O_3 (Christian et al., 1998) and to a dampened AHR response compared with a single day exposure in exercising human subjects exposed for 2 hours to 400 ppb O_3 (Dimeo et al., 1981). However, one group reported persistent small airway dysfunction despite attenuation of the FEV_1 response on the third day of consecutive O_3 exposure (250 ppb, 2 hours, with exercise) (Frank et al., 2001).

Studies in rodents also indicated an attenuation of the physiologic response measured by breathing patterns and tidal volume following five consecutive days of exposure to 0.35-1 ppm O_3 for 2.25 hours (Tepper et al., 1989). Attenuation of O_3-induced bradycardic responses, which also result from activation of neural reflexes, has been reported in rodents (0.5-0.6 ppm O_3, 2-6 h/dy, 3-5 days (Hamade and Tankersley, 2009; Watkinson et al., 2001).

Multi-day exposure to O_3 has been found to decrease some markers of inflammation compared with a single day exposure (Christian et al., 1998; Devlin et al., 1997). For example, in human subjects exposed for 4 hours to 200 ppb O_3 during moderate exercise, decreased numbers of BAL neutrophils and decreased levels of BALF fibronectin and IL-6 were observed after 4 days of consecutive exposure compared with responses after 1 day (Christian et al., 1998). Results indicated an attenuation of the inflammatory response in both proximal airways and distal lung. However markers of injury, such as lactate dehydrogenase (LDH) and protein in the BALF, were not attenuated in this study (Christian et al., 1998). Other investigators found that repeated O_3 exposure (200 ppb O_3 for 4 hours on 4 consecutive days with intermittent exercise) resulted in increased

numbers of neutrophils in bronchial mucosal biopsies despite decreased BAL neutrophilia (Jorres et al., 2000). Other markers of inflammation, including BALF protein and IL-6 remained elevated following the multi-day exposure (Jorres et al., 2000).

In rats, the increases in BALF levels of proteins, fibronectin, IL-6 and inflammatory cells observed after one day of exposure to 0.4 ppm O_3 for 12 hours were no longer observed after 5 consecutive days of exposure (Van Bree et al., 2002). A separate study in rats exposed to 0.35-1 ppm O_3 for 2.25 hours for 5 consecutive days demonstrated a lack of attenuation of the increase in BALF protein, persistence of macrophages in the centriacinar region and histological evidence of progressive tissue injury (Tepper et al., 1989). Findings that injury, measured by BALF markers or by histopathology, persist in the absence of BAL neutrophila or pulmonary function decrements suggested that repeated exposure to O_3 may have serious long-term consequences such as airway remodeling. In particular, the small airways were identified as a site where cumulative injury may occur (Frank et al., 2001).

Some studies examined the recovery of responses which were attenuated by repeated O_3 exposure. In a study of humans undergoing heavy intermittent exercise who were exposed for 2 hours to 400 ppb O_3 for five consecutive days (Devlin et al., 1997), recovery of the inflammatory responses which were diminished by repeated exposure required 10-20 days following the exposure (Devlin et al., 1997). In an animal study conducted in parallel (Van Bree et al., 2002), full susceptibility to O_3 challenge following exposure to O_3 for five consecutive days required 15-20 days recovery.

Several mechanisms have been postulated to explain the attenuation of responses observed in human subjects and animal models following repeated exposure to O_3. First, the upregulation of antioxidant defenses (or conversely, a decrease in critical O_3-reactive substrates) may protect against O_3-mediated adverse effects. Increases in antioxidant content of the BALF have been demonstrated in rats exposed to 0.25 and 0.5 ppm O_3 for several hours on consecutive days (Devlin et al., 1997; Wiester et al., 1996a; Tepper et al., 1989). Second, IL-6 was demonstrated to be an important mediator of attenuation in rats exposed to 0.5 ppm for 4 hours on two consecutive days (McKinney et al., 1998). Third, a protective role for increases in mucus producing cells and mucus concentrations in the airways has been proposed (Devlin et al., 1997). Fourth, epithelial hyperplasia or metaplasia may decrease susceptibility to subsequent O_3 challenge (Carey et al., 2007; Harkema et al., 1987a; Harkema et al., 1987b). These morphologic changes have been observed in nasal and lower airways in monkeys exposed chronically to 0.15-0.5 ppm O_3. Although there is some evidence to support these possibilities, there is no consensus on mechanisms underlying response attenuation. Recent studies demonstrating that O_3

activates TRP receptors suggest that modulation of TRP receptor number or sensitivity by repeated O_3 exposures may also contribute to the attenuation of responses.

5.4.2.6 Co-Exposures with Particulate Matter

Numerous studies have investigated the effects of co-exposure to O_3 and PM because of the prevalence of these pollutants in ambient air. Results are highly variable and depend on whether exposures are simultaneous or sequential, the type of PM employed and the endpoint examined. Additive and interactive effects have been demonstrated. For example, simultaneous exposure to O_3 (120 ppb for 2 hours at rest) and concentrated ambient particles (CAPs) in human subjects resulted in a diminished systemic IL-6 response compared with exposure to CAPs alone (Urch et al., 2010). However, exposure to O_3 alone did not alter blood IL-6 levels (Urch et al., 2010). The authors provided evidence that O_3 mediated a switch to shallow breathing which may have accounted for the observed antagonism (Urch et al., 2010). Further, simultaneous exposure to O_3 (114 ppb for 2 hours at rest) and CAPs but not exposure to either alone, resulted in increased diastolic blood pressure in human subjects (Fakhri et al., 2009). Mechanisms underlying this potentiation of response were not explored. In some strains of mice, pre-exposure to O_3 (0.5 ppm for 2 hours) modulated the effects of carbon black PM on heart rate, HRV and breathing patterns (Hamade and Tankersley, 2009). Another recent study in mice demonstrated that treatment with carbon nanotubes followed 12 hours later by O_3 exposure (0.5 ppm for 3 hours) resulted in a dampening of some of the pulmonary effects of carbon nanotubes measured as markers of inflammation and injury in the BALF (Han et al., 2008). Lastly, Harkema et al. (2005) found that epithelial and inflammatory responses in the airways of rats were enhanced by co-exposure to O_3 (0.5 ppm for 3 days) and LPS (used as a model of biogenic PM) or to O_3 (1 ppm for 2 days) and OVA (used as a model of an aeroallergen). Many of the demonstrated responses were more-than-additive. Overall, these findings are hard to interpret but demonstrate the complexity of responses following combined exposure to PM and O_3.

5.4.2.7 Summary

Collectively, these older and more recent studies provide evidence for mechanisms which may underlie the variability in responsiveness seen among individuals (Figure 5-10). Certain functional genetic polymorphisms, pre-existing conditions and diseases, nutritional status, lifestage and co-exposures contribute to altered risk of O_3-induced effects. Attenuation of responses may also be important, but it is incompletely understood, both in terms of the pathways involved and the resulting consequences.

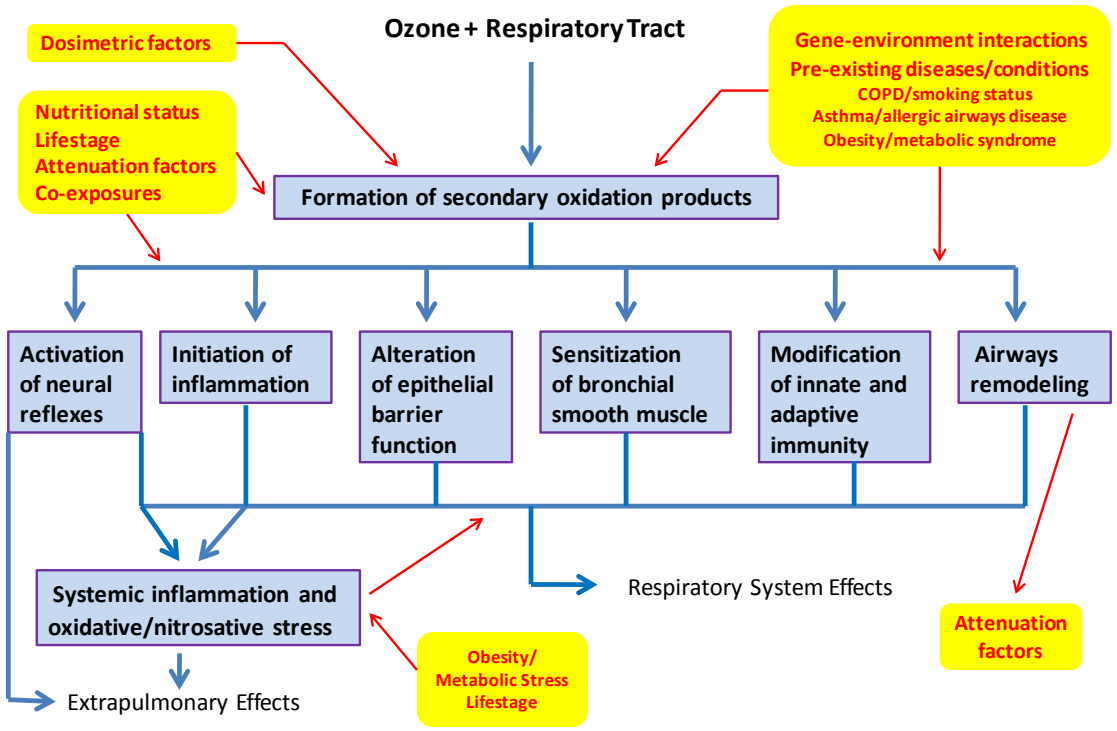


Figure 5-10 Factors which contribute to the interindividual variability in responses resulting from inhalation exposure to ozone.

5.5 Species Homology and Interspecies Sensitivity

The previous O_3 AQCDs discussed the suitability of animal models for comparison with human O_3 exposure and concluded that the acute and chronic functional responses of laboratory animals to O_3 appear qualitatively homologous to human responses. Thus, animal studies can provide important data in determining cause-effect relationships between exposure and health outcome that would be impossible to collect in human studies. Still, care must be taken when comparing quantitative dose-response relationships in animal models to humans due to obvious interspecies differences. This section will describe basic concepts in species homology concerning both dose and response to O_3 exposure. This will not be a quantitative extrapolation of doses where O_3 effects have been observed. Overall, there have been few new publications examining interspecies differences in dosimetry and response to O_3 since the last AQCD. These studies do not overtly change the conclusions discussed in the previous document.

5.5.1 Dosimetry

As discussed in Section 5.2.1, O_3 uptake depends on complex interactions between RT morphology, breathing route, rate, and depth, physicochemical properties of the gas, physical processes of gas transport, as well as the physical and chemical properties of the ELF and tissue layers. Understanding differences in these variables between humans and experimental animals is important to interpreting delivered doses in animal and human toxicology studies.

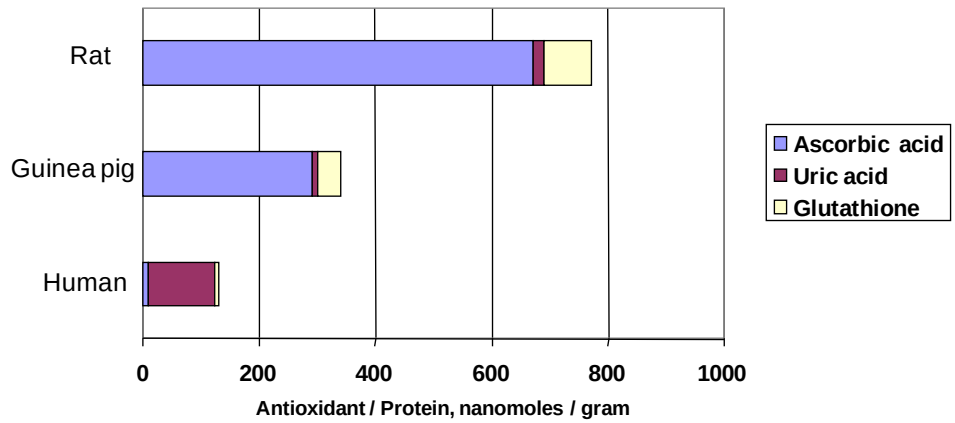
Physiological and anatomical differences exist between experimental species. The structure of the URT is vastly different between rodents and humans and scales according to body mass. The difference in the cross-sectional shape and size of the nasal passages affects bulk airflow patterns such that major airflow streams are created. The nasal epithelium is lined by squamous, respiratory, or olfactory cells, depending on location. The differences in airflow patterns in the URT mean that not all nasal surfaces and cell types receive the same exposure to inhaled O_3 leading to differences in local absorption and potential for site-specific tissue damage. The morphology of the LRT also varies within and among species. Rats and mice do not possess respiratory bronchioles; however, these structures are present in humans, dogs, ferrets, cats, and monkeys. Respiratory bronchioles are abbreviated in hamsters, guinea pigs, sheep, and pigs. The branching structure of the ciliated bronchi and bronchioles also differs between species from being a rather symmetric and dichotomous branching network of airways in humans and primates to a more monopodial branching network in other mammals. In addition, rodents have fewer terminal bronchioles due to a smaller lung size compared to humans or canines (McBride, 1992). The cellular composition in the pulmonary region is similar across mammalian species; at least 95% of the alveolar epithelial tissue is composed of Type I cells. However, significant differences exist between species in the number and type of cells in the TB airways. Differences also exist in breathing route and rate. Primates are oronasal breathers, while rodents are obligate nasal breathers. Past studies of the effect of body size on resting oxygen consumption also suggest that rodents inhale more volume of air per lung mass than primates. These distinctions as well as differences in nasal structure between primates and rodents could affect the amount of O_3 uptake.

As O_3 absorption and activity relies on ELF antioxidant substances as described in Section 5.2.3, variability in antioxidant concentrations and metabolism between species may affect dose and O_3-induced health outcomes. The thickness of the ELF in the TB airways varies among species. Mercer et al. (1992) found that the human ELF thickness in bronchi and bronchioles was 6.9 and 1.8 µm, respectively, compared to 2.6 and 1.9 µm for the same locations in the rat. Guinea pigs and mice have a lower basal activity of GSH transferase and GSH peroxidase, and lower α-TOH levels in the lung compared to

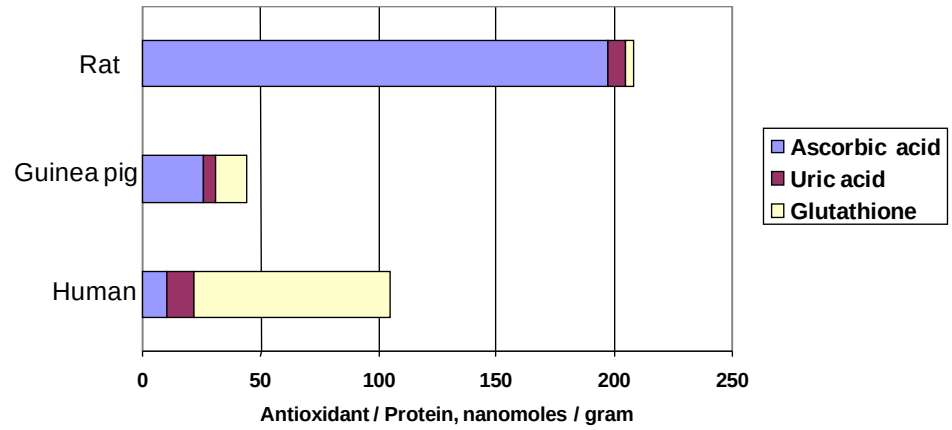
rats (Ichinose et al., 1988; Sagai et al., 1987). Nasal lavage fluid analysis shows that humans have a higher proportion of their nasal antioxidants as UA and low levels of AH_2 whereas mice, rats, or guinea pigs have high levels of AH_2 and undetectable levels of UA (Figure 5-11a). GSH is not detected in the nasal lavage of most of these species, but is present in monkey nasal lavage. Guinea pigs and rats have a higher antioxidant to protein ratio in nasal lavage and BALF than humans (Hatch, 1992). The BALF profile differs from the nasal lavage (Figure 5-11b). Humans have a higher proportion of GSH and less AH_2 making up their BALF content compared to the guinea pigs and rats (Slade et al., 1993; Hatch, 1992). Similar to the nose, rats have the highest antioxidant to protein mass ratio found in BALF (Slade et al., 1993). Antioxidant defenses also vary with age (Servais et al., 2005) and exposure history (Duan et al., 1996). Duan et al. (1996; 1993) reported that differences in antioxidant levels between species and lung regions did not appear to be the primary factor in O_3 induced tissue injury. However, a close association between site-specific O_3 dose, the degree of epithelial injury, and reduced glutathione depletion was later revealed in monkeys (Plopper et al., 1998).

Humans and animals are similar in the pattern of regional O_3 dose distribution. As discussed for humans in Section 5.2.2, O_3 flux to the air-liquid interface of the ELF slowly decreases distally in the TB region and then rapidly decreases distally in the alveolar region (Miller et al., 1985). Modeled tissue dose in the human RT, representing O_3 flux to the liquid-tissue interface, is very low in the trachea, increases to a maximum in the CAR, and then rapidly decreases distally in the alveolar region (Figure 5-12). Similar patterns of O_3 tissue dose profiles normalized to inhaled O_3 concentration were predicted for rat, guinea pig, and rabbit (Miller et al., 1988; Overton et al., 1987) (Figure 5-12a). Overton et al. (1987) modeled rat and guinea pig O_3 dose distribution and found that after comparing two different morphometrically based anatomical models for each species, considerable difference in predicted percent RT and alveolar region uptakes were observed. This was due to the variability between the two anatomical models in airway path distance to the first alveolated duct. As a result, the overall dose profile was similar between species however the O_3 uptake efficiency varied due to RT size and path length (Section 5.2.2). A similar pattern of O_3 dose distribution was measured in monkeys exposed to 0.4 and 1.0 ppm $^{18}O_3$ (Plopper et al., 1998) (Figure 5-12b). Less ^{18}O was measured in the trachea, proximal bronchus, and distal bronchus than was observed in the respiratory bronchioles. Again indicating the highest concentration of O_3 tissue dose to be localized to the CAR, which are the respiratory bronchioles in nonhuman primates. In addition, the lowest ^{18}O detected in the RT was in the parenchyma (i.e. alveolar region), mimicking the rapid decrease in tissue O_3 dose predicted by models for the alveolar regions of humans and other animals.

a.

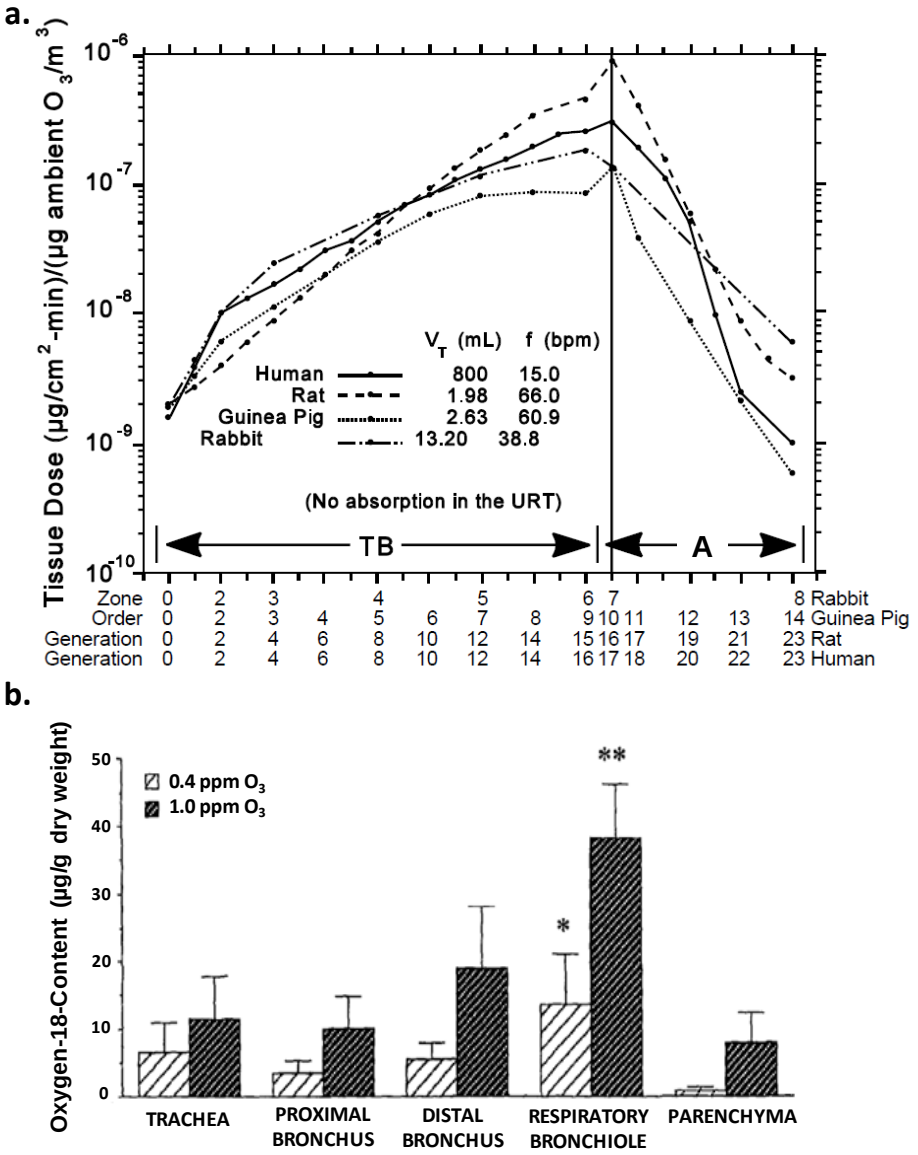


b.



Source: Adapted with permission from CRC Press, Inc. (Slade et al., 1993; Hatch, 1992)

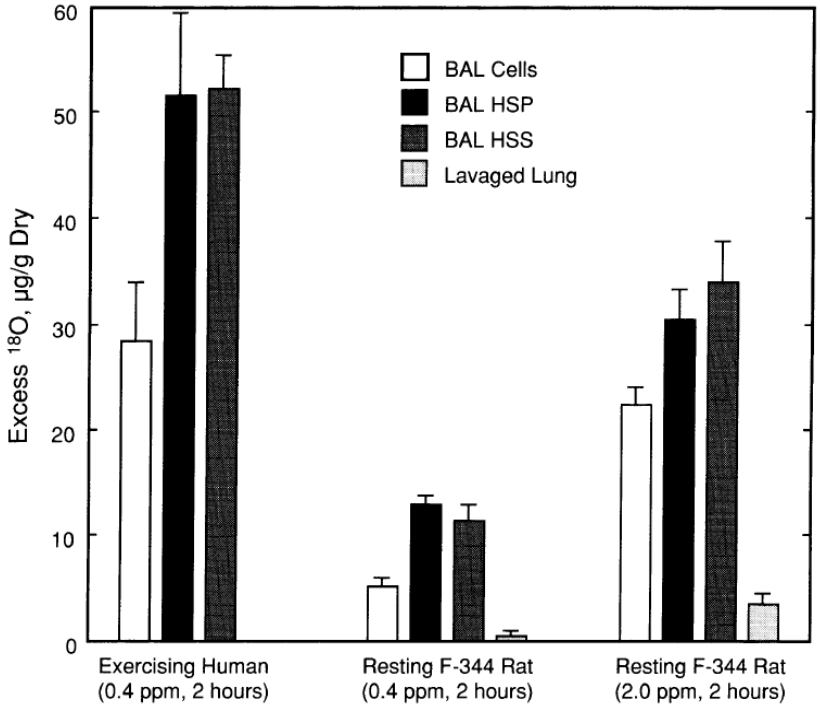
Figure 5-11 Species comparison of antioxidant / protein ratios of: (a) nasal lavage fluid and, (b) bronchoalveolar lavage fluid.



Source: Panel (a) U.S. EPA (1996a) (b) Plopper et al. (1998)

Figure 5-12 Humans and animals are similar in the regional pattern of O_3 tissue dose distribution. Panel (a) presents the predicted tissue dose of O_3 (as µg of O_3 per cm^2 of segment surface area per min, standardized to a tracheal O_3 value of 1 µg/m^3) for various regions of the rabbit, guinea pig, rat, and human RT. TB = tracheobronchial region, A = alveolar region. Panel (b) presents a comparison of excess ^{18}O in the five regions of the TB airways of rhesus monkeys exposed to O_3 for 2h. *p<0.05 comparing the same O_3 concentration across regions. **p<0.05 comparing different O_3 concentrations in the same region.

Humans and animal models are similar in the pattern of regional O_3 dose, but absolute values differ. Hatch et al. (1994) reported that exercising humans exposed to oxygen-18 labeled O_3 (400 ppb) accumulated 4-5 times higher concentrations of O_3 reaction product in BAL cells, surfactant and protein fractions compared to resting rats similarly exposed (0.4 ppm) (Figure 5-13). It was necessary to expose resting rats to 2 ppm O_3 to achieve the same BALF accumulation of ^{18}O reaction product that was observed in humans exposed to 400 ppb with intermittent heavy exercise (MV ~60 L/min). The concentration of ^{18}O reaction product in BALF paralleled the accumulation of BALF protein and cellular effects of the O_3 exposure observed such that these responses to 2.0 ppm O_3 were similar to those of the 400 ppb O_3 in exercising humans. This suggests that animal data obtained in resting conditions would underestimate the dose to the RT and presumably the resultant risk of effect for humans.



Source: Hatch et al. (1994)

Figure 5-13 Oxygen-18 incorporation into different fractions of BALF from humans and rats exposed to 0.4 and 2.0 ppm $^{18}O_3$.The excess ^{18}O in each fraction is expressed relative to the dry weight of that fraction. Fractions assayed include cells, high speed pellet (HSP), high speed supernatant (HSS), and lavaged lung homogenates.

Recently, a quantitative comparison of O_3 transport in the airways of rats, dogs, and humans was conducted using a three-compartment airways model, based on upper and lower airway casts and mathematical calculation for alveolar parameters (Tsujino et al., 2005). This model examined how interspecies anatomical and physiological differences affect intra-airway O_3 concentrations and the amount of gas absorbed. The model was designed as cylindrical tubes with constant volume and one-dimensional gas movement and no airway branching patterns. Peak, real-time, and mean O_3 concentrations were higher in the upper and lower airways of humans compared to rats and dogs, but lowest in the alveoli of humans. The amount of O_3 absorbed was lowest in humans when normalized by body weight. The intra-airway concentration decreased distally in all species. Sensitivity analysis demonstrated that V_T, f_B, and upper and lower airways surface area had a significant impact on model results. The model is limited in that it did not account for chemical reactions in the ELF or consider gas diffusion as a driving force for O_3 transport. Also, the model was run at a respiratory rate of 16/min simulating a resting individual, however exercise may cause a further deviation from animal models as was seen in Hatch et al. (1994).

Overall, animal models exhibit qualitatively similar patterns of O_3 net and tissue dose distribution with the largest tissue dose delivered to the CAR. However, due to anatomical and biochemical RT differences the absolute values of O_3 dose delivered differs. Past results suggest that animal data obtained in resting conditions would underestimate the dose to the RT and presumably the resultant risk of effect for humans, especially for humans during exercise.

5.5.2 Homology of Response

Risk of heath effects from O_3 varies between and within species, as well as between endpoints. Rodents appear to have a slightly higher tachypneic response to O_3 and are less sensitive to changes in pulmonary function test than humans (U.S. EPA, 1996a). However, rats experience attenuation of pulmonary function and tachypneic ventilatory responses, similar to humans (Wiester et al., 1996a). Hatch et al. (1986) reported that guinea pigs were the most responsive to O_3-induced inflammatory cell and protein influx. Rabbits were the least responsive and rats, hamsters, and mice were intermediate responders. Further analysis of this study by Miller et al. (1988) found that the protein levels in guinea pigs increased more rapidly with predicted pulmonary tissue dose than in rats and rabbits. Alveolar macrophages isolated from guinea pigs and humans mounted similar qualitative and quantitative cytokine responses to in vitro O_3 (0.1-1.0 ppm for 60 minutes) exposure (Arsalane et al., 1995).

Also, because of their higher body surface to volume ratio, rodents can rapidly lower body temperature during exposure leading to lowered O_3 dose and toxicity (Watkinson et al., 2003; Iwasaki et al., 1998; Slade et al., 1997). In addition to lowering the O_3 dose to the lungs, this hypothermic response may cause: (1) lower metabolic rate, (2) altered enzyme kinetics, and (3) altered membrane function. The thermoregulatory mechanisms also may affect disruption of heart rate which may lead to: (1) decreased cardiac output, (2) lowered blood pressure, and (3) decreased tissue perfusion (Watkinson et al., 2003). These responses have not been observed in humans except at very high exposures, thus further complicating extrapolation of effects from animals to humans.

Recently, the three-dimensional detail of the nasal passages of immature Rhesus macaque monkeys was analyzed for developing predictive dosimetry models and exposure-dose-response relationships (Carey et al., 2007). In doing so the authors reported that the relative amounts of the five epithelial cell types in the nasal airways of monkeys remains consistent between infancy and adulthood (comparing to (Gross et al., 1987; Gross et al., 1982). Ozone exposures (0.5 ppm, 8 h/day under acute [5 days] and episodic conditions [5 replicates of the acute paradigm spaced a week apart]) confirmed that the ciliated respiratory and transitional epithelium were the most sensitive cell types in the nasal cavity to O_3 exposure, showing 50-80% decreases in epithelial thickness and epithelial cell volume. The character and location of nasal lesions resulting from O_3 exposure were similar between adult and infant monkeys similarly exposed. However, infant monkeys did not undergo nasal airway epithelial remodeling or adaptation that occurs in adult animals and they may develop persistent necrotizing rhinitis following episodic longer-term exposures.

To further understand the genetic basis for age-dependent differential response to O_3, adult (15 week old) and neonatal (15-16 day old) mice from 8 genetically diverse strains were examined for O_3-induced (0.8 ppm for 5 hours) pulmonary injury and lung inflammation (Vancza et al., 2009). Ozone exposure increased polymorphonuclear leukocytes (PMN) influx in all strains of neonatal mice tested, but significantly greater PMNs occurred in neonatal compared to adult mice for only some sensitive strains, suggesting a genetic background effect. This strain difference was not due to differences in delivered dose of O_3 to the lung, evidenced by ^{18}O lung enrichment. The sensitivity of strains for O_3-induced increases in BALF protein and PMNs was different for different strains of mice suggesting that genetic factors contributed to heightened responses. Interestingly, adult mice accumulated more than twice the levels of ^{18}O reaction product of O_3 than corresponding strain neonates. Thus, it appeared that the infant mice showed a two- to threefold higher response than the adults when expressed relative to the accumulated O_3 reaction product in their lungs. The apparent decrease in delivered O_3

dose in neonates could be a result of a more rapid loss of body temperature in infant rodents incident to maternal separation and chamber air flow.

Further, O_3-induced injury and inflammation responses are variable between species. For example, Dormans et al. (1999) found that rats, mice, and guinea pigs all exhibited O_3-induced (0.2 - 0.4 ppm for 3-56 days) inflammation; however, guinea pigs were the most sensitive with respect to alveolar macrophage elicitation and pulmonary cell density in the centriacinar region. Mice were the most sensitive to bronchiolar epithelial hypertrophy and biochemical changes (e.g. LDH, glutathione reductase, glucose-6-phosphate dehydrogenase activity), and had the slowest recovery from O_3 exposure. All species displayed increased collagen in the ductal septa and large lamellar bodies in Type II pneumocytes at the longest exposure and highest concentration; whereas this response occurred in the rat and guinea pig at lower O_3 levels (0.2 ppm) as well. Overall, the authors rated mice as most sensitive, followed by guinea pigs, then rats (Dormans et al., 1999). Rats were also less sensitive to epithelial necrosis and inflammatory responses from O_3 (1.0 ppm for 8 hours) than monkeys and ferrets, which manifested a similar response (Sterner-Kock et al., 2000). These data suggest that ferrets may be a good animal model for O_3-induced airway effects due to the similarities in pulmonary structure between primates and ferrets. However, this study provided no dose metric and, it is possible that some of these differences may be attributable to disparate total inhaled dose or local organ dose.

5.5.3 Summary

In summary, for all species there are limitations that must be considered when attempting to extrapolate to human O_3 exposures. Rats required 4-5 times higher exposure to O_3 to achieve comparable increases in BALF protein and PMNs to exercising humans. New studies have shown that varied O_3 response in different mouse strains was not due to differences in delivered dose of O_3 to the lung but more likely genetic sensitivity, and that infant mice show greater toxicity relative to their smaller lung dose than adults. Even though interspecies differences limit quantitative comparison between species, the acute and chronic functional responses of laboratory animals to O_3 appear qualitatively homologous to those of the human making them a useful tool in determining mechanistic and cause-effect relationships with O_3 exposure.

5.6 Chapter Summary

Ozone is a highly reactive gas and a powerful oxidant with a short half-life. Both O_3 uptake and responses are dependent upon the formation of secondary reaction products in the ELF; however more complex interactions occur. Uptake in humans at rest is 80-95% efficient and it is influenced by a number of factors including RT morphology, breathing route, frequency, and volume, physicochemical properties of the gas, physical processes of gas transport, as well as the physical and chemical properties of the ELF and tissue layers. The primary uptake site of O_3 delivery to the lung epithelium is believed to be the CAR, however changes in a number of factors (e.g. physical activity) can alter the distribution of O_3 uptake in the RT. Ozone uptake is chemical reaction-dependent and the substances present in the ELF appear in most cases to limit interaction of O_3 with underlying tissues and to prevent penetration of O_3 distally into the RT. Still, reactions of O_3 with soluble ELF components or plasma membranes result in distinct products, some of which are highly reactive and can injure and/or transmit signals to RT cells.

Thus, in addition to contributing to the driving force for O_3 uptake, formation of secondary oxidation products initiates pathways that provide the mechanistic basis for health effects which are described in detail in Chapters 6 and 7 and which involve the RT as well as extrapulmonary systems. These pathways include activation of neural reflexes, initiation of inflammation, alteration of epithelial barrier function, sensitization of bronchial smooth muscle, modification of innate and adaptive immunity, airways remodeling, and systemic inflammation and oxidative/nitrosative stress. With the exception of airways remodeling, these pathways have been demonstrated in both animals and human subjects in response to the inhalation of O_3.

Both dosimetric and mechanistic factors contribute to the understanding of interindividual variability in responses to O_3. Interindividual variability is influenced by variability in RT volume and thus surface area, certain genetic polymorphisms, pre-existing conditions and disease, nutritional status, lifestages, attenuation, and co-exposures. Some of these factors are also influential in understanding species homology and sensitivity. Qualitatively, animal models exhibit similar patterns of O_3 net and tissue dose distribution with the largest tissue dose delivered to the CAR. However, due to anatomical and biochemical RT differences, the absolute value of delivered O_3 dose differs, with animal data obtained in resting conditions underestimating the dose to the RT and presumably the resultant risk of effect for humans, especially humans during exercise. Even though interspecies differences limit quantitative comparison between species, the acute and chronic functional responses of laboratory animals to O_3 appear qualitatively homologous to those of the human making them a useful tool in determining mechanistic and cause-effect relationships with O_3 exposure.

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6 INTEGRATED HEALTH EFFECTS OF SHORT-TERM OZONE EXPOSURE

6.1 Introduction

This chapter reviews, summarizes, and integrates the evidence for various health outcomes associated with short-term (i.e., hours, days, or weeks) exposures to O_3. Numerous controlled human exposure, epidemiologic, and toxicological studies have permitted evaluation of the relationships of short-term O_3 exposure with a range of endpoints related to respiratory effects (Section 6.2), cardiovascular effects (Section 6.3), and mortality (Sections 6.2, 6.3, and 6.6). A smaller number of studies are available to assess the effects of O_3 on other physiological systems such as the central nervous system (Section 6.4), liver and metabolism (Section 6.5.1), and cutaneous and ocular tissues (Section 6.5.2).

Evidence for the major health effect categories (e.g., respiratory, cardiovascular, mortality) is described in individual sections that include a brief summary of conclusions from the 2006 O_3 AQCD and an evaluation of recent evidence that is intended to build upon evidence from previous reviews. Within each section, results are organized by health endpoint (e.g., lung function, pulmonary inflammation) then by specific scientific discipline (e.g., controlled human exposure, epidemiology, and toxicology). Each major section (e.g., respiratory, cardiovascular, mortality) concludes with an integrated summary of the findings and a conclusion regarding causality. Based upon the framework described in the Preamble to this ISA, a determination of causality is made for a broad health effect category, such as respiratory effects, with coherence and plausibility being based on the evidence available across disciplines and also across the suite of related health endpoints, including cause-specific mortality.

6.2 Respiratory Effects

Based on evidence integrated across human controlled exposure, epidemiologic, and toxicological studies, the 2006 O_3 AQCD concluded that there was clear, consistent evidence of a causal relationship between short-term O_3 exposure and respiratory effects (U.S. EPA, 2006b). Contributing to this conclusion were consistent and coherent observations across scientific disciplines of associations of short-term O_3 exposures with pulmonary function decrements and increases in lung inflammation, lung permeability, and airway hyperresponsiveness. Collectively, these findings provided biological

plausibility for associations in epidemiologic studies of short-term ambient O_3 exposure with respiratory symptoms and respiratory-related hospitalizations and emergency department (ED) visits.

Controlled human exposure studies have provided strong and quantifiable exposure-response data on the human health effects of O_3. The most salient observations from studies reviewed in the 1996 and 2006 O_3 AQCDs were that: (1) young healthy adults exposed to O_3 concentrations $\geq$ 80 ppb develop significant reversible, transient decrements in pulmonary function if minute ventilation (V_E) or duration of exposure is increased sufficiently; (2) relative to young adults, children experience similar spirometric responses but lesser symptoms from O_3 exposure; (3) relative to young adults, O_3-induced spirometric responses are decreased in older individuals; (4) there is a large degree of intersubject variability in physiologic and symptomatic responses to O_3, but responses tend to be reproducible within a given individual over a period of several months; (5) subjects exposed repeatedly to O_3 for several days experience an attenuation of spirometric and symptomatic responses on successive exposures, that is lost after about a week without exposure; and (6) acute O_3 exposure initiates an inflammatory response that may persist for at least 18 to 24 hours postexposure.

Substantial evidence for biologically plausible O_3-induced respiratory morbidity has been derived from the coherence between toxicological and controlled human exposure studies examining parallel endpoints. For example, O_3-induced decrements in lung function have also been observed in animals, and as in humans, tolerance or attenuation has been demonstrated in animal models. Both humans and rodents exhibit increased airway hyperresponsiveness. This is an important consequence of exposure to ambient O_3, because the airways are then predisposed to narrowing upon inhalation of a variety of ambient stimuli. Additionally, airway hyperresponsiveness tends to resolve more slowly and appears less subject to attenuation. Increased permeability and inflammation have been observed in the airways of humans and animals alike after O_3 exposure, although these processes are not necessarily associated with immediate changes in lung function or hyperresponsiveness. Furthermore, the potential relationship between repetitive bouts of acute inflammation and the development of chronic respiratory disease is unknown. Another feature of O_3 exposure-related respiratory morbidity is impaired host defense and reduced resistance to lung infection, which has been strongly supported by toxicological evidence and to a limited extent by human data. Recurrent respiratory infection in early life is associated with increased incidence of asthma in humans.

In epidemiologic studies, short-term O_3-related respiratory morbidity has been assessed most frequently using lung function. Several studies of healthy children attending camps as well as studies of outdoor workers, groups exercising outdoors, and children with

asthma support O_3 effects on lung function decrements at ambient levels (U.S. EPA, 2006b, 1996a). In addition to lung function, ambient O_3 exposure has been associated with increases in respiratory symptoms (e.g., cough, wheeze, shortness of breath), especially in large U.S. panel studies of children with asthma (Gent et al., 2003; Mortimer et al., 2000). The evidence across disciplines for O_3 effects on a range of respiratory endpoints collectively provides support for epidemiologic studies that have demonstrated consistent positive associations between O_3 exposure and respiratory hospital admissions and ED visits, specifically during the summer or warm months. In contrast with other respiratory health endpoints, the association between short-term O_3 exposure and respiratory mortality is less clearly indicated. Although O_3 has been consistently associated with nonaccidental and cardiopulmonary mortality, the contribution of respiratory causes to these findings has been uncertain as the few studies that have examined mortality specifically from respiratory causes have reported inconsistent associations with ambient O_3 exposures.

As discussed throughout this section, consistent with the strong body of evidence presented in the 2006 O_3 AQCD, recent studies continue to support associations between short-term O_3 exposure and respiratory effects, in particular, lung function decrements in controlled human exposure studies, airway inflammatory responses in toxicological studies, and respiratory-related hospitalizations and ED visits. Recent epidemiologic studies contribute new evidence on at-risk populations and of associations of ambient O_3 exposures with biological markers of airway inflammation and oxidative stress, which is consistent with the extensive evidence from human controlled exposure and toxicological studies. Furthermore, extending the potential range of well-established O_3-associated respiratory effects, new multicity studies and a multicontinent study demonstrate associations between short-term ambient O_3 exposure and respiratory-related mortality.

6.2.1 Lung Function

6.2.1.1 Controlled Human Exposure

This section focuses on studies examining O_3 effects on lung function and respiratory symptoms in volunteers exposed, for periods of up to 8 hours to O_3 concentrations ranging from 40 to 500 ppb, while at rest or during exercise of varying intensity. Responses to acute O_3 exposures in the range of ambient concentrations include decreased inspiratory capacity; mild bronchoconstriction; rapid, shallow breathing patterns during exercise; and symptoms of cough and pain on deep inspiration (PDI). Reflex inhibition of inspiration 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 second (FEV_1).

In studies that have exposed subjects during exercise, the majority of shorter duration ($\leq$ 4-hour exposures) studies utilized an intermittent exercise protocol in which subjects rotated between 15-minute periods of exercise and rest. A limited number of 1- to 2-hour studies, mainly focusing on exercise performance, have utilized a continuous exercise regime. A quasi continuous exercise protocol is common to prolonged exposure studies where subjects complete 50-minute periods of exercise followed by 10-minute rest periods.

The majority of controlled human exposure studies have been conducted within chambers, although a smaller number of studies used a facemask to expose subjects to O_3. Little effort has been made herein to differentiate between facemask and chamber exposures as FEV_1 and respiratory symptom responses appear minimally affected by these exposure modalities. Similar responses between facemask and chamber exposures have been reported for exposures to 80 and 120 ppb O_3 (6.6 h, moderate quasi continuous exercise, 40 L/min) and 300 ppb O_3 (2 h, heavy intermittent exercise, 70 L/min) (Adams, 2003a, b, 2002).

The majority of controlled human exposure studies investigating the effects O_3 are of a randomized, controlled, crossover design in which subjects were exposed, without knowledge of the exposure condition and in random order to clean filtered air (FA; the control) and, depending on the study, to one or more O_3 concentrations. The FA control exposure provides an unbiased estimate of the effects of the experimental procedures on the outcome(s) of interest. Comparison of responses following this FA exposure to those following an O_3 exposure allows for estimation of the effects of O_3 itself on an outcome measurement while controlling for independent effects of the experimental procedures. As individuals may experience small changes in various health endpoints from exercise, diurnal variation, or other effects in addition to those of O_3 during the course of an exposure, the term "O_3-induced" is used herein to designate effects that have been corrected or adjusted for such extraneous responses as measured during FA exposures.

Spirometry, viz., FEV_1, is a common health endpoint used to assess effects of O_3 on respiratory health in controlled human exposure studies. In considering 6.6 hour exposures to FA, group mean FEV_1 changes have ranged from -0.7% (McDonnell et al., 1991) to 2.7% (Adams, 2006a). On average, across ten 6.6-hour exposure studies, there has been a 1.0% (n=279) increase in FEV_1 (Kim et al., 2011; Schelegle et al., 2009; Adams, 2006a, 2003a, 2002; Adams and Ollison, 1997; Folinsbee et al., 1994; McDonnell et al., 1991; Horstman et al., 1990; Folinsbee et al., 1988). Regardless of the reason for small changes in FEV_1 over the course of FA exposures, whether biologically

based or a systematic effect of the experimental procedures, the use of FA responses as a control for the assessment of responses following O_3 exposure in randomized exposure studies serves to eliminate alternative explanations other than those of O_3 itself in causing the measured responses.

Considering FEV_1 responses in young healthy adults, an O_3-induced change in FEV_1 is typically the difference between the decrement observed with O_3 exposure and the improvement observed with FA exposure. Noting that some healthy individuals experience small improvements while others have small decrements in FEV_1 following FA exposure, investigators have used the randomized, crossover design with each subject having their own control exposure to FA to discern relatively small effects with certainty since alternative explanations for these effects are controlled for by the nature of the experimental design. The utility of FA control exposures becomes more apparent when considering individuals with respiratory disease. The occurrence of exercise-induced bronchospasm is well recognized to in patients with asthma and COPD and may be experienced during both FA and O_3 exposures. Absent correction for FA responses, exercise-induced changes in FEV_1 could be mistaken for responses due to O_3. This biological phenomenon serves as an example to emphasize the need for a proper control exposure in assessing the effects of O_3 as well as the role of this control in eliminating the influence of other factors on the outcomes of interest.

Pulmonary Function Effects of Ozone Exposure in Healthy Subjects

Acute Exposure of Healthy Subjects

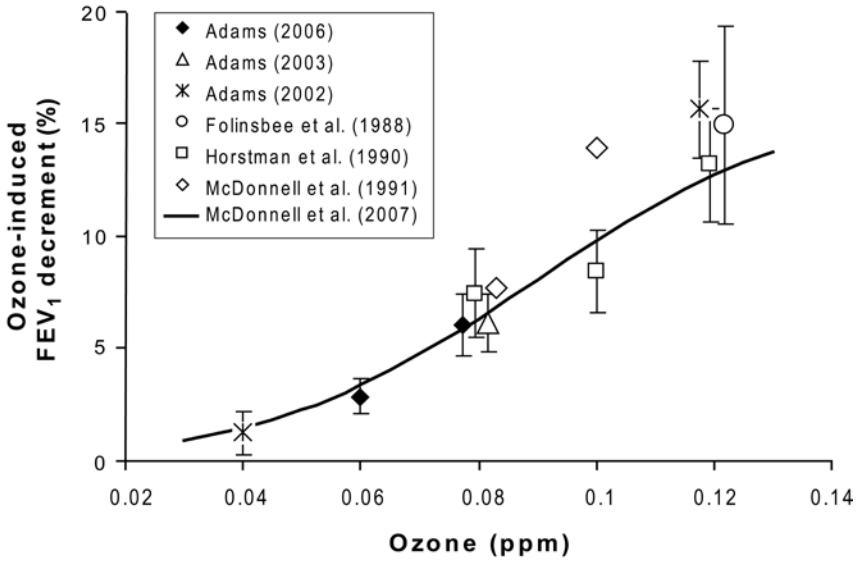
The majority of controlled human exposure studies have investigated the effects of exposure to O_3 in young healthy nonsmoking adults (18-35 years of age). These studies typically use fixed concentrations of O_3 under carefully regulated environmental conditions and subject activity levels. The magnitude of respiratory effects (decrements in spirometry and symptomatic response) in these individuals is a function of O_3 concentration (C), minute ventilation (V_E), and exposure duration (time). Any physical activity will increase minute ventilation and therefore the dose of inhaled O_3. Dose of inhaled O_3 to the lower airways is also increased due to a shift from nasal to oronasal breathing with a consequential decrease in O_3 scrubbing by the upper airways. Thus, the intensity of physiological response following an acute exposure will be strongly associated with minute ventilation.

The product of $C \times V_E \times$ time, although actually a measure of exposure, is commonly used as a surrogate for O_3 dose to the respiratory tract in controlled human exposure studies. The delivery of O_3 to the lower respiratory tract varies as a function of breathing conditions (route and pattern). And, the dose of O_3 to the lower respiratory tract can vary

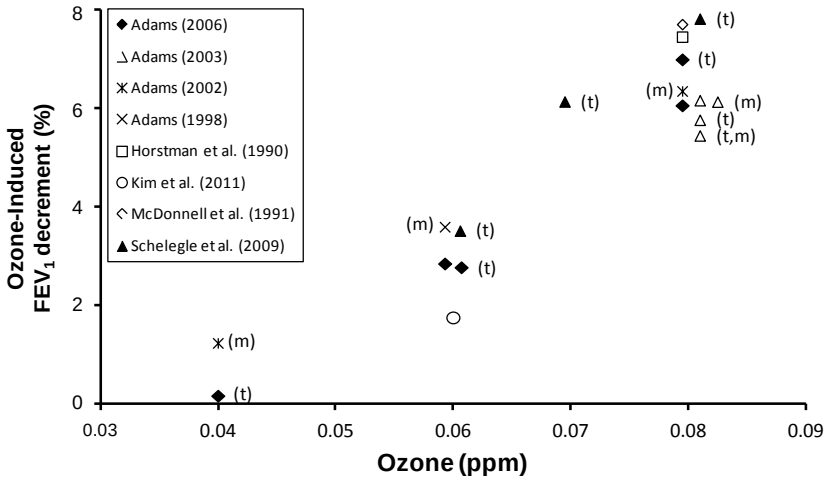
between similarly exposed individuals. In support of the use of the product ($C \times V_E \times$ time) as a surrogate for O_3 dose, differences in FEV_1 responses among young healthy adults (32 M, 28 F) exposed to O_3 (250 ppb, 30 L/min, 2 h) do not appear to be explained by intersubject differences in the fraction of inhaled O_3 retained in the lung (Ultman et al., 2004). Using the product of $C \times V_E \times$ time as a surrogate for O_3 dose is also useful in distinguishing between the well defined and characterized exposure of subjects in controlled human exposure studies as opposed to the use of ambient O_3 concentration to characterize exposure in epidemiologic studies.

For healthy young adults exposed at rest for 2 hours, 500 ppb is the lowest O_3 concentration reported to produce a statistically significant O_3-induced group mean FEV_1 decrement of 6.4% (n=10) (Folinsbee et al., 1978) to 6.7% (n=13) (Horvath et al., 1979). Airway resistance was not clearly affected during at-rest exposure to these O_3 concentrations. When exposed to 200 ppb for 2.25 h during intermittent periods of rest and brisk walking, young healthy subjects (83 M, 55 F) show a statistically significant group mean FEV_1 decrement of 8.8% following O_3 exposure (Que et al.). For exposures of 1-2 hours to $\geq$ 120 ppb O_3, statistically significant symptomatic responses and effects on FEV_1 are observed when V_E is sufficiently increased by exercise (McDonnell et al., 1999). For instance, 5% of young healthy adults exposed to 400 ppb for 2 h during rest experienced pain on deep inspiration. Respiratory symptoms were not observed at lower exposure concentrations (120-300 ppb) or with only 1 h of exposure. However, when exposed to 120 ppb for 2 h during moderate intermittent exercise, 9% of individuals experienced pain on deep inspiration, 5% experienced cough, and 4% experienced shortness of breath. With very heavy continuous exercise (V_E = 89 L/min), an O_3-induced group mean decrement of 9.7% in FEV_1 has been reported for healthy young adults exposed for 1 hour to 120 ppb O_3 (Gong et al., 1986). Symptoms are present and decrements in forced expiratory volumes and flows occur at 160-240 ppb O_3 following 1 hour of continuous heavy exercise ($V_E \approx$ 55 to 90 L/min (Gong et al., 1986; Avol et al., 1984; Folinsbee et al., 1984; Adams and Schelegle, 1983) and following 2 hours of intermittent heavy exercise ($V_E \approx$ 65-68 L/min) (Linn et al., 1986; Kulle et al., 1985; McDonnell et al., 1983). With heavy intermittent exercise (15-min intervals of rest and exercise [V_E = 68 L/min]), symptoms of breathing discomfort and a group mean O_3-induced decrement of 3.4% in FEV_1 occurred in young healthy adults exposed for 2 hours to 120 ppb O_3 (McDonnell et al., 1983).[1]

[1] In total, subjects were exposed to O_3 for 2.5 hours. Intermittent exercise periods, however, were only conducted for the first 2 hours of exposure and FEV_1 was determined 5 minutes after the exercise was completed.



Source: Brown et al. (2008)



Studies appearing in the figure legends are: Adams (2006a, 2003a, 2002, 1998), Folinsbee et al. (1988), Horstman et al. (1990), Kim et al. (2011), McDonnell et al. (2007; 1991), and Schelegle et al. (2009).

Top, panel A: all studies exposed subjects to a constant (square-wave) concentration in a chamber, except Adams (1998) where a facemask was used. The McDonnell et al. (2007) curve illustrates the predicted FEV_1 decrement at 6.6 hours as a function of ozone concentration for a 23-year old (the average age of subjects that participated in the illustrated studies). Note that this curve was not "fitted" to the plotted data. Error bars (where available) are the standard error of responses. Bottom, panel B: all studies used constant (square-wave) exposures in a chamber unless designated as triangular (t) and/or facemask (m) exposures.

Figure 6-1 Cross-study comparison of mean ozone-induced FEV_1 decrements following 6.6 hours of exposure to ozone. During each hour of the exposures, subjects were engaged in moderate quasi continuous exercise (40 L/min) for 50 minutes and rest for 10 minutes. Following the third hour, subjects had an additional 35-minute rest period for lunch. The data at 0.06, 0.08 and 0.12 ppm have been offset for illustrative purposes.

For prolonged (6.6 hours) exposures relative to shorter exposures, significant pulmonary function responses and symptoms have been observed at lower O_3 concentrations and at a moderate level of exercise (V_E = 40 L/min). The results from studies using 6.6 hours of constant or square-wave (S-W) exposures to between 40 and 120 ppb are illustrated in Figure 6-1(A). Figure 6-1(B) focuses on the range from 40 to 80 ppb and includes triangular exposure protocols as well as facemask exposures. Exposure to 40 ppb for 6.6 hours produces small, statistically insignificant changes in FEV_1 that are relatively similar to responses from FA exposure (Adams, 2002). Volunteers exposed to 60 ppb O_3 experience group mean O_3-induced FEV_1 decrements of about 3% (Kim et al., 2011; Brown et al., 2008) (Adams, 2006a)[1]; those exposed to 80 ppb have group mean decrements which range from 6 to 8% (Adams, 2006a, 2003a; McDonnell et al., 1991; Horstman et al., 1990); at 100 ppb, group mean decrements range from 8 to 14% (McDonnell et al., 1991; Horstman et al., 1990); and at 120 ppb, group mean decrements of 13 to 16% are observed (Adams, 2002; Horstman et al., 1990; Folinsbee et al., 1988). As illustrated in Figure 6-1, there is a smooth dose-response curve without evidence of a threshold for exposures between 40 and 120 ppb O_3. Taken together, these data indicate that mean FEV_1 is clearly decreased by 6.6-h exposures to 60 ppb O_3 and higher concentrations in subjects performing moderate exercise.

As opposed to constant or S-W concentration patterns used in the studies described above, many studies conducted at the levels of 40-80 ppb have used variable O_3 concentration patterns. It has been suggested that a triangular (variable concentration) exposure profile can potentially lead to higher FEV_1 responses than S-W profiles despite having at the same average O_3 concentration over the exposure period. Hazucha et al. (1992) were the first to investigate the effects of variable versus constant concentration exposures on responsiveness to O_3. In their study, volunteers were randomly exposed to a triangular concentration profile (averaging 120 ppb over the 8-h exposure) that increased linearly from 0-240 ppb for the first 4 hours of the 8-h exposure, then decreased linearly from 240 to 0 ppb over the next 4 hours of the 8-h exposure, and to an S-W exposure of 120 ppb O_3 for 8 hours. While the total inhaled O_3 doses at 4 hours and 8 hours for the S-W and the triangular concentration profile were almost identical, the FEV_1 response was dissimilar. For the S-W exposure, FEV_1 declined ~5% by the fifth hour and then remained at that level. With the triangular O_3 profile, there was minimal FEV_1 response over the first 3 hours followed by a rapid decrease in FEV_1 (-10.3%) over the next 3

[1] Adams (2006a) did not find effects on FEV_1 at 60 ppb to be statistically significant. In an analysis of the Adams (2006a) data, even after removal of potential outliers, Brown et al. (2008) found the average effect on FEV_1 at 60 ppb to be small, but highly statistically significant ($p < 0.002$) using several common statistical tests.

hours. During the seventh and eighth hours, mean FEV_1 decrements improved to -6.3% as the O_3 concentration decreased from 120 to 0 ppb (mean = 60 ppb). These findings illustrate that the severity of symptoms and the magnitude of spirometric responses are time-dependent functions of O_3 delivery rate with periods of both effect development and recovery during the course of an exposure.

Subsequently, others have also demonstrated that variable concentration exposures can elicit greater FEV_1 and symptomatic responses than do S-W exposures (Adams, 2006a, b, 2003a). Adams (2006b) reproduced the findings of Hazucha et al. (1992) at 120 ppb. However, Adams (2006a, 2003a) found that responses from an 80 ppb O_3 (average) triangular exposure did not differ significantly from those observed in the 80 ppb O_3 S-W exposure at 6.6 hours. Nevertheless, FEV_1 and symptoms were significantly different from pre-exposure at 4.6 hours (when the O_3 concentration was 150 ppb) in the triangular exposure, but not until 6.6 hours in the S-W exposure. At the lower O_3 concentration of 60 ppb, no temporal pattern differences in FEV_1 responses between S-W and triangular exposure profiles could be discerned (Adams, 2006a). However, total symptom scores were significantly increased for the 60 ppb triangular (but not the S-W) exposure following 5.6 and 6.6 hours of exposure. At 80 ppb, respiratory symptoms tended to increase more rapidly during the triangular than S-W exposure protocol, but then decreased during the last hour of exposure to be less for the triangular than the S-W exposure at 6.6 h. Both total symptom scores and pain on deep inspiration were significantly increased following exposures to 80 ppb relative to all other exposure protocols, i.e., FA, 40, and 60 ppb exposures. Following the 6.6-hour exposures, respiratory symptoms at 80 ppb were rougly 2-3 times greater than observed at 60 ppb. At 40 ppb, triangular and S-W patterns produced spirometric and subjective symptom responses similar to FA exposure (Adams, 2006a, 2002).

For exposures of 60 ppb and greater, these studies (Adams, 2006a, b, 2003a; Hazucha et al., 1992) demonstrate that during triangular exposure protocols, volunteers exposed during moderate exercise (V_E = 40 L/min) may develop greater spirometric and/or symptomatic responses during and following peak O_3 concentrations as compared to responses over the same time interval of S-W exposures. This observation is not unexpected since the inhaled dose rate during peaks of the triangular protocols approached twice that of the S-W protocols, e.g., 150 ppb versus 80 ppb peak concentration. At time intervals toward the end of an exposure, O_3 delivery rates for the triangular protocols were less than those of S-W. At these later time intervals, there is some recovery of responses during triangular exposure protocols, whereas there is a continued development of or a plateau of responses in the S-W exposure protocols. Thus, responses during triangular protocols relative to S-W protocols may be expected to diverge and be greater following peak exposures and then converge toward the end of an

exposure. The ensuing discussion on exposures between 40 and 80 ppb will focus on postexposure effects where the influence of triangular and S-W concentration patterns are minimal, i.e., FEV_1 pre-to-post effects are similar (although not identical) between triangular and S-W protocols having equivalent average exposure concentrations.

Schelegle et al. (2009) recently investigated the effects of 6.6 hours variable O_3 exposure protocols at mean concentrations of 60, 70, 80, and 87 ppb on respiratory symptoms and pulmonary function in young healthy adults (16 F, 15 M; 21.4 ± 0.6 years) exposed during moderate quasi continuous exercise (V_E = 40 L/min). The mean FEV_1 (±standard error) decrements at 6.6 hours (end of exposure relative to pre-exposure) were -0.80 ± 0.90%, 2.72 ± 1.48%, 5.34 ± 1.42%, 7.02 ± 1.60%, and 11.42 ± 2.20% for exposure to FA, 60, 70, 80, and 87 ppb O_3, respectively. Statistically significant decrements in FEV_1 and increases in total subjective symptom scores ($p < 0.05$) were found following exposure to mean concentrations of 70, 80, and 87 ppb O_3 relative to FA. Statistically significant effects were not found at 60 ppb. One of the expressed purposes of the Schelegle et al. (2009) study was to determine the minimal mean O_3 concentration that produces a statistically significant decrement in FEV_1 and symptoms in healthy individuals completing 6.6-h exposure protocols. At 70 ppb, Schelegle et al. (2009) observed a statistically significant O_3-induced of 6.1%. At 60 ppb, an O_3-induced 3.5% FEV_1 decrement was not found to be statistically significant. However, this effect is similar in magnitude to the 2.9% FEV_1 decrement at 60 ppb observed by Adams (2006a) that was found to be statistically significant by Brown et al. (2008).

More recently, Kim et al. (2011) investigated the effects of a 6.6-h exposure to 60 ppb O_3 during moderate quasi continuous exercise (V_E = 40 L/min) on pulmonary function and respiratory symptoms in young healthy adults (32 F, 27 M; 25.0 ± 0.5 year) that were roughly half GSTM1-null and half GSTM1-positive. Sputum neutrophil levels were also measured in a subset of the subjects (13 F, 11 M). The mean FEV_1 (±standard error) decrements at 6.6 hours (end of exposure relative to pre-exposure) were significantly different ($p = 0.008$) between the FA (0.002 ± 0.46%) and O_3 (1.76 ± 0.50%) exposures. The inflammatory response following O_3 exposure was also significantly ($p<0.001$) increased relative to the FA exposure. Respiratory symptoms were not affected by O_3 exposure. There was also no significant effect of GSTM1 genotype on FEV_1 or inflammatory responses.

Consideration of the minimal O_3 concentration producing statistically significant effects on FEV_1 following 6.6-h exposures warrants additional discussion. As discussed above, numerous studies have demonstrated statistically significant O_3-induced group mean FEV_1 decrements of 6-8% at 80 ppb. Schelegle et al. (2009) have now reported statistically significant O_3-induced group mean FEV_1 decrement of 6%, as well as

respiratory symptoms, at 70 ppb. At 60 ppb, there is information available from 4 separate studies (Adams, 1998)[1] (Kim et al., 2011; Schelegle et al., 2009; Adams, 2006a). The group mean O_3-induced FEV_1 decrements observed in these studies were 3.6% by Adams (1998)[2], 2.8% (triangular exposure) and 2.9% (S-W exposure) by Adams (2006a), 3.5% by Schelegle et al. (2009), and 1.8% by Kim et al. (2011). Based on data from these four studies, at 60 ppb, the weighted-average group mean O_3-induced FEV_1 decrement (i.e., adjusted for FA responses) is 2.7% (n=150) (Kim et al., 2011; Schelegle et al., 2009; Adams, 2006a, 1998). Although not consistently statistically significant, these group mean changes in FEV_1 at 60 ppb are consistent between studies, i.e., none observed an average improvement in lung function following a 6.6-h exposure to 60 ppb O_3. Indeed, as was illustrated in Figure 6-1, the FEV_1 responses at 60 ppb fall on a smooth dose-response curve for exposures between 40 and 120 ppb O_3. Furthermore, in a re-analysis of the 60 ppb S-W data from Adams (2006a), Brown et al. (2008) found the mean effects on FEV_1 to be highly statistically significant ($p<0.002$) using several common statistical tests even after removal of 3 potential outliers. The time-course and magnitude of FEV_1 responses at 40 ppb resemble those occurring during FA exposures (Adams, 2006a, 2002). Taken together, the available evidence shows that detectable effects of O_3 on group mean FEV_1 persist down to 60 ppb, but not 40 ppb in young healthy adults exposed for 6.6 hours during moderate exercise.

In addition to overt effects of O_3 exposure on the large airways indicated by spirometric responses, O_3 exposure also affects the function of the small airways and parenchymal lung. Foster et al. (1997; 1993) examined the effect of O_3 on ventilation distribution. In healthy adult males (n=6; 26.7 ± 7 years old) exposed to O_3 (330 ppb with light intermittent exercise for 2 h), there was a significant reduction in ventilation to the lower lung (31% of lung volume) and significant increases in ventilation to the upper- and middle-lung regions (Foster et al., 1993). In a subsequent study of healthy males (n=15; 25.4 ± 2 years old) exposed to O_3 (350 ppb with moderate intermittent exercise for 2.2 h), O_3 exposure caused a delayed gas washout (Foster et al., 1997). The pronounced slow phase of gas washout following O_3 exposure represented a 24% decrease in the washout rate. A day following O_3 exposure, 50% of the subjects still had (or developed) a delayed washout relative to the pre- O_3 maneuver. These studies suggest a prolonged O_3 effect on the small airways and ventilation distribution in healthy young individuals.

[1] The American Petroleum Institute has declined to provide a copy of this report to EPA.

[2] This information is from page 133 of Adams (2006a). This decrement may be increased due to a target VE of 23 L/min/m^2 BSA relative to other studies with which it is listed having the target VE of 20 L/min/m^2 BSA. It should also be noted that subjects were exposed via a facemask in this study. However, Adams (2003a, b, 2002) found very similar FEV_1 responses between facemask and chamber exposures.

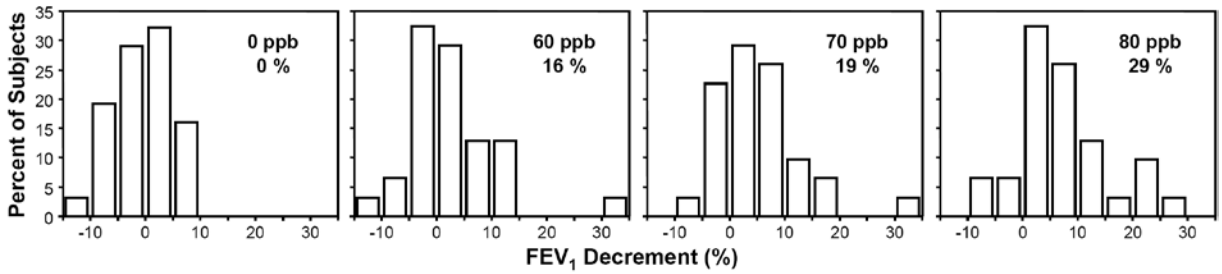
There is a rapid recovery of O_3-induced spirometric responses and symptoms; 40 to 65% recovery appears to occur within about 2 hours following exposure (Folinsbee and Hazucha, 1989). For example, following a 2-h exposure to 400 ppb O_3 with intermittent exercise, Nightingale et al. (2000) observed a 13.5% mean decrement in FEV_1. By 3 hours postexposure, however, only a 2.7% FEV_1 decrement persisted. Partial recovery also occurs following cessation of exercise despite continued exposure to O_3 (Folinsbee et al., 1977) and at low O_3 concentrations during exposure (Hazucha et al., 1992). A slower recovery phase, especially after exposure to higher O_3 concentrations, may take at least 24 hours to complete (Folinsbee and Hazucha, 2000; Folinsbee et al., 1993). Repeated daily exposure studies at higher concentrations typically show that FEV_1 response to O_3 is enhanced on the second day of exposure. This enhanced response suggests a residual effect of the previous exposure, about 22 hours earlier, even though the pre-exposure spirometry may be the same as on the previous day. The absence of the enhanced response with repeated exposure at lower O_3 concentrations may be the result of a more complete recovery or less damage to pulmonary tissues (Folinsbee et al., 1994).

Intersubject Variability in Response of Healthy Subjects

Consideration of group mean changes is important in discerning if observed effects are due to O_3 exposure rather than chance alone. Inter-individual variability in responses is, however, considerable and pertinent to assessing the fraction of the population that might actually be affected during an O_3 exposure. Hackney et al. (1975) first recognized a wide range in the sensitivity of subjects to O_3. The range in the subjects' ages (29 to 49 years) and smoking status (0 to 50 pack years) in the Hackney et al. (1975) study are now understood to affect the spirometric and symptomatic responses to O_3. Subsequently, DeLucia and Adams (1977) examined responses to O_3 in six healthy non-smokers and found that two exhibited notably greater sensitivity to O_3. Since that time, numerous studies have documented considerable variability in responsiveness to O_3 even in subjects recruited to assure homogeneity in factors recognized or presumed to affect responses.

An individual's FEV_1 response to a 2-h O_3 exposure is generally reproducible over several months and presumably reflects the intrinsic responsiveness of the individual to O_3 (Hazucha et al., 2003; McDonnell et al., 1985a). The frequency distribution of individual FEV_1 responses following these relatively short exposures becomes skewed as the group mean response increases, with some individuals experiencing large reductions in FEV_1 (Weinmann et al., 1995c; Kulle et al., 1985). For 2-h exposures with intermittent exercise causing a predicted average FEV_1 decrement of 10%, individual decrements ranged from approximately 0 to 40% in white males aged 18-36 years (McDonnell et al., 1997). For an average FEV_1 decrement of 13%, Ultman et al. (2004) reported FEV_1 responses ranging from a 4% improvement to a 56% decrement in young healthy adults

(32 M, 28 F) exposed for 1 hour to 250 ppb O_3. One-third of the subjects had FEV_1 decrements of >15%, and 7% of the subjects had decrements of >40%.



Source: Adapted with permission of American Thoracic Society (Schelegle et al., 2009)

During each hour of the exposures, subjects were engaged in moderate quasi continuous exercise (40 L/min) for 50 minutes and rest for 10 minutes. Following the third hour, subjects had an additional 35 minute rest period for lunch. Subjects were exposed to a triangular ozone concentration profile having the average ozone concentration provided in each panel. As average ozone concentration increased, the distribution of responses became asymmetric with a few individuals exhibiting large FEV_1 decrements. The percentage indicated in each panel is the portion of subjects having a FEV_1 decrement in excess of 10%.

Figure 6-2 Frequency distributions of FEV_1 decrements observed by Schelegle et al. (2009) in young healthy adults (16 F, 15 M) following 6.6-h exposures to ozone or filtered air.

Consistent with the 1- to 2-h studies, the distribution of individual responses following 6.6-h exposure studies becomes skewed with increasing exposure concentration and magnitude of the group mean FEV_1 response (McDonnell, 1996). Figure 6-2 illustrates frequency distributions of individual FEV_1 responses observed in 31 young healthy adults following 6.6-h exposures between 0 and 80 ppb. Schelegle et al. (2009) found >10% FEV_1 decrements in 16, 19, 29, and 42% of individuals exposed for 6.6 hours to 60, 70, 80, and 87 ppb, respectively. Just as there are differences in mean decrements between studies having similar exposure scenarios (Figure 6-1 at 80 and 120 ppb), there are also differences in the proportion of individuals affected with >10% FEV_1 decrements. At 80 ppb, the proportion affected with >10% FEV_1 decrements was 17% (n=30) by Adams (2006a)[1], 26% (n=60) by McDonnell (1996), and 29%(n=31) by Schelegle et al. (2009). At 60 ppb, the proportion with >10% FEV_1 decrements was 20% (n=30) by Adams (1998)[2], 3% (n=30) by Adams (2006a)[5], 16% (n=31) by Schelegle et al. (2009), and 5% (n=59) by Kim et al. (2011). Based on these studies, the weighted average proportion of

[1] Not assessed by Adams (2006a), the proportion was provided in Figure 8-1B of U.S. EPA (2006b).

[2] This information is from page 761 of Adams (2002).

individuals with >10% FEV_1 decrements is 10% following exposure to 60 ppb. Due to limited data within the published papers, these proportions were not corrected for responses to FA exposure where lung function typically improves in healthy adults. For example, uncorrected versus O_3-induced (i.e., adjusted for response during FA exposure) proportions of individuals having >10% FEV_1 decrements in the Adams (2006a)[1] study were, respectively, 3% versus 7% at 60 ppb and 17% versus 23% at 80 ppb. Thus, uncorrected proportions underestimate the actual fraction of healthy individuals affected.

Given considerable inter-individual variability in responses, the interpretation of biologically small group mean decrements requires careful consideration. Following prolonged 6.6-h exposures to an average level of 60 ppb O_3, data available from four studies yield a weighted-average group mean O_3-induced FEV_1 decrement (i.e., adjusted for FA responses) of 2.7% (n=150) (Kim et al., 2011; Schelegle et al., 2009; Adams, 2006a, 1998). The data from these studies also yield a weighted-average proportion (uncorrected for FA responses) of subjects with >10% FEV_1 decrements of 10% (n=150) (Kim et al., 2011; Schelegle et al., 2009; Adams, 2006a, 1998). In an individual with relatively "normal" lung function, recognizing technical and biological variability in measurements, confidence can be given that within-day changes in FEV_1 of $\geq$ 5% are clinically meaningful (Pellegrino et al., 2005; ATS, 1991). Here focus is given to individuals with >10% decrements in FEV_1 since some individuals in the Schelegle et al. (2009) study experienced 5-10% FEV_1 decrements following exposure to FA. A 10% FEV_1 decrement is also generally accepted as an abnormal response and as reasonable criterion for assessing exercise-induced bronchoconstriction (Dryden et al., 2010; ATS, 2000a). The data are not available in the published papers to determine the O_3-induced proportion for either the Adams (1998) or Schelegle et al. (2009) studies. As already stated, however, this uncorrected proportion likely underestimates that actual proportion of healthy individuals experiencing O_3-induced FEV_1 decrements in excess of 10%. Therefore, by considering uncorrected responses and those individuals having >10% decrements, 10% is an underestimate of the proportion of healthy individuals that are likely to experience clinically meaningful changes in lung function following exposure for 6.6 hours to 60 ppb O_3 during moderate exercise. Of the studies conducted at 60 ppb, only Kim et al. (2011) reported FEV_1 decrements at 60 ppb to be statistically significant. Although, Brown et al. (2008) found those from Adams (2006a) to be highly statistically significant. Though group mean decrements are biologically small and generally do not attain statistical significance, a considerable fraction of exposed individuals experience clinically meaningful decrements in lung function.

[1] Not assessed by Adams (2006a), uncorrected and O3-induced proportions are from Figures 8-1B and 8-2, respectively, of the 2006 O_3 AQCD (2006b).

Responses in Individuals with Pre-Existing Disease

Individuals with respiratory disease are of primary concern in evaluating the health effects of O_3 because a given change in function is likely to have more impact on a person with preexisting function impairment and reduced reserve.

Possibly due to the age of subjects studied, patients with COPD performing light to moderate exercise do not generally experience statistically significant pulmonary function decrements following 1- and 2-h exposures to ≤ 300 ppb O_3 (Kehrl et al., 1985; Linn et al., 1983; Linn et al., 1982b; Solic et al., 1982). Following a 4-hour exposure to 240 ppb O_3 during exercise, Gong et al. (1997b) found an O_3-induced FEV_1 decrement of 8% in COPD patients which was not statistically different from the decrement of 3% in healthy subjects. Demonstrating the need for control exposures and presumably due to exercise, four of the patients in the Gong et al. (1997b) study had FEV_1 decrements of >14% following both the FA and O_3 exposures. Although the clinical significance is uncertain, small transient decreases in arterial blood oxygen saturation have also been observed in some of these studies.

Based on studies reviewed in the 1996 and 2006 O_3 AQCDs, asthmatic subjects appear to be at least as sensitive to acute effects of O_3 as healthy nonasthmatic subjects. Horstman et al. (1995) found the O_3-induced FEV_1 decrement in mild-to-moderate asthmatics to be significantly larger than in healthy subjects (19% versus 10%, respectively) exposed to 160 ppb O_3 during exercise for 7.6-h exposure. In asthmatics, a significant positive correlation between O_3-induced spirometric responses and baseline lung function was observed, i.e., responses increased with severity of disease. Such differences in pulmonary function between asthmatics and healthy individuals were not found in shorter duration studies. Alexis et al. (2000) and Jörres et al. (1996) reported a tendency for slightly greater FEV_1 decrements in asthmatics than healthy subjects. Several studies reported similar responses between asthmatics and healthy individuals (Scannell et al., 1996; Hiltermann et al., 1995; Basha et al., 1994). The lack of differences in the Hiltermann et al. (1995) and Basha et al. (1994) studies was not surprising, however, given extremely small sample sizes and corresponding lack of statistical power. One study reported a tendency for asthmatics to have smaller O_3-induced FEV_1 decrements than healthy subjects (3% versus 8%, respectively) when exposed to 200 ppb O_3 for 2 hours during exercise (Mudway et al., 2001). However, the asthmatics in that study also tended to be older than the healthy subjects, which could partially explain their lesser response since FEV_1 responses to O_3 diminish with age.

Some, but not all, studies have also reported that asthmatics have a somewhat exaggerated airway inflammatory response to acute O_3 exposure relative to healthy control subjects (Holz et al., 2002; Peden, 2001; Newson et al., 2000; Hiltermann et al.,

1999; Michelson et al., 1999; Vagaggini et al., 1999; Hiltermann et al., 1997; Peden et al., 1997; Scannell et al., 1996; Peden et al., 1995; Basha et al., 1994; McBride et al., 1994). For example, at 18 hours post-O_3 exposure (200 ppb, 4 hours with exercise) and corrected for FA responses, Scannell et al. (1996) found significantly increased neutrophils in 18 asthmatics (12%) compared to 20 healthy subjects (4.5%). This difference in inflammatory response was observed despite no group differences in spirometric responses to O_3.

Vagaggini et al. (2010) exposed mild-to-moderate asthmatics (n=23; 33 ± 11 years) to 300 ppb O_3 for 2 hours with moderate exercise. Although the group mean O_3-induced FEV_1 decrement was only 4%, eight subjects were categorized as "responders" with >10% FEV_1 decrements. There were no baseline differences between responders and nonresponders. At 6 hours post O_3 exposure, sputum neutrophils were significantly increased by 15% relative to FA in responders. The neutrophil increase in responders was also significantly greater than the 0.2% increase in nonresponders. Across all subjects, there was a significant ($r=0.61$, $p = 0.015$) correlation between changes in FEV_1 and changes in sputum neutrophils. Prior studies have reported that inflammatory responses do not appear to be correlated with lung function responses in either asthmatic or healthy subjects (Holz et al., 1999; Balmes et al., 1997; Balmes et al., 1996; Devlin et al., 1991). Interestingly, the nonresponders in the Vagaggini et al. (2010) study experienced a significant O_3-induced 11.3% increase in sputum eosinophils, while responders had an nonsignificant 2.6% decrease. Six of the subjects were NQO1 wild type and GSTM1 *null*, but this genotype was not found to be associated with the changes in lung function or inflammatory responses to O_3.

A few recent studies have evaluated the effects of corticosteroid usage on the response of asthmatics to O_3. Vagaggini et al. (2007) evaluated whether corticosteroid usage would prevent O_3-induced lung function decrements and inflammatory responses in a group of subjects with mild persistent asthma (n=9; 25 ± 7 years). In this study, asthmatics were randomly exposed on four occasions to 270 ppb O_3 or FA for 2 hours with moderate exercise. Exposures were preceded by four days of treatment with prednisone or placebo. Pretreatment with corticosteroids prevented an inflammatory response in induced sputum at 6 hours postexposure. FEV_1 responses were, however, not prevented by corticosteroid treatment and were roughly equivalent to those observed following placebo. Vagaggini et al. (2001) also found budesonide to decrease airway neutrophil influx in asthmatics following O_3 exposure. In contrast, inhalation of corticosteroid budesonide failed to prevent or attenuate O_3-induced responses in healthy subjects as assessed by measurements of lung function, bronchial reactivity and airway inflammation (Nightingale et al., 2000). High doses of inhaled fluticasone and oral prednisolone have

each been reported to reduce inflammatory responses to O_3 in healthy individuals (Holz et al., 2005).

More recently, Stenfors et al. (2010) exposed persistent asthmatics (n=13; aged 33 years) receiving chronic inhaled corticosteroid therapy to 200 ppb O_3 for 2 hours with moderate exercise. An average O_3-induced FEV_1 decrement of 8.4% was observed, whereas, only a 3.0% FEV_1 decrement is predicted for similarly exposed age-matched healthy controls (McDonnell et al., 2007). At 18 hours postexposure, there was a significant O_3-induced increase in bronchioalveolar lavage (BAL) neutrophils, but not eosinophils. Bronchial biopsy also showed a significant O_3-induced increase in mast cells. This study suggests that the protective effect of acute corticosteroid therapy against inflammatory responses to O_3 in asthmatics demonstrated by Vagaggini et al. (2007) may be lost with continued treatment regimes.

Factors Modifying Responsiveness to Ozone

Physical activity increases V_E and therefore the dose of inhaled O_3. Consequently, the intensity of physiological response during and following an acute O_3 exposure will be strongly associated with minute ventilation. Apart from inhaled O_3 dose and related environmental factors (e.g., repeated daily exposures), individual-level factors, such as health status, age, gender, ethnicity, race, smoking habit, diet, and socioeconomic status (SES) have been considered as potential modulators of a physiologic response to such exposures.

Children, adolescents, and young adults (<18 years of age) appear, on average, to have nearly equivalent spirometric responses to O_3, but have greater responses than middle-aged and older adults when exposed to comparable O_3 doses (U.S. EPA, 1996a). Symptomatic responses to O_3 exposure, however, appear to increase with age until early adulthood and then gradually decrease with increasing age (U.S. EPA, 1996a). For example, healthy children (aged 8-11 y) exposed to 120 ppb O_3 (2.5 h; heavy intermittent exercise) experienced similar spirometric responses but lesser symptoms than similarly exposed young healthy adults (McDonnell et al., 1985b). For subjects aged 18-36 years, McDonnell et al. (1999) reported that symptom responses from O_3 exposure also decrease with increasing age. Diminished symptomatic responses in children and the elderly might put these groups at increased risk for continued O_3 exposure, i.e., a lack of symptoms may result in their not avoiding or ceasing exposure. Once lung growth and development reaches the peak (18-20 years of age in females and early twenties in males), pulmonary function, which is at its maximum as well, begins to decline progressively with age as does O_3 sensitivity.

In healthy individuals, the fastest rate of decline in O_3 responsiveness appears between the ages of 18 and 35 years (Passannante et al., 1998; Seal et al., 1996), more so for females then males (Hazucha et al., 2003). During the middle age period (35-55 years), O_3 sensitivity continues to decline but at a much lower rate. Beyond this age (>55 years), acute O_3 exposure elicits minimal spirometric changes. Whether the same age-dependent pattern of O_3 sensitivity decline also holds for nonspirometric pulmonary function, airway reactivity or inflammatory endpoints has not been determined. Although there is considerable evidence that spirometric and symptomatic responses to O_3 exposure decrease with age beyond young adulthood, this evidence comes from cross-sectional analyses and has not been confirmed by longitudinal studies of the same individuals.

Several studies have suggested that physiological differences between sexes may predispose females to a greater susceptibility to O_3. In females, lower plasma and nasal lavage fluid (NLF) levels of uric acid (the most prevalent antioxidant), the initial defense mechanism of O_3 neutralization in airway surface liquid, may be a contributing factor (Housley et al., 1996). Consequently, reduced absorption of O_3 in the upper airways may promote its deeper penetration. Dosimetric measurements have shown that the absorption distribution of O_3 is independent of gender when absorption is normalized to anatomical dead space (Bush et al., 1996). Thus, a gender-related differential removal of O_3 by uric acid seems to be minimal. In general, the physiologic response of young healthy females to O_3 exposure appears comparable to the response of young males (Hazucha et al., 2003). Several studies have investigated the effects of the menstrual cycle on responses to O_3 in healthy young women. In a study of 9 women exposed during exercise to 300 ppb O_3 for an hour, Fox et al. (1993) found lung function responses to O_3 significantly enhanced during the follicular phase relative to the luteal phase. However, Weinmann et al. (1995a) found no difference in responses between the follicular and luteal phases as well as no significant differences between 12 males and 12 females exposed during exercise to 350 ppb O_3 for 2.15 h. Seal et al. (1996) also reported no effect of menstrual cycle phase in their analysis of responses of 150 women (n=25 per exposure group; 0, 120, 240, 300, and 400 ppb O_3). Seal et al. (1996) conceded that the methods used by Fox et al. (1993) more precisely defined menstrual cycle phase.

Only two controlled human exposure studies have assessed differences in lung function responses between races. Seal et al. (1993) compared lung function responses of whites (93 M, 94 F) and blacks (undefined ancestry; 92 M, 93 F) exposed to a range of O_3 concentrations (0-400 ppb). The main effects of gender-race group and O_3 concentration were statistically significant (both at $p < 0.001$), although the interaction between gender-race group and O_3 concentration was not significant ($p = 0.13$). These findings indicate some overall difference between the gender-race groups that is independent of O_3 concentration, i.e., the concentration-response curves for the four gender-race groups are

parallel. In a multiple comparison procedure on data collapsed across all O_3 concentrations for each gender-race group, both black men and black women had significantly larger decrements in FEV_1 than did white men. The authors noted that the O_3 dose per unit of lung tissue would be greater in blacks and females than whites and males, respectively. That this difference in tissue dose might have affected responses to O_3 cannot be ruled out. The college students recruited for the Seal et al. (1993) study are probably from better educated and SES advantaged families, thus reducing potential influence of these variables on results. In a follow-up analysis, Seal et al. (1996) reported that, of three SES categories, individuals in the middle SES category showed greater concentration-dependent decline in percent-predicted FEV_1 (4-5% at 400 ppb O_3) than low and high SES groups. The authors did not have an "immediately clear" explanation for this finding.

More recently, Que et al. assessed pulmonary responses in blacks of African American ancestry (22 M, 24 F) and Caucasians (55 M, 28 F) exposed to 220 ppb O_3 for 2.25 h (alternating 15 min periods of rest and brisk treadmill walking). On average, the black males experienced a 16.8% decrement in FEV_1 following O_3 exposure which was significantly larger than mean FEV_1 decrements of 6.2, 7.9, and 8.3% in black females and Caucasian males and Caucasian females, respectively. In the study by Seal et al. (1993), there was potential that the increased FEV_1 decrements in blacks relative to whites were due to increased O_3 tissue doses since exercise rates were normalized to BSA. Differences in O_3 tissue doses between the races should not have occurred in the Que et al. study, however, since exercise rates were normalized to lung volume (viz., 6-8 times FVC). Thus, the increased mean FEV_1 decrement in black males is not likely attributable to systematically larger O_3 tissue doses in blacks relative to whites.

Smokers are less responsive to O_3 than nonsmokers. Spirometric and plethysmographic pulmonary function decline, nonspecific airway hyperreactivity, and inflammatory response of smokers to O_3 were all weaker than data reported for nonsmokers. Although all of these responses are intrinsically related, the functional association between them, as in nonsmokers, has been weak. Similarly, the time course of development and recovery of these effects as well their reproducibility was not different from nonsmokers. Chronic airway inflammation with desensitization of bronchial nerve endings and an increased production of mucus may plausibly explain the reduced responses to O_3 in smokers relative to nonsmokers (Frampton et al., 1997b; Torres et al., 1997).

The first line of defense against oxidative stress is antioxidants-rich ELF which scavenges free radicals and limit lipid peroxidation. Exposure to O_3 depletes the antioxidant level in nasal ELF probably due to scrubbing of O_3 (Mudway et al., 1999a), however, the concentration and the activity of antioxidant enzymes either in ELF or

plasma do not appear to be related to O_3 responsiveness (Samet et al., 2001; Avissar et al., 2000; Blomberg et al., 1999). Carefully controlled studies of dietary antioxidant supplementation have demonstrated some protective effects of α-tocopherol and ascorbate on spirometric lung function from O_3 but not on the intensity of subjective symptoms and inflammatory response including cell recruitment, activation and a release of mediators (Samet et al., 2001; Trenga et al., 2001). Dietary antioxidants have also been reported to attenuate O_3-induced bronchial hyperresponsiveness in asthmatics (Trenga et al., 2001).

A number of studies(e.g., Romieu et al., 2004a; David et al., 2003; Corradi et al., 2002; Bergamaschi et al., 2001) have reported that genetic polymorphisms of antioxidant enzymes may modulate pulmonary function and inflammatory response to O_3 challenge. It appears that healthy carriers of NQO1 wild type in combination with GSTM1 null genotype are more responsive to O_3. Adults with GSTM1 null only genotype did not show O_3 hyperresponsiveness. In contrast, asthmatic children with GSTM1 null genotype (Romieu et al., 2004a) were reported to be more responsive to O_3. However, in a controlled exposure of mild-to-moderate asthmatics (n=23; 33 ± 11 years) to 300 ppb O_3 for 2 hours with moderate exercise, Vagaggini et al. (2010) found that six of the subjects had a NQO1*wt* and GSTM1 *null*, but this genotype was not associated with the changes in lung function or inflammatory responses to O_3.

Kim et al. (2011) also recently reported that GSTM1 genotype was not predictive of FEV_1 responses in young healthy adults (32 F, 27 M; 25.0 ± 0.5 year) that were roughly half GSTM1-null and half GSTM1-sufficient. Sputum neutrophil levels, measured in a subset of the subjects (13 F, 11 M), were also not significantly associated with GSTM1 genotype.

In a study of healthy volunteers with GSTM1 sufficient (n=19; 24 ± 3) and GSTM1 null (n=16; 25 ± 5) genotypes exposed to 400 ppb O_3 for 2 hours with exercise, Alexis et al. (2009) found that inflammatory responses but not lung function responses to O_3 were dependent on genotype. At 4 hours post O_3 exposure, both GSTM1 genotype groups had significant increases in sputum neutrophils with a tendency for a greater increase in GSTM1 sufficient than nulls. At 24 h postexposure, sputum neutrophils had returned to baseline levels in the GSTM1 sufficient individuals. In the GSTM1 null subjects, however, sputum neutrophil levels increased from 4 h to 24 h and were significantly greater than both baseline levels and levels at 24 h in the GSTM1 sufficient individuals. Since there was no FA control in the Alexis et al. (2009) study, effects of the exposure other than O_3 itself cannot be ruled out. In general, the findings between studies are inconsistent. Additional studies that include control exposures are needed to clarify the influence of genetic polymorphisms on O_3 responsiveness.

In a retrospective analysis of data from 541 healthy, nonsmoking, white males between the ages of 18-35 years from 15 studies conducted at the U.S. EPA Human Studies Facility in Chapel Hill, North Carolina, McDonnell et al. (2010) found that increased body mass index (BMI) was associated with enhanced FEV_1 responses. The BMI effect was of the same order of magnitude but in the opposite direction of the age effect where by FEV_1 responses diminish with increasing age. In a similar retrospective analysis, Bennett et al. (2007) found enhanced FEV_1 decrements following O_3 exposure with increasing BMI in a group of 75 healthy, nonsmoking, women (age 24 ± 4 years; BMI range 15.7 to 33.4), but not 122 healthy, nonsmoking, men (age 25 ± 4 years; BMI range 19.1 to 32.9). In the women, greater O_3-induced FEV_1 decrements were seen in overweight (BMI >25) than in normal weight (BMI from 18.5 to 25), and in normal weight than in underweight (BMI <18.5) (P trend ≤ 0.022). Together, these results indicate that higher BMI may be a risk factor for pulmonary effects associated with O_3 exposure.

Repeated Ozone Exposure Effects

Based on studies reviewed in previous O_3 AQCDs, several conclusions can be drawn about repeated 1to 2 h O_3 exposures. Repeated exposures to O_3 causes enhanced (i.e., greater decrements) FVC and FEV_1 responses on the second day of exposure. The enhanced response appears to depend to some extent on the magnitude of the initial response (Horvath et al., 1981). Small responses to the first O_3 exposure are less likely to result in an enhanced response on the second day of O_3 exposure (Folinsbee et al., 1994). With continued daily exposures (i.e., beyond the second day) there is a substantial (or even total) attenuation of pulmonary function responses, typically on the third to fifth days of repeated O_3 exposure. This attenuation of responses is lost in 1 week (Kulle et al., 1982; Linn et al., 1982a) or perhaps 2 weeks (Horvath et al., 1981) without O_3 exposure. In temporal conjunction with pulmonary function changes, symptoms induced by O_3 (e.g., cough, pain on deep inspiration, and chest discomfort), are also increased on the second exposure day and attenuated with repeated O_3 exposure thereafter (Folinsbee et al., 1998; Foxcroft and Adams, 1986; Linn et al., 1982a; Folinsbee et al., 1980). In longer-duration (4-6.6 hours), lower-concentration studies that do not cause an enhanced second-day response, the attenuation of response to O_3 appears to proceed more rapidly (Folinsbee et al., 1994).

Consistent with other investigators, Frank et al. (2001) found FVC and FEV_1 decrements to be significantly attenuated following four consecutive days of exposure to O_3 (250 ppb, 2 h). However, the effects of O_3 on the small airways (assessed by a combined index of isovolumetric FEF_{25-75}, $Vmax_{50}$ and $Vmax_{75}$) showed a persistent functional reduction from Day 2 through Day 4. Notably, in contrast to FVC and FEV_1 which exhibited a

recovery of function between days, there was a persistent effect of O_3 on small airways function such that the baseline function on Day 2 through Day 4 was depressed relative to Day 1. Frank et al. (2001) also found neutrophil (PMN) numbers in BAL remained significantly higher following O_3 (24 h after last O_3 exposure) compared to FA. Inflammatory markers from bronchioalveolar lavage fluid (BALF) following 4 consecutive days of both 2-h (Devlin et al., 1997) and 4-h (Jorres et al., 2000; Christian et al., 1998) exposures have indicated ongoing cellular damage irrespective of the attenuation of some cellular inflammatory responses of the airways, lung function and symptoms response. These data suggest that the persistent small airways dysfunction assessed by Frank et al. (2001) is likely induced by both neurogenic and inflammatory mediators, since the density of bronchial C-fibers is much lower in the small than large airways.

Summary of Controlled Human Exposure Studies on Lung Function

Responses in humans exposed to ambient O_3 concentrations include: decreased inspiratory capacity; mild bronchoconstriction; rapid, shallow breathing pattern during exercise; and symptoms of cough and pain on deep inspiration (U.S. EPA, 2006b, 1996a). Discussed in subsequent Sections 6.2.2.1 and 6.2.3.1, exposure to O_3 also results in airway hyperresponsiveness, pulmonary inflammation, immune system activation, and epithelial injury (Que et al.; Mudway and Kelly, 2004a). Reflex inhibition of inspiration results in a decrease in forced vital capacity and, in combination with mild bronchoconstriction, contributes to a decrease in the FEV_1. Healthy young adults exposed to O_3 concentrations $\geq$ 60 ppb develop statistically significant reversible, transient decrements in lung function if minute ventilation or duration of exposure is increased sufficiently. With repeated O_3 exposures over several days, FEV_1 and symptom responses become attenuated in both healthy individuals and asthmatics, but this tolerance is lost after about a week without exposure (Gong et al., 1997a; Folinsbee et al., 1994; Kulle et al., 1982). In contrast to the attention of FEV_1 responses, there appear to be persistent O_3 effects on small airways function as well as ongoing cellular damage during repeated exposures.

There is a large degree of intersubject variability in lung function decrements (McDonnell, 1996). However, these lung function responses tend to be reproducible within a given individual over a period of several months indicating differences in the intrinsic responsiveness of individuals (Hazucha et al., 2003; McDonnell et al., 1985a). In healthy young adults, O_3-induced decrements in FEV_1 do not appear to depend on gender (Hazucha et al., 2003), body surface area or height (McDonnell et al., 1997), lung size or baseline FVC (Messineo and Adams, 1990). There is limited evidence that blacks may experience greater O_3-induced decrements in FEV_1 than age-matched whites (Que et al.;

Seal et al., 1993). Healthy children experience similar spirometric responses but lesser symptoms from O_3 exposure relative to young adults (McDonnell et al., 1985b). On average, spirometric and symptom responses to O_3 exposure appear to decline with increasing age beyond about 18 years of age (McDonnell et al., 1999; Seal et al., 1996). There is a tendency for slightly increased spirometric responses in mild asthmatics and allergic rhinitics relative to healthy young adults (Jorres et al., 1996). Spirometric responses in asthmatics appear to be affected by baseline lung function, i.e., responses increase with disease severity (Horstman et al., 1995).

Available information on recovery of lung function following O_3 exposure indicates that an initial phase of recovery in healthy individuals proceeds relatively rapidly, with acute spirometric and symptom responses resolving within about 2 to 4 h (Folinsbee and Hazucha, 1989). Small residual lung function effects are almost completely resolved within 24 h. One day following O_3 exposure, persisting effects on the small airways assessed by decrements in FEF_{25-75} and altered ventilation distribution have been reported (Frank et al., 2001; Foster et al., 1997).

6.2.1.2 Epidemiology

The O_3-induced lung function decrements consistently demonstrated in controlled human exposure studies (Section 6.2.1.1) provide biological plausibility for the epidemiologic evidence presented in the 1996 and 2006 O_3 AQCDs, in which short-term ambient O_3 exposure was consistently associated with lung function decrements in diverse populations (U.S. EPA, 2006b, 1996a). Coherence between the two disciplines was found not only for effects observed in groups with higher expected personal O_3 exposures and higher exertion levels, including children attending summer camps and adults exercising or working outdoors, but also for effects observed in children and individuals with pre-existing respiratory disease such as asthma (U.S. EPA, 2006b, 1996a). Recent epidemiologic studies focused more on children with asthma rather than on groups with increased outdoor exposures or other healthy populations. Whereas a majority of recent studies conducted in children with asthma indicated decreases in lung function in association with increases in ambient O_3 exposure, recent studies in adults with asthma and individuals without asthma found both O_3-associated decreases and increases in lung function. Recent studies also provided additional data to assess whether particular lags of O_3 exposure were more strongly associated with decrements in lung function; whether O_3 associations were confounded by copollutant exposures; and whether risk was affected by factors such as corticosteroid (CS) use, genetic polymorphisms, elevated BMI, and diet.

Table 6-1 Mean and upper percentile concentrations of ozone in epidemiologic studies examining lung function in populations with increased outdoor exposures

Study	Location	Years/Season	O_3 Averaging Time	Mean/Median Concentration (ppb)	Upper Percentile Concentrations (ppb)
Korrick et al. (1998)	Mt. Washington, NH	1991, 1992 Warm season	Hike-time avg (2-12 h)	40	Max: 74
Thurston et al. (1997)	Connecticut River Valley, CT	1991-1993 Warm season	1-h max	83.6	Max: 160
Spektor et al. (1988b)	Tuxedo, NY	1985 Warm season	1-h avg	NR	Max: 124
Spektor et al. (1988a)	Fairview Lake, NJ	1984 Warm season	1-h avg[a]	53	Max (1-h max): 113
Spektor and Lippmann (1991)	Fairview Lake, NJ	1988 Warm season	1-h avg[a]	69	Max (1-h max): 137
Berry et al. (1991)	Hamilton, NJ	July 1988	1-h max	NR	Max: 204
Neas et al. (1999)	Philadelphia, PA	1993 Warm season	12-h avg (9:00 a.m.9:00 p.m.)	57.5 (Camp 1) 55.9 (Camp 2)	Max (Camp 1): 106
Girardot et al. (2006)	Great Smoky Mountain NP, TN	2002-2003 Warm season	Hike-time avg (2-9 h)	48.1[b]	Max: 74.2[b]
Selwyn et al. (1985)	Houston, TX	1981 Warm season	15-min max	47	Max: 135
Thaller et al. (2008)	Galveston, TX	2002-2004 Warm season	1-h max	35 (median)	Max: 118
Higgins et al. (1990)	San Bernardino, CA	1987 Warm season	1-h avg[a]	123	Max: 245
Avol et al. (1990)	Idyllwild, CA	1988 Warm season	1-h avg[a]	94	Max: 161
Burnett et al. (1990)	Lake Couchiching, Ontario, CA	1983 Warm season	1-h avg[a]	59	Max: 95
Raizenne et al. (1989)	Lake Erie, Ontario, CA	1986 Warm season	1-h avg[a]	71	Max (1-h max): 143
Brauer et al. (1996)	British Columbia, Canada	1993 Warm season	1-h max	40	Max: 84
Castillejos et al. (1995)	Mexico City, Mexico	June 1990-October 1991	1-h max	179	Max: 365
Romieu et al. (1998a)	Mexico City, Mexico	March-August 1996	Work shift avg (6-12 h)	67.3	95th: 105.8
Nickmilder et al. (2007)	Southern Belgium	2002 Warm season	1-h max 8-h max	NR	Max (across 6 camps): 24.5-112.7[c] Max (across 6 camps): 18.9-81.1[c]
Brunekreef et al. (1994)	Netherlands	1981 Warm season	Exercise-time avg (10-145 min)	42.8[c]	Max: 99.5[c]
Hoek et al. (1993)	Wageningen, Netherlands	1989 Warm season	1-h max	NR	Max: 122[c]
Braun-Fahrlander et al. (1994)	Southern Switzerland	1989 Warm season	30-min avg	NR	Max: 80[c]
Hoppe et al. (1995); Hoppe et al. (2003)	Munich, Germany	1992 Warm season	30-min max (1:00 p.m.-4:00 p.m.)	High O_3 days: 65.9 Control O_3 days: 27.2	Max (high O_3 days): 86
Chan et al. (2005)	Taichung City, Taiwan	2001 Cold season	8-h avg (9:00 a.m.-5:00 p.m.)	35.6	Max: 65.1

Max = Maximum; NR = not reported
[a]1-h avg, preceding lung function measurement.
[b]Individual-level exposure estimates were derived based on time-activity diary data.
[c]Concentrations were converted from µg/m^3 to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

Populations with Increased Outdoor Exposures

Few epidemiologic studies characterizing acute O_3-related respiratory morbidity have accounted for time spent outdoors, which may be an important determinant of interindividual variability in personal O_3 exposure. Among epidemiologic studies, studies of individuals engaged in outdoor recreation, exercise, or work are more comparable to controlled exposure studies because of improved estimates O_3 exposures, measurement of lung function before and after discrete periods of outdoor activity, and examination of O_3 effects during exertion when the dose of O_3 reaching the lungs may be higher because of higher ventilation and inhalation of larger volumes of air. Characteristics and ambient O_3 concentration data from epidemiologic studies of populations with increased outdoor exposures are presented in Table 6-1. Similar to findings from controlled human exposure studies, the collective body of epidemiologic evidence clearly demonstrates decrements in lung function in association with O_3 exposures during periods of outdoor activity or exercise of varying intensity and duration (15 minutes to 12 hours) (Figures 6-3 to 6-5 and Tables 6-2 to 6-4).

Children Attending Summer Camps

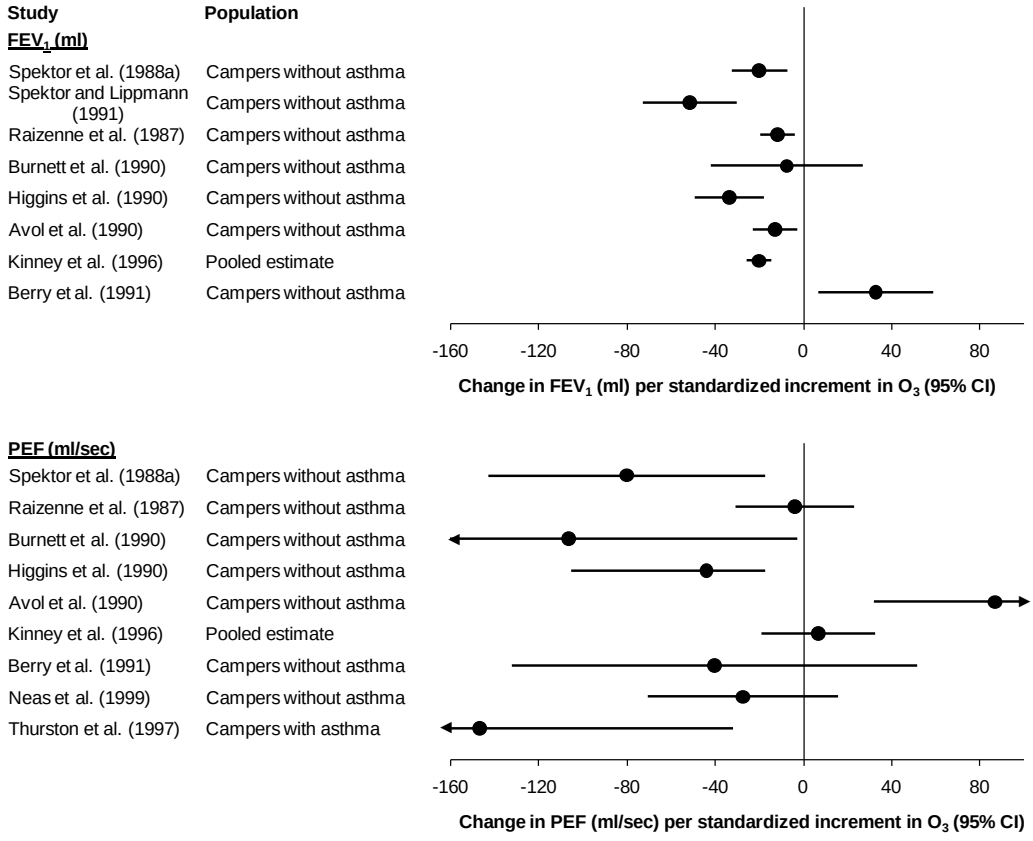
Studies of children attending summer camps, most of which were discussed in the 1996 O_3 AQCD, have provided important understanding of the impact of ambient O_3 exposure on respiratory effects in young, healthy children. These studies were noted for their on-site measurement of ambient O_3 and daily assessment of lung function by trained staff over 1- to 2-week periods (Thurston et al., 1997; Berry et al., 1991; Spektor and Lippmann, 1991; Avol et al., 1990; Burnett et al., 1990; Higgins et al., 1990; Raizenne et al., 1989; Spektor et al., 1988a; Raizenne et al., 1987).

In groups mostly comprising healthy children (ages 7-17 years), decrements in FEV_1 were found to be associated consistently with ambient O_3 exposures averaged over the 1-8 hours preceding lung function measurement (Figure 6-3 and Table 6-2). Kinney et al. (1996) corroborated this association in a reanalysis combining 5367 lung function measurements collected from 616 healthy children from six studies (Spektor and Lippmann, 1991; Avol et al., 1990; Burnett et al., 1990; Higgins et al., 1990; Spektor et al., 1988a; Raizenne et al., 1987). Based on uniform statistical methods, a 40-ppb increase in concurrent-hour O_3 exposure was associated with a -20 ml (95% CI: -25, -14) change in afternoon FEV_1[1] (Kinney et al., 1996). In these studies conducted in locations

[1] To facilitate comparisons among epidemiologic studies, for all health endpoints in Chapter 6, effect estimates are presented in terms of a standard increment in ambient O_3 concentration, one for each of the three commonly examined O_3 averaging times (1-h max, 8-h max, and 24-h average). These standard increments are 40 ppb, 30 ppb, and 20 ppb for 1-h max, 8-h max, and 24-h avg O_3, respectively, and are based on annual mean to 95th percentile differences that are representative of measurements from nationwide O_3 monitors in U.S. Metropolitan Statistical Areas as described in detail in Section 7.1.3.2 of the 2006 O_3 AQCD (U.S. EPA, 2006b).

across the Northeast U.S. and Canada and California (Table 6-1) with varying pollutant mix, a wide range in effect estimates was found. Study-specific effect estimates ranged between a 0.76 and 48 ml decrease or a 0.3% to 2.2% decrease in study mean FEV_1.

Associations between ambient O_3 exposure and peak expiratory flow (PEF) in camp studies were more variable than were those with FEV_1, as indicated by the wider range in effect estimates and wider 95% CIs (Figure 6-3 and Table 6-2). Nonetheless, most effect estimates indicated decreases in PEF in association with ambient O_3 exposure. The largest effect (mean 2.8% decline per 40-ppb increase in 1-h max O_3) was estimated in a group of campers with asthma (Thurston et al., 1997). In this study, O_3 also was associated with increases in chest symptoms and bronchodilator use, suggesting that the observed decreases in PEF may have been indicative of clinically significant effects.



Effect estimates are from single-pollutant models and are standardized to a 40-ppb increase for 1-h avg or 1-h max ozone exposures and a 30-ppb increase for 12-h avg ozone exposures.

Figure 6-3 Changes in FEV_1 (ml) or PEF (ml/sec) in association with ambient ozone exposure in studies of children attending summer camp.

Table 6-2 Additional characteristics and quantitative data for studies represented in Figure 6-3

Study	Location	Population	Standardized percent change (95% CI)[a]	Standardized effect estimate (95% CI)[a]
FEV_1				**(ml)**
Spektor et al. (1988a)	Fairview Lake, NJ	Campers without asthma	-0.93 (-1.5, -0.35)	-20.0 (-32.5, -7.5)
Spektor and Lippmann (1991)	Fairview Lake, NJ	Campers without asthma	-2.2 (-3.1, -1.3)	-51. 6 (-72.8, -30.4)
Raizenne et al. (1989)	Lake Erie, Ontario, Canada	Campers without asthma	-0.48 (-0.80, -0.16)	-11.6 (-19.4, -3.8)
Burnett et al. (1990)	Lake Couchiching, Ontario, Canada	Campers without asthma	-0.32 (-1.8, 1.2)	-7.6 (-42.1, 26.9)
Higgins et al. (1990)	San Bernardino, CA	Campers without asthma	-1.6 (-2.4, -0.87)	-33.6 (-49.3, -17.9)
Avol et al. (1991)	Pine Springs, CA	Campers without asthma	-0.58 (-1.1, -0.12)	-12.8 (-23.0, -2.6)
Kinney et al. (1996)	Pooled analysis	Campers without asthma	-0.90 (-1.2, -0.65)	-20.0 (-25.5, -14.5)
Berry et al. (1991)	Hamilton, NJ	Campers without asthma	Data not available	32.8 (6.9, 58.7)
PEF				**(ml/sec)**
Spektor et al. (1988a)	Lake Fairview, NJ	Campers without asthma	-1.8 (-3.3, -0.40)	-80.0 (-142.7, -17.3)
Raizenne et al. (1989)	Lake Erie, Ontario, Canada	Campers without asthma	-0.07 (-0.56, 0.41)	-4.0 (-30.7, 22.7)
Burnett et al. (1990)	Lake Couchiching, Ontario, Canada	Campers without asthma	-1.9 (-3.8, -0.05)	-106.4 (-209.9, -2.9)
Higgins et al. (1990)	San Bernardino, CA	Campers without asthma	-0.87 (-2.1, -0.34)	-44.0 (-105, -17.2)
Avol et al. (1991)	Pine Springs, CA	Campers without asthma	1.9 (0.71, 3.1)	86.8 (31.9, 142)
Kinney et al. (1996)	Pooled analysis	Campers without asthma	0.31 (-0.88, 1.5)	6.8 (-19.1, 32.7)
Berry et al. (1991)	Hamilton, NJ	Campers without asthma	Data not available	-40.4 (-132.1, 51.3)
Neas et al. (1999)	Philadelphia, PA	Campers without asthma	-0.58 (-1.5, 0.33)	-27.5 (-70.8, 15.8)
Thurston et al. (1997)	CT River Valley, CT	Campers with asthma	-2.8 (-4.9, -0.59)	-146.7 (-261.7, -31.7)

[a]All effect estimates are standardized to a 40-ppb increase in 1-h avg or 1-h max O_3, except that from Neas et al. (1999), which is standardized to a 30-ppb increase in 12-h avg (9:00 a.m.-9:00 p.m.) O_3.

As has been observed in controlled human exposure studies, FEV_1 and PEF responses to ambient O_3 exposure varied among individual campers. Based on separate regression analyses of data from individual subjects, O_3 exposure was associated with a wide range of changes in lung function across subjects (Berry et al., 1991; Higgins et al., 1990; Spektor et al., 1988a). For example, in the study of children attending camp in Fairview Lake, NJ, 36% of subjects had statistically significant O_3-associated decreases in FEV_1, and the upper decile of response was a 6.3% decrease in FEV_1 per a 40-pbb increase in 1-h avg O_3 (Spektor et al., 1988a).

In contrast with these previous studies, a recent cross-sectional study of children attending six different summer camps in Belgium did not find an association between ambient O_3 exposure and lung function. The ambient O_3 concentrations in this recent study was in the range of those in previous studies (Table 6-1); however, this recent study

differed from previous studies in that each subject was examined only on one day, and investigators performed between-camp comparisons rather than within-subject comparisons. Camps with higher daily 1-h max O_3 concentrations did not consistently have larger decreases in mean intraday FEV_1 or FEV_1/FVC (Nickmilder et al., 2007).

Populations Exercising Outdoors

Similar to camp studies, studies of individuals exercising outdoors were noted for the serial examination of subjects over days with a wide range in ambient O_3 concentrations and onsite assessment of O_3 exposures during discrete periods of outdoor exercise. These studies collectively show that mean O_3 exposures ranging from 40 to 66 ppb during exercise of variable duration and intensity are associated with small (< 1 to 4% per standardized increment in O_3[1]) decreases in lung function in adults (Figure 6-4 and Table 6-3). Similar observations were made in children exercising outdoors (Table 6-3). For both adults and children, evidence was provided largely by older studies that were reviewed in the 1996 and 2006 O_3 AQCDs.

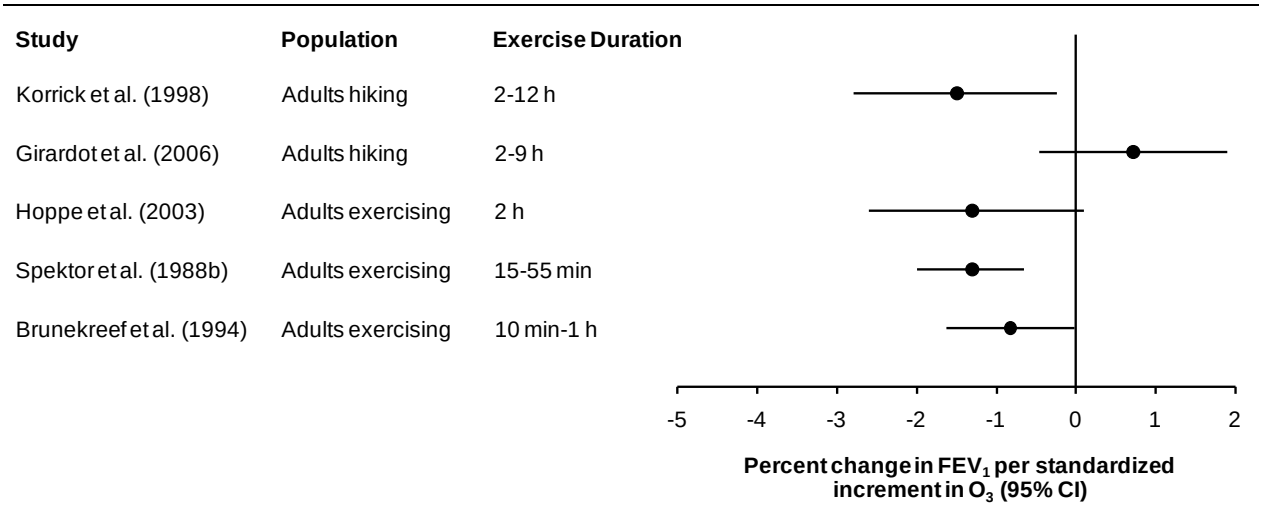


Figure 6-4 Percent change in FEV_1 in association with ambient ozone exposures of adults exercising outdoors. Studies generally are organized in order of decreasing exercise duration. Effect estimates are from single-pollutant models and are standardized to a 40-ppb increase for ozone exposures averaged over 15 minutes to 1 hour and a 30-ppb increase for ozone exposures averaged over 3 to 8 hours.

[1] Effect estimates were standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max, and 24-h avg O_3.

Table 6-3 Additional characteristics and quantitative data for studies represented in Figure 6-4 and results from studies in children exercising outdoors

Study	Location	Population	Exercise duration	O_3 Averaging Time	Parameter	Standardized percent change (95% CI)[a]
Studies of adults						
Korrick et al. (1998)	Mt. Washington, NH	Adult day hikers	2-12 h	Hike duration	FEV_1	-1.5 (-2.8, -0.24)
Girardot et al. (2006)	Great Smoky Mt, TN	Adult day hikers	2-9 h	Hike duration	FEV_1	0.72 (-0.46, 1.90)
Hoppe et al. (2003)	Munich, Germany	Adults exercising	2 h	30-min max (1:00 p.m.-4:00 p.m.)	FEV_1 PEF	-1.3 (-2.6, 0.13) -2.8 (-5.9, 0.44)
Selwyn et al. (1985)[b]	Houston, TX	Adults exercising	NR	15-min max	FEV_1	-16 ml (-31.1, -0.87)[c]
Spektor et al. (1988a)[b]	Tuxedo, NY	Adults exercising	15-55 min	30-min avg	FEV_1	-1.31 (-2.0, -0.65)
Brunekreef et al. (1994)	Netherlands	Adults exercising	10 min-1 h	Exercise duration	FEV_1	-0.82 (-1.6, -0.02)
Studies of children not included in Figure 6-4						
Braun-Fahrlander et al. (1994)	Switzerland	Children exercising	10 min	30-min avg	PEF	-3.8 (-6.9, -0.96)
Castillejos et al. (1995)	Mexico City, Mexico	Children exercising	15 min (2 periods)	1-h avg	FEV_1	-0.48 (-0.72, -0.24)
Hoek et al. (1993)	Wageningen, Netherlands	Children exercising	1 h	1-h avg	PEF	-2.2 (-4.9, 0.55)

NR = Not reported.

[a]Effect estimates are standardized to a 40-ppb increase for O_3 exposures averaged over 15 min to 1 h and a 30-ppb increase for O_3 exposures averaged over 3 to 8 h.

[b]Results not included in the figure because data were not provided to calculate percent change in lung function.

[c]The 95% CI was constructed using a standard error that was estimated from the p-value

Two studies of adult day-hikers of similar design and ambient O_3 concentrations produced contrasting results (Girardot et al., 2006; Korrick et al., 1998). These studies mostly comprised white, healthy adults and examined changes in lung function associated with O_3 exposures during multihour (2-12 h) periods of outdoor exercise. Although analyses of day-hikers were based on a one-time assessment of lung function, they included much larger sample sizes compared with panel studies of individuals exercising outdoors. Among 530 hikers on Mt. Washington, NH, Korrick et al. (1998) reported posthike declines in FEV_1 and FVC of approximately 0.7-1.5% per a 30-ppb increase in 2- to 12-h avg O_3. In contrast, among 354 hikers in Great Smoky Mountains National Park, TN, Girardot et al. (2006) more recently found that O_3 exposure was associated with posthike increases in many of the same lung function indices. Several differences in study characteristics were used by Girardot et al. (2006) to explain discrepant results, including their use of a larger number of less-well trained technicians, shorter mean duration of hike (5 hours versus 8 hours), and older mean age of their subjects.

As was observed in camp studies, the magnitudes of O_3-associated decreases in lung function varied among individual subjects. Korrick et al. (1998) found larger O_3-

associated decreases in FEV_1 among hikers who were male, had history of asthma or wheeze, were never smokers, and hiked greater than 8 hours. Additionally, O_3 was associated with an increased odds of a greater than 10% decline in $FEF_{25-75\%}$ among hikers (OR: 2.3 [95% CI: 1.2, 6.7] per 30-ppb increase in 2- to 12-h avg O_3) (Korrick et al., 1998). Likewise, Hoppe et al. (2003) found that on days with 30-min max (1:00 p.m.-4:00 p.m.) ambient O_3 concentrations above 50 ppb, 14% of athletes had at least a 20% decrease in lung function or 10% increase in airway resistance.

Outdoor Workers

The 2006 O_3 AQCD indicated that ambient O_3 exposure was associated consistently with decrements in lung function among outdoor workers (U.S. EPA, 2006b), and recent studies produced similar findings (Thaller et al., 2008; Chan and Wu, 2005) (Figure 6-5 and Table 6-4). Although most of these studies assessed O_3 exposures using central site measurements, they were noteworthy for the long periods of time spent outdoors (6-14 hours across studies). Further, associations between O_3 exposure and lung function decrements were found for time periods during which ambient O_3 concentrations did not exceed 80 ppb (Table 6-1) (Chan and Wu, 2005; Brauer et al., 1996; Hoppe et al., 1995). In particular, Many studies of outdoor workers found that in addition to same-day exposures, O_3 exposures lagged 1 or 2 days (Chan and Wu, 2005; Brauer et al., 1996) or exposures averaged over 2 days (Romieu et al., 1998a) were associated with equal or larger decrements in lung function (Figure 6-5 and Table 6-4).

Similar to other populations with increased outdoor exposure, the magnitudes of O_3-associated lung function decrements in outdoor workers were small. Per standardized increment in O_3 concentration[1], decreases in lung function ranged between less than 1% and 3.6%. The magnitude of decrease was not found to depend strongly on duration of outdoor work or ambient O_3 concentration. The largest decrease (6.4% per 40-ppb increase in 1-h max O_3) was observed among berry pickers in British Columbia who were exposed to relatively low ambient O_3 concentrations (work shift mean: 26.0 ppb [SD: 11.8]) but had longer periods of outdoor work (8-14 hours) (Brauer et al., 1996) (Figure 6-5 and Table 6-4). However, a much smaller O_3-associated decrease in FEV_1 was found among street workers in Mexico City who were exposed to higher O_3 concentrations (work shift mean: 67.3 ppb [SD: 24]) during a similar duration of outdoor work. Among studies of outdoor workers, the smallest magnitude of decrease (0.4% decrease (95% CI: -0.8, 0) in afternoon FEV_1/FVC per 40-ppb increase in 1-h max O_3) was observed among lifeguards in Galveston, TX (Thaller et al., 2008) whose outdoor work periods were shorter than those of the berry pickers but who were exposed to a similar range of

[1]Effect estimates were standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max, and 24-h avg O_3.

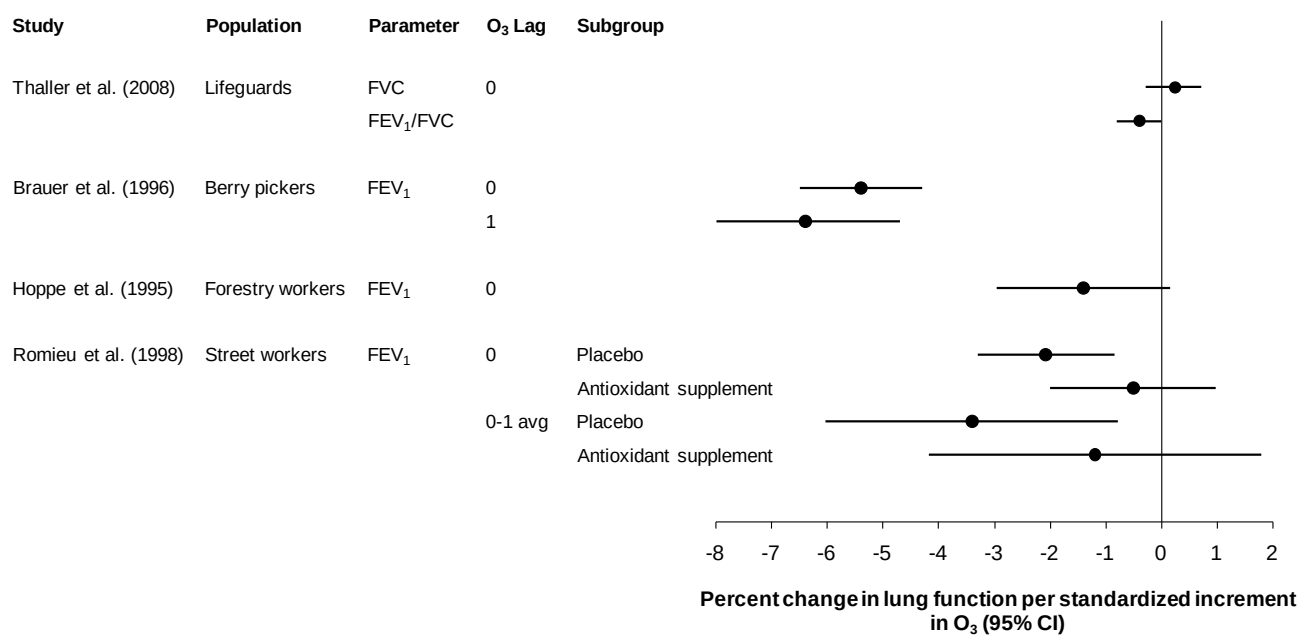


Figure 6-5 Percent change in lung function in association with ambient ozone exposures among outdoor workers. Studies generally are organized in order of increasing mean ambient ozone concentration. Effect estimates are from single-pollutant models and are standardized to a 40-ppb increase for 30-min or 1-h max ozone exposures.

Table 6-4 Additional characteristics and quantitative data for studies represented in Figure 6-5

Study	Location	Population	Parameter	Duration of outdoor work	O_3 Averaging Time	O_3 Lag	Subgroup	Standardized percent change (95% CI)[a]
Thaller et al. (2008)	Galveston, TX	Lifeguards	FVC	6-8 h	1-h max	0		0.24 (-0.28, 0.72)
			FEV_1/FVC					-0.40 (-0.80, 0)
Brauer et al. (1996)	British Columbia, Canada	Berry pickers	FEV_1	8-14 h	1-h max	0		-5.4 (-6.5, -4.3)
						1		-6.4 (-8.0, -4.7)
Hoppe et al. (1995)	Munich, Germany	Forestry workers	FEV_1	NR	30-min max (1:00 p.m.-4:00 p.m.)	0		-1.4 (-3.0, 0.16)
Romieu et al. (1998a)	Mexico City, Mexico	Male street workers	FEV_1	Mean (SD): 9 h (1)	1-h max	0	Placebo	-2.1 (-3.3, -0.85)
						0-1 avg	Antioxidant	-0.52 (-2.0, 0.97)
							Placebo	-3.4 (-6.0, -0.78)
							Antioxidant	-1.2 (-4.2, 1.8)
Chan et al. (2005)[b]	Taichung City, Taiwan	Mail carriers	PEF	8 h	8-h avg (9:00 a.m.-5:00 p.m.)	0		-1.0 (-1.3, -0.66)
						1		-1.1 (-1.5, -0.78)

NR = Not reported.

[a]Effect estimates are standardized to a 40-ppb increase for 30-min or 1-h max O_3 and a 30-ppb increase for 8-h max O_3.

[a]PEF results not included in figure.

ambient O_3 concentrations. Few studies provided information on ventilation rate or pulse rate, thus it was difficult to ascertain whether differences in the magnitudes of O_3-associated decreases in lung function were related to differences in workers' levels of exertion.

Associations at lower ozone concentrations

Studies of populations engaged in outdoor activity examined and found that associations between O_3 and lung function decrements persisted at lower O_3 concentrations (Table 6-5). Among adults exercising outdoors, Spektor et al. (1988b) found that associations persisted in analyses restricted to 30-min max ambient O_3 concentrations less than 80 ppb, and for most lung function parameters, effect estimates were similar to those obtained for the full range of O_3 concentrations (Table 6-5). In a study of children attending summer camp, similar effects were estimated for the full range of 1-h avg O_3 concentrations and those less than 60 ppb (Spektor et al., 1988a). Brunekreef et al. (1994) found ambient O_3 exposure (10-min to 1-h) during outdoor exercise to be associated with decreases in lung function in analyses restricted to concentrations less than 61 (Table 6-5) and 51 ppb. However, effect estimates were near zero with O_3 concentrations less than 41 ppb (Brunekreef et al., 1994). In contrast, Brauer et al. (1996) found associations persisted with 1-h max O_3 concentrations less than 40 ppb.

Table 6-5 Associations between ambient ozone exposure and lung function decrements in different ranges of ambient ozone concentrations

Study	Location	Population	Parameter	O_3 Averaging Time	O_3 Concentration Range	Standardized percent change (95% CI)[a]
Brunekreef et al. (1994)	Netherlands	Adults exercising	% change FEV_1	10-m to 1-h	Full range	-0.82 (-1.6, -0.02)
				Lag 0	O_3 < 61 ppb	-2.1 (-4.5, 0.32)
Spektor et al. (1988b)	Tuxedo, NY	Adults exercising	FEV_1 (ml)	30-min avg	Full range	-54 (-84, -27)[b]
				Lag 0	O_3 < 80 ppb	-52 (-101, -3.4)[b]
Spektor et al. (1988a)	Fairview Lake, NJ	Campers without asthma	% change FEV_1	1-h avg	Full range	-2.7 (-3.3, -2.0)
				Lag 0	O_3 < 80 ppb	-1.4 (-2.5, -0.34)
					O_3 < 60 ppb	-2.2 (-3.7, -0.80)
Korrick et al. (1998)	Mt. Washington, NH	Adult day hikers	% change FEV_1	Hike duration (2-12 h) Lag 0	Full range	-1.5 (-2.8, -0.24)
					O_3 > 40 ppb	-2.6 (-4.9, -0.32)

[a]Effect estimates are standardized to a 40-ppb increase for O_3 exposures averaged over 10 min to 1 h and a 30-ppb increase for O_3 exposures averaged over 2 to12 h.

[b]Data were not provided to calculate percent change.

Korrick et al. (1998) examined associations with hike-time average O_3 exposures (2-12 h) and found effect estimates that were more negative in analyses restricted to O_3 concentrations greater than 40 ppb. Based on the results from a nonparametric model in

Korrick et al. (1998), it appeared that the association between O_3 exposure and lung function decrements in this population was limited to 2- to 12-h avg O_3 exposures above 40 ppb.

Children with Asthma

Associations between ambient O_3 exposures and lung function decrements in children with asthma have been examined in epidemiologic studies conducted across diverse geographical locations and a range of ambient O_3 concentrations (Table 6-6). Whereas studies of populations with increased outdoor exposures monitored O_3 exposures at the site of subjects' outdoor activities and used trained staff to measure lung function, studies of children with asthma relied more heavily on O_3 measured at central monitoring sites and lung function measured by subjects. However, studies of children with asthma have provided more information on factors that may confer increased susceptibility to the respiratory effects of O_3 exposure, confounding by copollutant exposure or meteorology, and the potential clinical significance of O_3-associated changes in lung function with the concurrent assessment of respiratory symptoms.

Collectively, the large body of evidence, which includes large U.S. multicity studies and several smaller studies conducted in the U.S., Mexico City, and Europe, demonstrates that increases in ambient O_3 exposure (various averaging times and lags) are associated with decrements in FEV_1 (Figure 6-6 and Table 6-7) and PEF (Figure 6-7 and Table 6-8) in children with asthma. In addition to examining a single lung function measurement per day, several studies examined associations of O_3 exposure with measures of lung function variability. Although different definitions of variability were used, studies consistently found that O_3-associated changes in lung function variability were indicative of poorer lung function, whether characterized as a decrease from the individual's mean lung function over the study period (Jalaludin et al., 2000), a decrease in lung function over the course of the day (Lewis et al., 2005), or a decrease in the lowest daily measurement (Just et al., 2002).

Studies of children with asthma that were restricted to winter months provided little evidence of an association between various single- and multi-day lags of ambient O_3 exposure and changes in lung function; several studies reported O_3-associated increases in lung function (Dales et al., 2009; Liu et al., 2009a; Rabinovitch et al., 2004). In colder months, ambient O_3 concentrations are low and in many locations, children remain primarily indoors. Thus, it is less likely that effects will be demonstrated for O_3. As noted in previous AQCDs for lung function and other endpoints such as respiratory hospital admissions, ED visits, and mortality, associations with O_3 generally are greater in the warm season.

Table 6-6 Mean and upper percentile concentrations of ozone in epidemiologic studies examining lung function in children with asthma

Study	Location	Years/Season	O_3 Averging Time	Mean/Median Concentration (ppb)	Upper Percentile Concentrations (ppb)
Mortimer et al. (2002) Mortimer et al. (2000)	Bronx, East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI, Cleveland, OH; Chicago,IL; St. Louis, MO (NCICAS)	1993 Warm season	8-h avg (10:00a.m.-6:00 p.m.)	48	NR
O'Connor et al. (2008)	Boston, MA; Bronx, Manhattan NY; Chicago, IL; Dallas, TX, Seattle, WA; Tucson, AZ (ICAS)	1998-2001 All-year	24-h avg	NR	NR
Thurston et al. (1997)	Connecticut River Valley, CT	1991-1993 Warm season	1-h max	83.6[a]	Max: 160
Lewis et al. (2005)	Detroit, MI	2001-2002 All-year	8-h max	Eastside: 40.4[a] Westside: 41.4[a]	Overall max: 92.0[a]
Rabinovitch et al. (2004)	Denver, CO	1999-2002 Cold season	1-h max	28.2	Max 70.0
Delfino et al. (2004)	Alpine, CA	September-October 1999 April-June 2000	8-h max	62.9	90th: 83.9, Max: 105.9
Dales et al. (2009) Liu et al. (2009a)	Windsor, ON, Canada	2005 Cold season	24-h avg 1-h max	14.1 27.2	75th: 17.8 75th: 32.8
Romieu et al. (1996)	Northern Mexico City, Mexico	April-July 1991 November 1991-February 1992	1-h max	190	Max: 370
Romieu et al. (1997)	Southern Mexico City, Mexico	April-July 1991 November 1991-February 1992	1-h max	196	Max: 390
Romieu et al. (2002); Romieu et al. (2004a); Romieu et al. (2006)	Mexico City, Mexico	1998-2000 All-year	8-h max 1-h max	69 102	Max: 184 Max: 309
Barraza-Villarreal et al. (2008); Romieu et al. (2009)	Mexico City, Mexico	2003-2005 All-year	8-h max 1-h max	31.6 86.5	Max (8-h): 86.3
Hernández-Cadena et al. (2009)	Mexico City, Mexico	2005 Warm season	24-h avg 1-h max	26.3 74.5	75th: 35.3; Max: 62.8 75th: 92.5; Max: 165.0
Gielen et al. (1997)	Amsterdam, Netherlands	1995 Warm season	8-h max	34.2	Max: 56.5
Just et al. (2002)	Paris, France	April-June 1996	24-h avg	30.0	Max: 61.7
Hoppe et al. (2003)	Munich, Germany	1992-1995 Warm season	30-min max (1:00 p.m.-4:00 p.m.)	High O_3 days: 66.9 Control O_3 days: 32.5	Max: 91 (high O_3 days) 39 (control O_3 days)
Wiwatanadate and Trakultivakorn (2010)	Chiang Mai, Thailand	August 2005-June 2006	24-h avg	17.5	90th: 26.82 Max: 34.65
Jalaludin et al. (2000)	Sydney, Australia	February-December 1994	15-h avg (6:00 a.m.-9:00 p.m.)	12	Max: 43

NCICAS = National Cooperative Inner-City Asthma Study, NR = Not Reported, ICAS = Inner City Asthma Study, Max = Maximum.
[a]Measured at sites established by investigators.

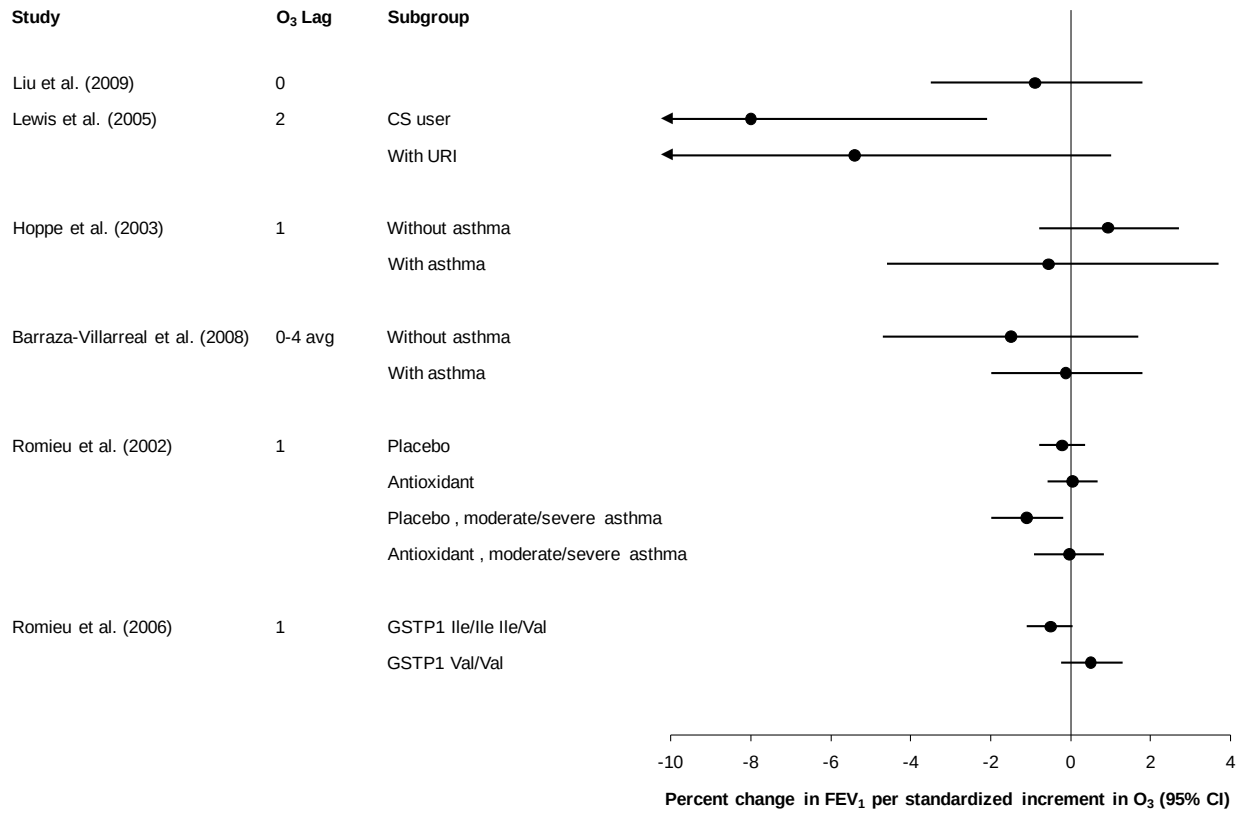


Figure 6-6 Percent change in FEV_1 in association with ambient ozone exposures among children with asthma. Results generally are presented in order of increasing mean ambient ozone concentration. CS = Corticosteroid, URI = Upper respiratory infection. Effect estimates are from single-pollutant models and are standardized to a 40-ppb increase for 30-min or 1-h max ozone exposures, a 30-ppb increase for 8-h max or 8-h avg ozone exposures, and a 20-ppb increase for 24-h avg ozone exposures.

Table 6-7 Additional characteristics and quantitative data for studies represented in Figure 6-6

Study	Location/ Population	O_3 Averaging Time	O_3 Lag	Parameter	Subgroup	Standardized percent change (95% CI)[a]
Liu et al. (2009a)	Windsor, ON, Canada Children with asthma	24-h avg	0	FEV_1		-0.89 (-3.5, 1.8)
Lewis et al. (2005)	Detroit, MI Children with asthma	8-h max	2	Lowest daily FEV_1	CS user With URI	-8.0 (-13.5, -2.1) -5.4 (-11.3, 1.0)
Hoppe et al. (2003)	Munich, Germany Children	30-min max (1:00p.m.-4:00p.m.)	1	Afternoon FEV_1 Afternoon FVC	Without asthma With asthma Without asthma With asthma	0.93 (-0.80, 2.7) -0.56 (-4.6, 3.7) -0.09 (-1.7, 1.6) -3.5 (-5.9, -1.0)
Barraza-Villarreal et al. (2008)	Mexico City, Mexico Children	8-h max	0-4 avg	FEV_1	Without asthma With asthma	-1.5 (-4.7, 1.7)[b] -0.12 (-2.0, 1.8)[b]
Romieu et al. (2002)	Mexico City, Mexico Children with asthma	1-h max	1	FEV_1	Placebo Antioxidant Placebo,moderate/severe asthma Antioxidant, moderate/severe asthma	-0.21 (-0.78, 0.36)[b] 0.05 (-0.59, 0.69)[b] -1.1 (-2.0, -0.19)[b] -0.04 (-0.92, 0.83)[b]
Romieu et al. (2006)	Mexico City, Mexico Children with asthma	1-h max	1	FEV_1	GSTP1 Ile/Ile or Ile/Val GSTP1 Val/Val	-0.51 (-1.1, 0.05) 0.50 (-0.25, 1.3)
Studies not included in Figure 6-6[b]						
Dales et al. (2009)	Windsor, ON, Canada Children with asthma	1-h max	0	Evening % predicted FEV_1		-0.47 (-1.9, 0.95)
Rabinovitch et al. (2004)	Denver, CO Children with asthma	1-h max	0-2 avg	Morning FEV_1 (ml)		53 (-2.4, 108)
O'Connor et al. (2008)	7 U.S. communities Children with asthma	24-h avg	1-5 avg	Change in % predicted FEV_1		-0.41 (-1.0, 0.21)

CS = corticosteroid, URI = Upper respiratory infection.

[a]Effect estimates are standardized to a 40-ppb increase for 30-min or 1-h max O_3, a 30-ppb increase for 8-h max O_3, and a 20-ppb increase for 24-h avg O_3.

[c]Results not presented in Figure 6-6 because a different form of FEV_1 with a different scale was examined or because sufficient data were not provided to calculate percent change in lung function.

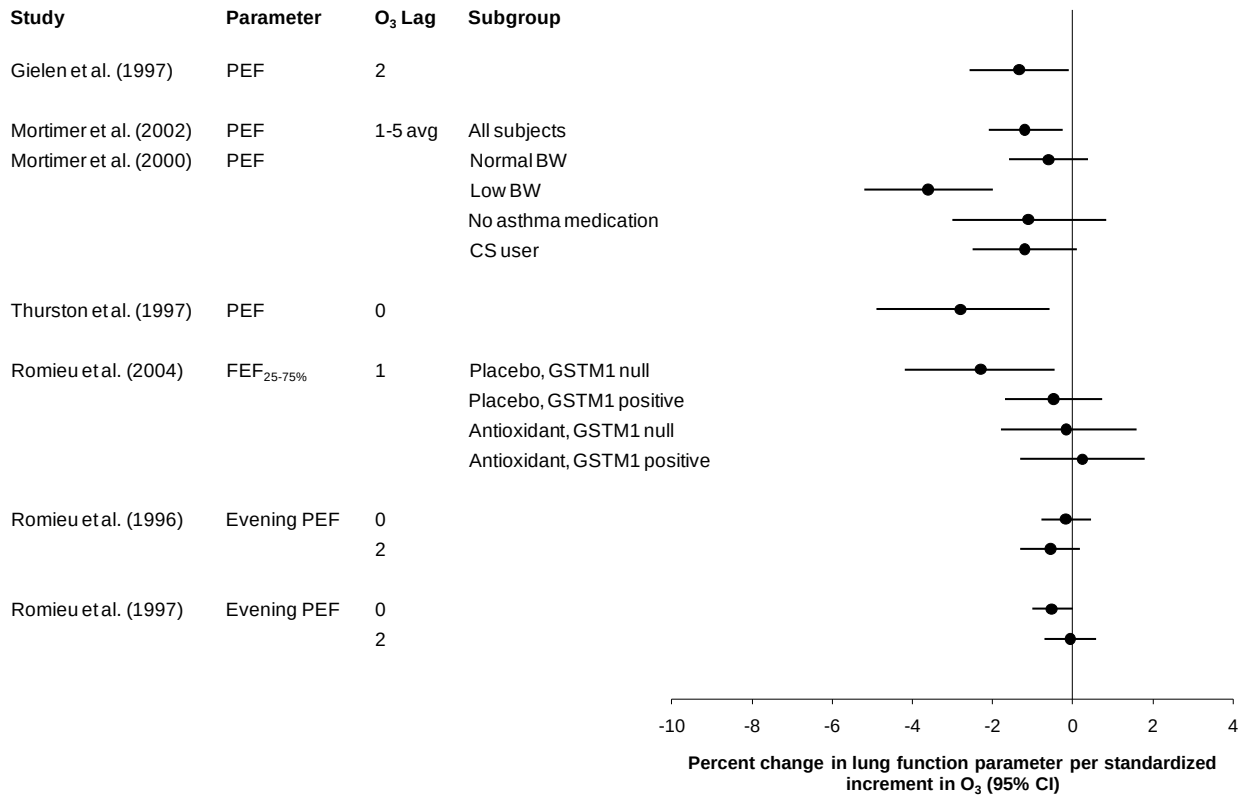


Figure 6-7 Percent change in PEF or $FEF_{25-75\%}$ in association with ambient ozone exposures among children with asthma. Results generally are presented in order of increasing mean ambient ozone concentration. BW = birth weight, CS = Corticosteroid. Effect estimates are from single pollutant models and are standardized to a 40-ppb increase for 1-h max ozone exposures and a 30-ppb increase for 8-h max or 8-h avg ozone exposures.

Table 6-8 Additional characteristics and quantitative data for studies represented in Figure 6-7

Study	Location/ Population	O_3 Averaging Time	O_3 Lag	Parameter	Subgroup	Standardized percent change (95% CI)[a]
Gielen et al. (1997)	Amsterdam, Netherlands Children w/asthma	8-h max	2	PEF		-1.3 (-2.6, -0.10)
Mortimer et al. (2002)	8 U.S. communities Children w/asthma	8-h avg (10:00a.m.-6:00p.m.)	1-5 avg	PEF	All subjects	-1.2 (-2.1, -0.26)
Mortimer et al. (2000)	8 U.S. communities Children w/asthma	8-h avg (10:00a.m.-6:00p.m.)	1-5 avg	PEF	Normal BW Low BW No medication CS user	-0.60 (-1.6, 0.39) -3.6 (-5.2, -2.0) -1.1 (-3.0, 0.84) -1.2 (-2.5, 0.11)
Thurston et al. (1997)	CT River Valley, CT Children w/asthma	1-h avg	0	Intraday change PEF		-2.8 (-4.9, -0.59)
Romieu et al. (2004a)	Mexico City, Mexico Children w/asthma	1-h max	1	$FEF_{25-75\%}$	Placebo, GSTM1 null Placebo, GSTM1 positive Antioxidant, GSTM1 null Antioxidant, GSTM1 positive	-2.3 (-4.2, -0.44) -0.48 (-1.7, 0.74) -0.16 (-1.8, 1.6) 0.24 (-1.3, 1.8)
Romieu et al. (1996)	Northern Mexico City, Mexico Children w/asthma	1-h max	0 2	Evening PEF		-0.17 (-0.79, 0.46) -0.55 (-1.3, 0.19)
Romieu et al. (1997)	Southern Mexico City, Mexico Children w/asthma	1-h max	0 2	Evening PEF		-0.52 (-1.0, -0.007) -0.06 (-0.70, 0.58)
Studies not included in Figure 6-7[b]						
Jalaludin et al. (2000)	Sydney, Australia Children w/asthma	24-h avg	0	% variability PEF	Wheeze, no asthma Asthma, no AHR Asthma, with AHR	3.8 (0.25, 7.38)[c] -0.71 (-2.6, 1.2)[c] -5.2 (-8.3, -2.2)[c]
Wiwatanadate and Trakultivakorn (2010)	Chiang Mai, Thailand Children w/asthma	24-h avg	0 5	Daily avg PEF (L/min)		1.0 (-1.6, 3.6) -2.6 (-5.2, 0)
O'Connor et al. (2008)	7 U.S. communities Children w/asthma	24-h avg	1-5 avg	Change in % predicted PEF		-0.22 (-0.86, 0.43)

BW = birth weight, CS = corticosteroid, AHR = Airway hyperresponsiveness.

[a]Effect estimates are standardized to a 40-ppb increase for 1-h max O_3, a 30-ppb increase for 8-h max or 8-h avg O_3, and a 20-ppb increase for 24-h avg O_3.

[b]Results are not presented in Figure 6-7 because a different form of PEF with a different scale was examined or because sufficient data were not provided to calculate percent change in lung function.

[c] Outcome defined as the percent deviation from individual mean PEF during the study period. Group-stratified effect estimates were provided only for models that included PM_{10} and NO_2.

The most geographically representative data were provided by the large, multi-U.S. city National Cooperative Inner City Asthma Study (NCICAS) (Mortimer et al., 2002; Mortimer et al., 2000) and Inner-City Asthma Study (ICAS) (O'Connor et al., 2008). Although the two studies differed in the cities, seasons, racial distribution of subjects, and lung function indices examined, results were fairly similar. In ICAS, which included children with asthma and atopy (i.e., allergic sensitization) and year-round examinations of lung function, a 20-ppb increase in the lag 1-5 average of 24-h avg O_3 was associated with a 0.41-point decrease in percent predicted FEV_1 (95% CI: -1.0, 0.21) and a 0.22-point decrease in percent predicted PEF (95% CI: -0.86, 0.43).

Lag 1-5 avg O_3 (8-h avg, 10:00 a.m.-6:00 p.m.) also was associated with declines in PEF in NCICAS, which included different U.S. cities, summer-only measurements, larger proportions of Black and Hispanic children, and fewer subjects with atopy (79%) (Mortimer et al., 2002). NCICAS additionally identified groups potentially at increased risk of O_3-associated decrements in PEF. Larger effects were estimated in males, children of Hispanic ethnicity, children living in crowded housing, and as indicated in Figure 6-7 and Table 6-8, children with low birth weight (Mortimer et al., 2000). Somewhat paradoxically, O_3 was associated with a larger decrease in PEF among subjects taking cromolyn, medication typically used to treat asthma due to allergy, but a smaller decrease among subjects with positive atopy (as determined by skin prick test). Similar to observations from studies of populations with increased outdoor exposures, Mortimer et al. (2002) found that associations persisted at lower ambient O_3 concentrations. At concentrations below 80 ppb, a 30-ppb increase in lag 1-5 of 8-h avg O_3 was associated with a 1.4% decrease (95% CI: -2.6, -0.21) in PEF, which was similar to the effect estimated for the full range of O_3 concentrations (Figure 6-7 and Table 6-8). In a study of children with asthma in the Netherlands, Gielen et al. (1997) estimated similar effects for the full range of 8-h max O_3 concentrations and concentrations below 51 ppb.

The results from studies of children with asthma indicated that factors in addition to asthma influenced associations between ambient O_3 exposure and changes in lung function. In comparisons between children with and without asthma, Hoppe et al. (2003) and Jalaludin et al. (2000) generally found larger O_3-associated lung function decrements in children with asthma; whereas Raizenne et al. (1987) did not consistently demonstrate differences between campers with and without asthma. In their study of children in Mexico City, Barraza-Villarreal et al. (2008) estimated larger O_3-associated decreases in children without asthma; however, 72% of these children had atopy. These findings indicated that in addition to asthma, atopy, a condition also characterized by airway inflammation and similar respiratory symptoms, may increase the risk for O_3-associated respiratory effects.

As indicated in Figures 6-6 and 6-7 and Tables 6-7 and 6-8, in most studies of children with asthma, standardized increments in ambient O_3 exposure[1] were associated with decreases in lung function that ranged from less than 1% to 2%. Larger magnitudes of decreases (3-8% per standardized increments in O_3) were found in children with asthma who also were using CS, had a concurrent upper respiratory infection (URI), were GSTM1 null, had low birth weight, or had increased outdoor exposure (Romieu et al., 2006; Lewis et al., 2005; Romieu et al., 2004a; Jalaludin et al., 2000) than among children with asthma overall (Barraza-Villarreal et al., 2008; Lewis et al., 2005; Delfino

[1]Effect estimates were standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max, and 24-h avg O_3.

et al., 2004; Romieu et al., 2002). For example, Jalaludin et al. (2000) estimated a -5.2% deviation from mean FEV_1 per a 20-ppb increase in 24-h avg O_3 among children with asthma and airway hyperresponsiveness and a much smaller -0.71% deviation among children with asthma without airway hyperresponsiveness. In a group of 86 children with asthma in Detroit, MI, Lewis et al. (2005) also reported that associations between O_3 exposure and lung function decrements were confined largely to children with asthma who used CS or had a concurrent URI. These two groups were observed to have the largest O_3-associated decrements in lung function among all studies of children with asthma. A 30-ppb increase in 8-h max ambient O_3 exposure was associated with a 8.0% decrease in the mean of lowest daily FEV_1 among CS users and a 5.4% decrease among subjects reporting concurrent URI (Lewis et al., 2005) (Figure 6-6 and Table 6-7).

Heterogeneity in lung function responses to ambient O_3 exposure also has been demonstrated as inter-individual variability in the magnitude of O_3-associated changes in lung function. Mortimer et al. (2002) found that for a 30-ppb increase in lag 1-5 avg of 8-h avg O_3, there was a 30% (95% CI: 4, 61) increase in the incidence of a greater than 10% decline in PEF. Likewise, Hoppe et al. (2003) found that while the percentages of change in individual lung function parameters were variable and small, 47% of children with asthma in their study experienced greater than 10% decline in FEV_1, FVC, or PEF or 20% increase in airway resistance on days with 30-min (1:00 p.m.-4:00 p.m.) max ambient O_3 concentrations greater than 50 ppb relative to days with less than 40 ppb O_3. In addition to finding groups of children with asthma with increased sensitivity to O_3 exposure, epidemiologic studies have indicated that the decreases in lung function observed in association with increases in ambient O_3 exposure may be clinically significant by finding that the same or similar lag of O_3 exposure was associated with decrements in lung function and increases in concurrently assessed respiratory symptoms (Just et al., 2002; Mortimer et al., 2002; Gielen et al., 1997; Romieu et al., 1997; Thurston et al., 1997; Romieu et al., 1996) (see Figure 6-12 and Table 6-19 for symptom results).

Effect modification by corticosteroid use

In controlled human exposure studies, CS treatment of subjects with asthma generally has not prevented O_3-induced FEV_1 decrements (Section 6.2.1.1). In epidemiologic studies reviewed in the 2006 O_3 AQCD, evidence was equivocal, as use of inhaled CS showed both protective (Delfino et al., 2002; Mortimer et al., 2000) and exacerbating (Gent et al., 2003) effects on respiratory endpoints. Among recent studies, evidence for effect modification of lung function responses by CS use also was mixed. In Lewis et al. (2005), analyses of interactions between O_3 exposure and CS use indicated stronger associations among CS users than among CS nonusers (quantitative results not reported

for CS nonusers). Among the 11 (12.8%) CS users, a 30-ppb increase in lag 2 of 8-h max O_3 was associated with an 8.0% decrease (95% CI: -13.5, -2.1) in lowest daily FEV_1 and a 6.7% increase (95% CI: 0.60, 13.2) in diurnal FEV_1 variability (indicating a decrease from morning to evening). Other lags (1 or 3-5 avg) or averaging times (24-h avg) of exposure were estimated to have less impact. In contrast to Lewis et al. (2005), Hernández-Cadena et al. (2009) observed greater O_3-related decrements in FEV_1 among the 60 CS nonusers than among the 25 CS users. In two winter-only studies, consideration of CS use did not largely influence associations between ambient O_3 and lung function parameters (Liu et al., 2009a; Rabinovitch et al., 2004).

Although studies varied in populations and season examined, the inconsistency in effect modification by CS use may be explained, at least in part, by differences in the severity of asthma among CS users and the definition of CS use. Hernández-Cadena et al. (2009) did not define CS use; however, the group of CS nonusers included both children with intermittent and persistent asthma. In Lewis et al. (2005), most children with moderate to severe asthma (91%) were included in the group of CS users (use for at least 50% of study days); however, these subjects had a higher percent predicted FEV_1. Liu et al. (2009a) did not provide information on asthma severity; however, they defined CS use more stringently as daily use. Differences in asthma severity and definition of CS use may explain why both CS use and nonuse could serve as indicators of severe or uncontrolled asthma across studies. Additionally, investigators did not assess adherence to reported CS regimen, and misclassification of CS use may bias findings.

Effect modification by antioxidant capacity

Ozone is a powerful oxidant whose secondary oxidation products are recognized to initiate the key modes of action, including the activation of neural reflexes that mediate decreases in lung function (Section 5.3.2). Additionally, O_3 exposure of humans and animals induces changes in the levels of antioxidants in the ELF (Section 5.3.3). These observations support the biological plausibility for diminished antioxidant capacity increasing the risk of O_3-associated respiratory effects and augmented antioxidant capacity decreasing risk. Controlled human exposure studies have demonstrated protective effects of α-tocopherol (vitamin E) and ascorbate (vitamin C) supplementation on O_3-induced lung function decrements (Section 6.2.1.1), and epidemiologic studies of children with asthma conducted in Mexico City have had similar findings. Particularly among children with moderate to severe asthma, ambient O_3 exposure was associated with a smaller decrease in FEV_1 in the group supplemented with vitamin C and E as compared with the placebo group (Romieu et al., 2002) (Figure 6-6 and Table 6-7). Similarly, Romieu et al. (2009) observed protective effect for diets high in vitamins C and E as well as omega-3 fatty acids. Subjects were assigned to a fruits and vegetables

index (FVI) that characterized consumption of vitamins C and E and a Mediterranean diet index (MDI) that additionally represented the intake of omega-3 fatty acids, which have anti-inflammatory effects. At lag 0-4 avg of 8-h max O_3 concentrations ≥ 38 ppb, a 1-unit increase in FVI was associated with a 137 ml (95% CI: 8, 266) increase in FEV_1. This protective effect of FVI was diminished at O_3 concentrations ≤ 25 ppb (65 ml [95% CI: -70, 200] increase in FEV_1 per 1-unit increase in FVI). Similar results were obtained for MDI.

Antioxidant capacity also can be characterized by variants in genes encoding xenobiotic metabolizing enzymes with different enzymatic activities. Ambient O_3 exposure has been associated with greater decreases in lung function among children with asthma with the GSTM1 null genotype, which is associated with lack of oxidant metaboilizing activity (Romieu et al., 2004a). The difference in response between GSTM1 null and positive subjects was minimal in children supplemented with antioxidant vitamins (Figure 6-7 and Table 6-8). Although these findings are biologically plausible given the well-characterized evidence for O_3 effects mediated by secondary oxidation products, it is important to note that a larger body of controlled human exposure studies has not consistently found larger O_3-induced lung function decrements in GSTM1 null subjects (Section 6.2.1.1). Effect modification by the GSTP1 variant is less clear. Romieu et al. (2006) observed larger O_3-associated decreases in FEV_1 in children with asthma with the GSTP1 Ile/Ile or Ile/Val variant, both of which are associated with normal oxidative metabolism activity (Figure 6-6 and Table 6-7). Also unexpectedly, O_3 exposure was associated with an increase in FEV_1 among children with the GSTP1 Val/Val variant, which is associated with reduced oxidative metabolism. Rather than reflecting effect modification by the GSTP1 variant, these results may reflect effect modification by asthma severity, as 77% of subjects with the GSTP1 Ile/Ile genotype had moderate to severe asthma. Supporting evidence is provided by an earlier analysis of the same cohort, in which the effect of antioxidant supplementation was demonstrated more strongly in the smaller group of children with moderate to severe asthma than among all subjects with asthma (Romieu et al., 2002).

Adults with Respiratory Disease

Relative to studies in children with asthma, studies of adults with asthma or COPD have been limited in number. Characteristics and ambient O_3 concentration data from these studies are presented in Table 6-9. Studies that included both children and adults with asthma did not consistently demonstrate associations between ambient O_3 exposure and decrements in lung function (Ross et al., 2002; Delfino et al., 1997). Ross et al. (2002) found that a 20-ppb increase in lag 0 of 24-h avg O_3 was associated with a 2.6 L/min decrease (95% CI: -4.3, -0.90) in evening PEF among subjects ages 5-49 years. This

decrement may have been indicative of a clinically significant effect, as lag 0 O_3 exposure also was associated with an increase in symptom score. In another panel study, neither ambient nor personal O_3 12-h avg exposure was reported to be associated with a decrease in lung function among subjects ages 9-46 years (Delfino et al., 1997).

Comparisons of adults with and without asthma did not conclusively demonstrate that adults with asthma were at increased risk of O_3-associated respiratory effects. In the recent panel study of 16- to 27-year-old lifeguards in Galveston, TX, a larger O_3-associated decrement in FEV_1/FVC was found among the 16 lifeguards with asthma (-1.6% [95% CI: -2.8, -0.4] per 40 ppb increase in 1-h max O_3) than among the 126 lifeguards without asthma (-0.40% [95% CI: -0.80, 0] per 40 ppb increase in 1-h max O_3) (Brooks, 2010). In the studies of day-hikers, Korrick et al. (1998) found that the O_3-associated lung function decrements observed among all hikers were driven by associations observed in hikers with history of asthma or wheeze (-4.4% [95% CI: -7.5, -1.2] in FEV_1 per 30-ppb increase in 2-9 hr avg O_3). In contrast, Girardot et al. (2006) did not find ambient O_3 exposure to be consistently associated with decrements in lung function in subjects with or without respiratory disease history. In another cross-sectional study of 38 adults with asthma and 13 adults without asthma, atopy was observed to be a stronger susceptibility factor than was asthma (Khatri et al., 2009). Investigators reported a larger decrease in percent predicted FEV_1/FVC per 30-ppb increase in lag 2 of 8-h max O_3 among the 38 subjects with atopy (with or without asthma) (-12 points [95% CI: -21, -3]) than among subjects with asthma (-4.7 points [95% CI: -11, 2.3]). Additionally, among adults with asthma, O_3 was associated with an increase in FEV_1. Based on correlations observed between decreases in lung function and decreases in quality of life scores, investigators inferred the O_3-associated decreases in lung function to be clinically significant. They suggested that atopy may influence responses to ambient O_3 exposure because during the summer, high ambient O_3 concentrations may increase the allergenicity of pollens.

O_3 was not found to have a strong effect on the lung function of adults with asthma in panel studies conducted in Europe and Asia during low ambient O_3 periods (Wiwatanadate and Liwsrisakun, 2011; Lagorio et al., 2006; Park et al., 2005a), including one study conducted in Korea during a period of dust storms (Park et al., 2005a). In these studies that examined multiple lags of O_3 exposure, O_3 generally was associated with increases in lung function.

Controlled human exposure studies demonstrate robust O_3-induced spirometric responses in children and young adults but diminished, statistically nonsignificant responses in older adults, both healthy and with COPD (Section 6.2.1.1). Similarly, in a recent epidemiologic study that followed 94 adults with COPD (ages 40-83 years) daily over a

2-year period, an increase in ambient O_3 exposure was not associated consistently with decreases PEF, FEV_1, and FVC (Peacock et al., 2011). For example, in an analysis restricted to the summer of 1996, a 30-ppb increase in 8-h max O_3 was associated with a 1.7 L/min decrease (95% CI: -3.1, -0.39) in PEF. However, during the summer of 1997, O_3 was found to have little effect on PEF (-0.21 L/min [95% CI: -2.4, 2.0] per 30-ppb increase in 8-h max O_3). Further, in this study, an increase in ambient O_3 exposure was associated with a lower odds of a large PEF decrement (OR for a greater than 20% drop from an individual's median value: 0.89 [95% CI: 0.72, 1.10] per 30-ppb increase in lag 1 of 8-h max O_3) and was not consistently associated with increases in respiratory symptoms (Peacock et al., 2011). Ozone exposure also was not consistently associated with decreases in lung function in a smaller panel study of 11 adults with COPD (mean age 67 years) (Lagorio et al., 2006). Together, these finding do not provide strong evidence that increases in O_3 exposure are associated with lung function decrements in adults with COPD.

Table 6-9 Mean and upper percentile concentrations of ozone in epidemiologic studies examining lung function in adults with respiratory disease

Study	Location	Years/Season	O_3 Averaging Time	Mean/Median Concentration (ppb)	Upper Percentile Concentrations (ppb)
Korrick et al. (1998)	Mt. Washington, NH	1991, 1992 Warm season	Hike-time avg (2-12 h)	40	Max: 74
Khatri et al. (2009)	Atlanta, GA	2003, 2005, 2006 Warm season	8-h max	59 (median)[a]	75th: 73[a]
Ross et al. (2002)	East Moline, IL	April-October 1994	8-h avg	41.5	Max: 78.3
Thaller et al. (2008)	Galveston, TX	2002-2004 Warm season	1-h max	35 (median)	Max: 118
Delfino et al. (1997)	Alpine, CA	1994 Warm season	12-h avg personal (8:00 a.m.-8:00 p.m.)	18	90th: 38 Max: 80
Lagorio et al. (2006)	Rome, Italy	1999 Spring and winter	24-h avg	Spring: 36.2[b] Winter: 8.0[b]	Overall max: 48.6[b]
Peacock et al. (2011)	London, England	1995-1997 All-year	8-h max	15.5	Autumn/Winter Max: 32 Spring/Summer Max: 74
Wiwatanadate et al. (2011)	Chiang Mai, Thailand	August 2005 - June 2006	24-h avg	17.5	90th: 26.82 Max: 34.65
Park et al. (2005a)	Incheon, Korea	March-June 2002	24-h avg	Dust event days: 23.6 Control days: 25.1	NR

NR = Not reported, Max = Maximum.
[a]Individual-level exposure estimates were derived based on time spent in the vicinity of various O_3 monitors.
[b]Concentrations converted from µg/m^3 to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

Populations Not Restricted to Individuals with Asthma

Several studies have examined associations between ambient O_3 exposure and lung function in children; however, a limited number of studies have examined other

populations not restricted to individuals with asthma or other healthy populations. Characteristics and ambient O_3 concentration data from studies not restricted to individuals with asthma are presented in Table 6-10.

Table 6-10 Mean and upper percentile concentrations of ozone in epidemiologic studies examining lung function in populations not restricted to individuals with asthma

Study	Location	Years/Season	Metric	Mean/Median Concentration (ppb)	Upper Percentile Concentrations (ppb)
Alexeef et al. (2007) Alexeef et al. (2008)	Greater Boston, MA	1995-2005 All-year	24-h avg	24.4[a]	NR
Naeher et al. (1999)	Vinton, VA	1995-1996 Warm season	8-h max	34.87	Max: 56.63
Avol et al. (1998a)	6 southern CA communities	1994 Spring and summer	24-h avg personal	NR	NR
Linn et al. (1996)	Rubidoux, Upland, Torrence, CA	1992-1993, 1993-1994 Fall and spring	24-h avg	23	Max: 53
Gold et al. (1999)	Mexico City, Mexico	1991 Winter, spring, fall	24-h avg	52.0	Max: 103
Scarlett et al. (1996)	Surrey, England	1994 Warm season	8-h max	50.7[b]	Max: 128[b]
Ward et al. (2002)	Birmingham and Sandwell, England	1997 Winter and summer	24-h avg	Winter median: 13.0 Summer median: 22.0	Winter Max: 33 Summer Max: 41
Ulmer et al. (1997)	Freudenstadt and Villingen, Germany	1994 March-October	30-min max	Freudenstadt median: 50.6 Villingen median: 32.1	Freudenstadt 95th: 89.7 Villingen 95th: 70.1
Hoppe et al. (2003)	Munich, Germany	1992-1995 Warm season	30-min max (1:00 p.m.-4:00 p.m.)	High O_3 days: 70.4 Control O_3 days: 29.8	Max (high O_3 days): 99 Max (control O_3 days): 39
Neuberger et al. (2004)	Vienna, Austria	June-October 1999, January-April 2000	NR	NR	NR
Steinvil et al. (2009)	Tel Aviv, Israel	2002-2007 All-year	8-h avg (10:00 a.m. – 6:00 p.m.)	41.1	75^{th}: 48.7 Max: 72.8
Chen et al. (1999)	3 Taiwan communities	1995-1996 May-January	1-h max	NR	Max: 110.3[b]
Son et al. (2010)	Ulsan, Korea	2003-2007 All-year	8-h max	35.86	Max: 59.53

NR = Not Reported, Max = Maximum.

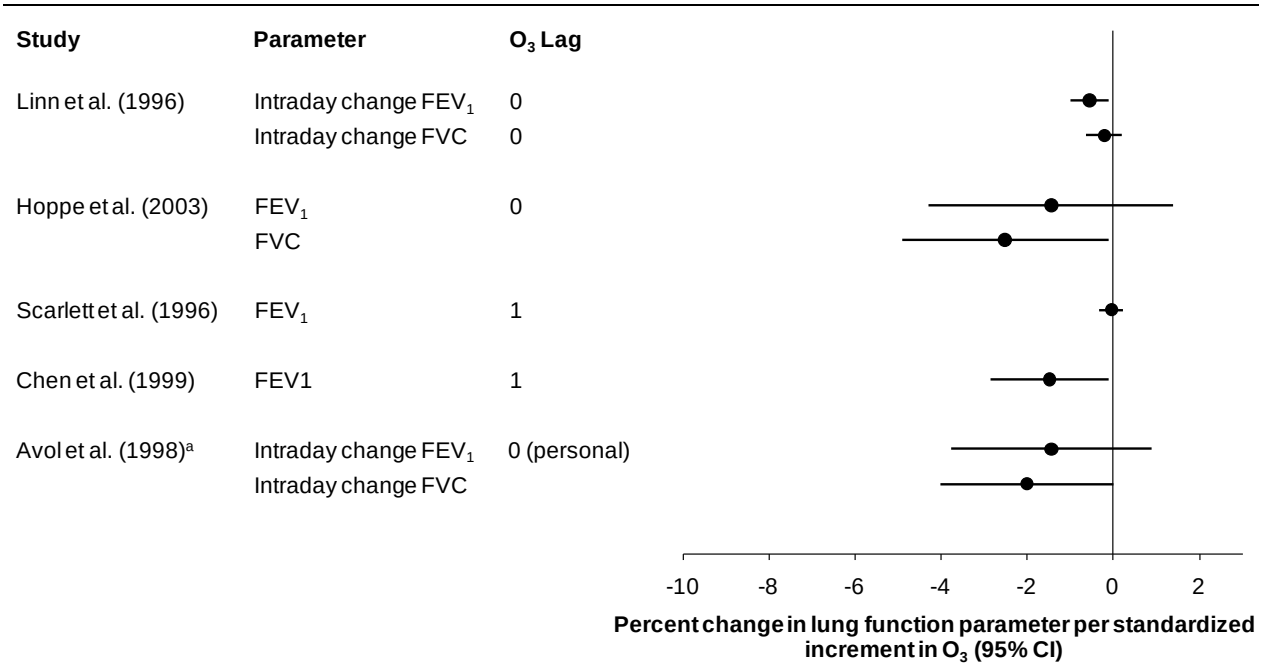
[a]Measured at central monitoring sites established by investigators. Concentations were averaged across all monitors.

[b]Measured at subjects' schools where lung function measurements were performed.

Children

The 2006 O_3 AQCD identified children as a potentially at-risk population based on consistent evidence of association between ambient O_3 exposure and decrements in FEV_1 and PEF (U.S. EPA, 2006b) (Figure 6-8 and Table 6-11). No new studies in children without asthma are available to compare with previous findings. Hoppe et al. (2003) O_3 exposure to be associated with decreses in healthy children in Munich, Germany (Figure 6-8 and Table 6-11). In another panel study of healthy children in Vienna, Austria, O_3 was not associated with decrements in total lung capacity (Neuberger et al., 2004). Most

of the studies in children did not exclusively examine healthy children. However, several studies of children that included small proportions (4- 10%) of children with history of respiratory disease or symptoms and found associations between O_3 exposure and decrements in lung function (Chen et al., 1999; Ulmer et al., 1997; Scarlett et al., 1996). Based on interactions between O_3 exposure and asthma/wheeze history, Avol et al. (1998a) and Ward et al. (2002) did not find lung function responses to ambient O_3 exposure to differ between children with history of asthma or wheeze and healthy children. Combined, these lines of evidence indicate that the associations observed between ambient O_3 exposure and decreases in lung function in children are not driven by effects in children with asthma or respiratory symptoms, and that healthy children also may represent a population at increased risk of O_3-associated respiratory effects.



Results generally are presented in order of increasing mean ambient ozone concentration.

[a]The 95% CI was constructed using a standard error that was estimated from the p-value. Effect estimates are from single-pollutant models and are standardized to a 40-, 30-, and 20-ppb increase for a 1-h (or 30-min) max, 8-h max, and 24-h avg ozone exposures, respectively.

Figure 6-8 Percent change in lung function in association with ambient ozone exposures in studies not restricted to children with asthma.

Table 6-11 Additional characteristics and quantitative data for studies represented in Figure 6-8 and results from other studies in children

Study	Location/ Population	O_3 Lag	O_3 Averaging Time	Parameter	Effect Estimate (95% CI)[a]
Linn et al. (1996)	3 southern CA communities Children	0	1-h avg	Intraday change FEV_1 Intraday change FVC	-0.56 (-0.99, -0.12) -0.21 (-0.62, 0.20)
Hoppe et al. (2003)	Munich, Germany Children	0	30-min max (1:00 p.m.-4:00 p.m.)	FEV_1 FVC	-1.4 (-4.3, 1.4) -2.5 (-4.9, -0.10)
Scarlett et al. (1996)	Surrey, England Children	1	8-h max	FEV_1	-0.04 (-0.32, 0.23)
Chen et al. (1999)	3 Taiwan communities Children	1	1-h max	FEV_1	-1.5 (-2.8, -0.12)
Avol et al. (1998a)	3 southern CA communities Children	0 (personal)	24-h avg	Intraday change FEV_1 Intraday change FVC	-1.4 (-3.8, 0.90)[b] -2.0 (-4.0, 0.01)[b]
Studies of children not included in Figure 6-8[c]					
Ulmer et al. (1997)	Freudenstadt and Villingen, Germany Children	1	1/2-h max	FEV_1 (ml)	-5.9 (-10.4, 1.3)[b]
Ward et al. (2002)	Birmingham and Sandwell, England Children	0 0-6 avg	24-h avg	PEF (L/min)	-3.2 (-8.3, 2.0)[d] -11.1 (-22.0, -0.18)[d]
Gold et al. (1999)	Mexico City, Mexico Children	1 1-10 avg	24-h avg	Intraday change PEF (% change)	-0.54 (-1.1, 0.05)

[a]Effect estimates are standardized to a 40-, 30-, and 20-ppb increase for 1-h (or 30-min) max, 8-h max, and 24-h avg O_3, respectively.
[b]The 95% CI was constructed using a standard error that was estimated from the p-value.
[c]Results are not presented in Figure 6-8 because sufficient data were not provided to calculate percent change in lung function or PEF was analyzed.[d]Effect estimates are from analyses restricted to summer months.

Among the studies of children, the magnitudes of decrease in lung function per standardized increment in ambient O_3 exposure[1] ranged from less than 1 to 4%, a range similar to that estimated in children with asthma. However, in contrast with studies of children with asthma, studies of children in the general population did not consistently find that O_3-associated decreases in lung function were accompanied by increases in respiratory symptoms. Gold et al. (1999) found that lag 1 of O_3 exposure was associated with both decreases in PEF and increases in phlegm; however, the increase in phlegm was associated with O_3 exposure lagged one day whereas the PEF decrement was driven by exposures lagged 2 to 4 days. Ozone was weakly associated with cough and shortness of breath among children in England (Ward et al., 2002), and O_3 was associated with a decrease in respiratory symptom score among children in California (Linn et al., 1996). These findings indicate that while the magnitudes of O_3-associated decrease in lung function may be similar in children with and without asthma, because of the higher overall lung function in healthy children, the decrements may not be large enough to be clinically significant in healthy children.

[1]Effect estimates were standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max, and 24-h avg O_3.

Adults

In the small body of studies conducted in adults, O_3 has been associated with decrements in lung function in both healthy adults and those with comorbid factors (Table 6-12). In a cohort of mostly healthy women, ages 19-43 years, followed for one summer season, Naeher et al. (1999) observed associations between 8-h max ambient O_3 exposure and decreases in PEF. In a large cross-sectional study of 2,380 healthy adults (75th percentile of age: 52 years) in Tel Aviv, Israel, across several lags of exposure (single day lags 0-7 and 0-6 avg), O_3 was associated mostly with increases in FEV_1, FVC, and FEV_1/FVC (Steinvil et al., 2009). Another large cross-sectional study was conducted in 2,102 children and adults (mean age: 45 years) living near a petrochemical plant in Ulsan, Korea (Son et al., 2010). Multiple O_3 exposure metrics, including concentrations averaged across 13 city monitors, concentrations from the nearest monitor, inverse distance-weighted concentrations, and estimates from kriging, were associated with decrements in lung function; however, no particular metric consistently showed a larger effect across the various lags of O_3 exposure examined. Lag 0-2 avg of 8-h max O_3 exposure was associated with the largest decrements in percent predicted FEV_1 (1.4-point decrease [95% CI: -2.7, -0.08] per 30-ppb increase in the 8-h max of lag 0-2 avg O_3 averaged across all monitors). Although the health status of subjects was not reported, the mean percent predicted FEV_1 in the study population was 82.85%, indicating a large proportion of subjects with underlying airway obstruction. Results from this study were not adjusted for meteorological factors and thus, confounding cannot be ruled out.

As described in Section 6.2.1.1, controlled human exposure studies have not consistently found O_3-induced decreases in lung function in older adults. In an earlier study of adults ages 69-95 years, Hoppe et al. (2003) did not find ambient O_3 exposure-associated decreases in lung function. However, recently, the Normative Aging Study found that ambient O_3 exposure was associated with decrements in FEV_1 and FVC in a group of older men (Alexeeff et al., 2008). This study in the Greater Boston area conducted spirometry once every 3 years for 10 years in 900 older men (mean [SD] age = 68.9 [7.2] years), most of whom were white and healthy. Among all subjects, several lags of 24-h avg O_3 exposure (1- to 7-day avg) were associated with decreases in FEV_1 (Alexeeff et al., 2008). Additionally, larger effects were estimated in adults with elevated BMI ($\geq$ 30), airway hyperresponsiveness, and reduced activity in antioxidant enzymes (i.e., GSTP1 Ile/Val or Val/Val variant) (Alexeeff et al., 2008; Alexeeff et al., 2007) (Table 6-12). Larger O_3-related decrements in FEV_1 and FVC also were observed in subjects with long GT dinucleotide repeats in the promoter region of the antioxidant enzyme heme oxygenase-1 (Alexeeff et al., 2008), which has been associated with reduced inducibility (Hiltermann et al., 1998). The largest O_3-related percentages of decrease in lung function were observed in the group of men with airway hyperresponsiveness and elevated BMI (-

5.3% FEV_1 [95% CI: -8.3, -2.4] per 20-ppb increase in lag 0-1 avg of 24-h avg O_3). In this cohort, O_3 also was associated with decreases in lung function in adults without airway hyperresponsiveness and BMI < 30, indicating the effects of O_3 on lung function in older adults extends to healthy older adults. However, importantly, the findings may be generalizable only to older white men.

Table 6-12 Associations between ambient ozone exposure and changes in lung function in studies of adults

Study	Location/ Population	O_3 Lag	O_3 Averaging Time	Parameter	O_3 Assessment Method/Subgroup	Effect Estimate (95% CI)[a]
Son et al. (2010)	Ulsan, Korea Children and adults, ages 7-97 yr	0-2 avg	8-h max	Change in % predicted FEV_1	All monitor avg Nearest monitor IDW Kriging	-1.4 (-2.7, -0.08) -0.76 (-1.8, 0.25) -1.1 (-2.2, 0.05) -1.4 (-2.6, -0.11)
Steinvil et al. (2009)	Tel Aviv, Israel Healthy adults, mean age 43 yr, 75th %-ile: 52 yr	0 0-6 avg	8-h avg (10:00 a.m-6:00 p.m.)	FEV_1 (ml)		40 (0, 80) 94 (33, 156)
Naeher et al. (1999)	Vinton, VA Healthy women, ages 19-43 yr	0 0-4 avg	24-h avg	Evening PEF (L/min)		-0.06 (-0.11, 0) -5.1 (-8.7, -1.5)
Hoppe et al. (2003)	Munich, Germany Older adults, ages 69-95 yr	0 1	30-min max (1:00p.m.-4:00p.m.)	% change in evening FEV_1		0.75 (-2.1, 3.7) 1.2 (-1.3, 3.6)
Alexeeff et al. (2008)	Greater Boston, MA Older adults, mean (SD) age: 68.8 yr (7.3)	0-1 avg	24-h avg	% change in FEV_1	GSTP1 Ile/Ile GSTP1 Ile/Val Val/Val	-1.0 (-2.2, 0.19) -2.3 (-3.5, -1.0)
Alexeef et al. (2007)	Greater Boston, MA Older adults, mean (SD) age: 68.8 yr (7.3)	0-1 avg	24-h avg	% change in FEV_1	BMI < 30 BMI ≥ 30 No AHR AHR BMI ≥ 30 and AHR	-1.5 (-2.5, -0.52) -3.5 (-5.1, -1.9) -1.7 (-2.7, -0.73) -4.0 (-6.2, -1.8) -5.3 (-8.2, -2.3)

IDW = Inverse distance weighting, BMI = Body mass index, AHR = airway hyperresponsiveness.
[a]Effect estimates are standardized to a 40-ppb increase for 30-min max O_3, 30-ppb increase for 8-h max or 8-h avg O_3, and 20-ppb increase for 24-h avg O_3.

Confounding in epidemiologic studies of lung function

The 1996 O_3 AQCD noted uncertainty regarding confounding by temperature and pollen (U.S. EPA, 1996a); however, studies collectively do not provide strong evidence of confounding by these factors. Most studies, whether they involved year-round or summer-only examinations, included temperature in statistical analyses and found associations between O_3 exposure and decreases in lung function. Across studies, temperature has shown inconsistent associations with lung function, even among studies conducted in the summer and in the same geographic region. For example, in studies of children attending summer camps conducted in the Northeast U.S., temperature was associated with an increase (Berry et al., 1991) (Thurston et al., 1997) and decrease (Raizenne et al., 1987) in lung function. In the reanalysis of six camp studies, investigators did not include temperature in models because temperature within the normal ambient range had not been shown to affect O_3-induced lung function responses in controlled human exposure studies (Kinney et al., 1996). In two summer camp studies

conducted in the Northeast U.S., O_3 was associated with decreases in lung function in models without and with temperature (Thurston et al., 1997; Spektor et al., 1988a). In both studies, temperature and O_3 were measured on site of the camps. Spektor et al. (1988a) estimated similar effects in a model with and without a temperature-humidity index, and Thurston et al. (1997) found that compared with a univariate model, O_3 was associated with a nearly 2-fold greater decrease in PEF when temperature was added to the model.

Although evaluated in fewer studies, the evidence does not indicate that associations between ambient O_3 exposure and lung function are confounded by pollen. Some camp studies found that pollen independently was not associated with lung function decrements (Thurston et al., 1997; Avol et al., 1990). A few studies of children with asthma with follow-up over multiple seasons found O_3 to be associated with decrements in lung function in models that adjusted for pollen counts (Just et al., 2002; Ross et al., 2002; Jalaludin et al., 2000; Gielen et al., 1997). In these studies, large percentages of subjects had positive atopy (22-98%), with some studies examining large percentages of subjects specifically with pollen allergy(Ross et al., 2002; Gielen et al., 1997).

A relatively larger number of studies provided information on potential confounding by copollutants such as $PM_{2.5}$, PM_{10}, NO_2, or SO_2. In most cases, investigators indicated that associations between O_3 exposure and lung function were not driven by copollutant confounding; however, studies varied in how they considered confounding. Studies of subjects exercising outdoors indicated that ambient concentrations of copollutants such as NO_2, sulfur dioxide, or acid aerosol were low and thus, not likely to confound the observed O_3 effects (Hoppe et al., 2003; Brunekreef et al., 1994; Hoek et al., 1993). In other studies of children with increased outdoor exposures, O_3 was consistently associated with decreases in lung function, whereas other pollutants such as $PM_{2.5}$, sulfate, and acid aerosol individually showed variable associations across studies (Thurston et al., 1997; Castillejos et al., 1995; Berry et al., 1991; Avol et al., 1990; Spektor et al., 1988a).

Among studies that conducted copollutant modeling, associations between O_3 exposure and lung function decrements were observed to be robust (Figure 6-9 and Table 6-13). In copollutant models, O_3 effect estimates generally fell within the 95% CI of the single-pollutant model effect estimates. Whereas some studies used the same averaging time for all pollutants (Lewis et al., 2005; Jalaludin et al., 2000), most examined 1-h max or 8-h max O_3 exposures and 24-h avg copollutant exposures (Son et al., 2010; Chen et al., 1999; Romieu et al., 1997; Romieu et al., 1996). In a Philadelphia-area summer camp study, Neas et al. (1999) was among the few studies to find that the effect of O_3 was

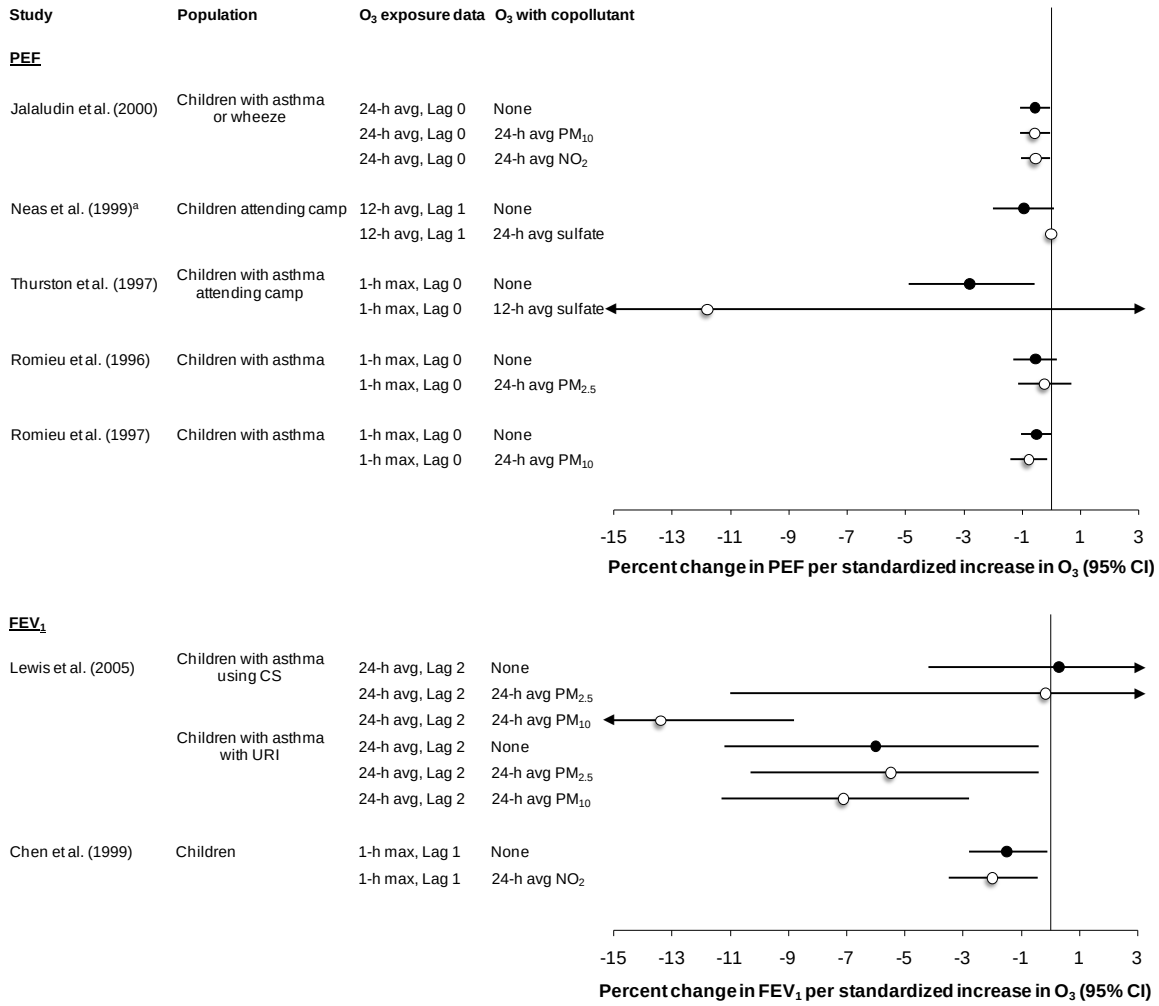
attenuated in a copollutant model. In a copollutant model with 24-h avg sulfate, the 12-h avg O_3 effect estimate was attenuated to near zero (Figure 6-9 and Table 6-13).

In studies with copollutant modeling, ambient O_3 concentrations showed a wide range of correlations with concentrations of copollutants (r=-0.31 to 0.74). Among children with asthma in Sydney, Australia, Jalaludin et al. (2000) found low correlations of 24-h avg O_3 with 24-h avg PM_{10} (r = 0.13) and NO_2 (r = -0.31), and in two-pollutant models, PM_{10} and NO_2 continued to be associated with increases in PEF, and O_3 continued to be associated with decreases in PEF. In a study of children with asthma in Detroit, MI, 24-h avg O_3 was moderately correlated with 24-h avg $PM_{2.5}$ (Pearson r= 0.57) and 24-h avg PM_{10} (Pearson r=0.59) (Lewis et al., 2005). Inclusion of PM_{10} or $PM_{2.5}$ in models resulted in larger changes in O_3 effect estimates than those observed in other studies. As illustrated in Figure 6-9 and Table 6-13, the magnitude of change was not consistent between the two subgroups. Among subjects with a concurrent URI, O_3-associated decreases in lowest daily FEV_1 were robust to the inclusion of PM_{10} or $PM_{2.5}$. Among CS users, O_3 was associated a much larger decrease in FEV_1 when PM_{10} was included in the model (Lewis et al., 2005).

Studies conducted in Mexico City found small changes in O_3-associated lung function decrements in copollutant models, although different averaging times were used for different pollutants (Romieu et al., 1997; Romieu et al., 1996) (Figure 6-9 and Table 6-13). In these studies, O_3 was moderately correlated with co-pollutants such as NO_2 and PM_{10} (range of Pearson r = 0.38-0.58). Studies conducted in Asia also found that associations between O_3 and lung function were robust to the inclusion of weakly- to moderately-correlated copollutants (Son et al., 2010; Chen et al., 1999). Copollutant effect estimates generally were attenuated, indicating that O_3 may confound the results of copollutants.

In a summer camp study conducted in Connecticut, Thurston et al. (1997) found ambient concentrations of 1-h max O_3 and 12-h avg sulfate to be highly correlated (r = 0.74), making it more difficult to separate their independent effects. With sulfate in the model, a larger decrease in PEF was estimated for O_3; however, the 95% CI was much wider (Figure 6-9 and Table 6-13). Investigators found that the association between sulfate and PEF was driven by one day when the ambient concentrations of both pollutants were at their peak. With the removeal of this influential day, the sulfate effect was attenuated, whereas O_3 effects remained robust (Thurston et al., 1997). Among children with asthma in Thailand, the O_3-associated decrease in PEF was robust to the adjustment of SO_2; however, different lags were examined for O_3 (lag 5) and SO_2 (lag 4) (Wiwatanadate and Trakultivakorn, 2010). Some studies did not provide quantitative results but reported that O_3 effects on lung function decrements remained statistically significant in models that

included copollutants such as PM_{10}, NO_2, sulfate, nitrate, or ammonium (Romieu et al., 1998a; Brauer et al., 1996; Linn et al., 1996; Spektor et al., 1988b).



Results are presented for PEF then FEV_1 and then in order of increasing mean ambient ozone concentration. [a]Information was not available to calculate 95% CI of the copollutant model. CS = corticosteroid, URI = Upper respiratory infection. Effect estimates are standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 12-h avg, and 24-h avg ozone, respectively. Black circles represent ozone effect estimates from single pollutant models, and open circles represent ozone effect estimates from copollutant models.

Figure 6-9 Comparison of ozone-associated changes in lung function in single- and copollutant models.

Table 6-13 Additional characteristics and quantitative data for studies presented in Figure 6-9

Study	Location/ Population	O_3 Exposure Data	Parameter	O_3-associated Percent Change in Single-Pollutant Model (95% CI)[a]	O_3-associated Percent Change in Copollutant Model (95% CI)[a]
PEF					
Jalaludin et al. (2000)	Sydney, Australia Children with asthma or wheeze	24-h avg Lag 0	Intraday change PEF	-0.57 (-1.1, -0.06)	with 24-h avg PM_{10}, -0.57 (-1.1, -0.06) with 24-h avg NO_2 -0.55 (-0.1, -0.04)
Neas et al. (1999)	Philadelphia, PA Children attending summer camp	12-h avg Lag 1	Morning PEF	-0.94 (-2.0, 0.08)	with 24-h avg sulfate -0.02[b]
Thurston et al. (1997)	CT River Valley Children with asthma attending summer camp	1-h max Lag 0	Intraday change PEF	-2.8 (-4.9, -0.59)	with 12-h avg sulfate -11.8 (-31.6, 8.1)
Romieu et al. (1996)	Mexico City, Mexico Children with asthma	1-h max Lag 0	Evening PEF	-0.55 (-1.3, 0.19)	with 24-h avg $PM_{2.5}$ -0.24 (-1.2, 0.68)
Romieu et al. (1997)	Mexico City, Mexico Children with asthma	1-h max Lag 0	Evening PEF	-0.52 (-1.0, -0.01)	with 24-h avg PM_{10} -0.79 (-1.4, -0.16)
FEV_1					
Lewis et al. (2005)	Detroit, MI Children with asthma using CS Children with asthma with URI	24-h avg Lag 2	Lowest daily FEV_1	0.29 (-4.2, 5.0) -6.0 (-11.2, -0.41)	with 24-h avg $PM_{2.5}$ -0.18 (-11.0, 11.9) with 24-h avg PM_{10} -13.4 (-17.8, -8.8) with 24-h avg $PM_{2.5}$ -5.5 (-10.3, -0.42) with 24-h avg PM_{10} -7.1 (-11.3, -2.8)
Chen et al. (1999)	3 Taiwan communities Children	1-h max Lag 1	FEV_1	-1.5 (-2.8, -0.12)	with 24-h avg NO_2 -2.0 (-3.5, 0.42)
Results not included in Figure 6-9					
Wiwatanadate and Trakultivakorn (2010)	Chiang Mai, Thailand Children with asthma	24-h avg Lag 5	Evening PEF (L/min)	-2.6 (-5.2, 0)	with Lag 4 SO_2 -3.2 (-6.2, -0.2)
Son et al. (2010)	Ulsan, Korea Children and adults	8-h max Lag 0-2 avg (kriging)	Change in % predicted FEV_1	-1.4 (-2.6, -0.11)	with PM_{10} -1.8 (-3.4, -0.25)

CS = Corticosteroid, URI = Upper respiratory infection.

[a]Results represent percent changes in lung function parameter per the following standardized increase in ambient O_3 concentration: 40 ppb for 1-h max O_3, 30 ppb for 8-h max or 12-h avg O_3, and 20 ppb for 24-h avg O_3.

Several studies examined multi-pollutant models that most often included O_3, NO_2, and either $PM_{2.5}$ or PM_{10}. Ozone exposure was associated with similar or larger magnitudes of decrease lung function in multi-pollutant models (O'Connor et al., 2008; Thaller et al., 2008; Chan and Wu, 2005; Romieu et al., 2002; Korrick et al., 1998; Higgins et al., 1990); however, the independent effects of O_3 exposure are more difficult to assess in relation to incremental changes in more than one copollutant.

Summary of Epidemiologic Studies of Lung Function

The cumulative body of epidemiologic evidence strongly supports associations between ambient O_3 exposure and decrements in lung function in children, particularly, those with asthma. While little new research is available, previous AQCDs have presented epidemiologic evidence of heightened effects in children and adults exercising or working outdoors during periods of relatively low ambient O_3 concentrations (Table 6-1). These epidemiologic results are well-supported by observations from controlled human exposure studies in which exposures to lower O_3 concentrations induce lung function decrements when combined with exercise as compared with exposures during rest.

Recent epidemiologic investigation continued to focus on children with asthma, and most recent results in this population indicated associations between O_3 exposure and decrements in lung function (Figures 6-6 anf 6-7 and Tables 6-7 and 6-8). Based on a small number of within-study comparisons of groups with and without asthma, larger effects were not conclusively estimated for groups with asthma. It is important to note that most of these studies were not designed to assess between-group differences, and in some studies, the high prevalence of atopy may have contributed to larger associations in subjects without asthma (Khatri et al., 2009; Barraza-Villarreal et al., 2008). A large body of previous studies demonstrated associations in children. Whereas the 2006 O_3 AQCD reported weak evidence, a new study indicates that O_3 exposure may be associated with decrements in lung function in older adults.

Across the diverse populations examined in epidemiologic studies, ambient O_3 exposure was associated with 1-8% decreases in lung function per standardized increment in O_3 concentration[1]. Larger decreases (3-8%) usually were observed in children with asthma or older adults with CS use, concurrent URI, airway hyperresponsiveness, or reduced activity of antioxidant enzymes. These results indicate that common comorbid and genetic factors may increase the risk of O_3-associated respiratory effects. High dietary antioxidant intake was found to attenuate O_3-associated lung function decrements. Each of these potential susceptibility or protective factors has been examined in one to two populations, and further investigation in diverse populations is warranted. Heterogeneity in response also was demonstrated by observations that increases in ambient O_3 exposure were associated with increased incidence of a greater than 10% decline in lung function in children with asthma (Hoppe et al., 2003; Mortimer et al., 2002). In considering the clinical significance of more subtle health outcomes such as lung function changes, it is important to note that a small shift in the population mean likely will have a disproportionate effect in the extreme ends of the distribution of lung function where these small magnitudes of decrease lead to clinically-significant airway resistance or

[1] Effect estimates were standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max, and 24-h avg O_3.

obstruction and where individuals likely have concurrent symptoms. Several epidemiologic studies have demonstrated the clinical significance of O_3-associated lung function decrements, primarily in individuals with asthma, by finding concomitant increases in respiratory symptoms (Khatri et al., 2009; Just et al., 2002; Mortimer et al., 2002; Ross et al., 2002; Gielen et al., 1997; Romieu et al., 1997; Thurston et al., 1997; Romieu et al., 1996).

Collectively, epidemiologic studies have examined and found decreases in lung function in association with single-day O_3 concentrations lagged from 0 to 7 days as well concentrations averaged over 2-10 days. A large body of evidence indicates decreases in lung function in association with O_3 exposures over the duration of outdoor activity, same-day, or previous-day O_3 exposures (Son et al., 2010; Alexeeff et al., 2008; Lewis et al., 2005; Ross et al., 2002; Jalaludin et al., 2000; Chen et al., 1999; Romieu et al., 1997; Brauer et al., 1996; Romieu et al., 1996; Spektor et al., 1988b). Fewer studies find associations with longer lags of ambient O_3 exposures (5-7 days) (Wiwatanadate and Trakultivakorn, 2010; Hernández-Cadena et al., 2009; Steinvil et al., 2009). However, associations with multiday averages of exposure (Son et al., 2010; Liu et al., 2009a; Barraza-Villarreal et al., 2008; O'Connor et al., 2008; Alexeeff et al., 2007; Mortimer et al., 2002; Ward et al., 2002; Gold et al., 1999; Naeher et al., 1999; Neas et al., 1999) indicate that exposures accumulated over several days may be important. For single- and multi-day O_3 exposures, associations with lung function decrements were observed for 1-h max, 8-h max, and 24-h avg O_3, without a clear indication that the strength of evidence varied among the averaging times. Within studies, O_3 exposure for various lag periods were associated with lung function decrements, possibly indicating that multiple modes of action may be involved in the responses. Activation of bronchial C-fibers (Section 5.3.2) may lead to decreases in lung function as an immediate response to O_3 exposure, and increased airway hyperresponsiveness resulting from sensitization of airways (Section 5.3.5) may mediate lung function responses associated with the lagged or multiday O_3 exposures (Peden, 2011).

Several studies found that associations with lung function decrements persisted at lower ambient O_3 concentrations. For exposures averaged up to 1 hour during outdoor activity, multiple studies in individuals engaged in outdoor activities found associations with O_3 concentrations limited to those below 80 ppb (Spektor et al., 1988a; Spektor et al., 1988b), 60 ppb (Brunekreef et al., 1994; Spektor et al., 1988a), and 50 ppb (Brunekreef et al., 1994). Among outdoor workers, Brauer et al. (1996) found a robust association with daily 1-h max O_3 concentrations below 40 ppb. For 8-h average O_3 exposures, associations with lung function decrements in children with asthma were found to persist at concentrations less than 80 ppb in a U.S. multicity study (for lag 1-5 avg) (Mortimer et

al., 2002) and less than 51 ppb in a study conducted in the Netherlands (for lag 2) (Gielen et al., 1997).

Several studies of lung function evaluated confounding by meterological factors and copollutant exposures. Most O_3 effect estimates remained robust in models that adjusted for temperature, humidity, and co-pollutants such as $PM_{2.5}$, PM_{10}, NO_2, or SO_2. Although examined in relatively few epidemiologic studies, O_3 was associated with decreases in lung function in models that included pollen or acid aerosols. The consistency of association in the collective body of evidence with and without adjustment for copollutant exposures and meterological factors combined with evidence from controlled human exposure studies for the direct effect of O_3 exposure provide substantial evidence for the independent effects of ambient O_3 exposure on lung function decrements.

6.2.1.3 Toxicology

The 2006 O_3 AQCD concluded that pulmonary function decrements occur in a number of species with acute exposures ($\leq$ 1 week), ranging from 0.25 to 0.4 ppm O_3 (U.S. EPA, 2006b). Early work has demonstrated that during acute exposure of ~0.2 ppm O_3 in rats, the most commonly observed alterations are increased frequency of breathing and decreased tidal volume (i.e., rapid, shallow breathing). Decreased lung volumes are observed in rats with acute exposures to 0.5 ppm O_3. At concentrations of $\geq$1 ppm, breathing mechanics (compliance and resistance) are also affected. Exposures of 6 h/day for 5 days create a pattern of attenuation of pulmonary function decrements in both rats and humans without concurrent attenuation of lung injury and morphological changes, indicating that the attenuation did not result in protection against all the effects of O_3 (Wiester et al., 1996b). A number of studies examining the effects of O_3 on pulmonary function in rats, mice, and dogs are described in Table 6-13 on p. 6-91 of the 1996 O_3 AQCD and Table AX5-11 on p. AX5-34 of the 2006 O_3 AQCD (U.S. EPA, 2006b, 1996a). Recent lung imaging studies using hyperpolarized ^{3}He provide evidence of ventilation abnormalities in rats following exposure to 0.5 ppm O_3 (Crémillieux et al., 2008). Rats were exposed to 0.5 ppm O_3 for 2 or 6 days, either continuously (22 h/day) or alternating (12 h/day). Dynamic imaging of lung filling (2 mL/s) revealed delayed and incomplete filling of lung segments and lobes. Abnormalities were mainly found in the upper regions of the lungs and proposed due to the spatial distribution of O_3 exposure within the lung. Although the small number of animals used in the study (n = 3 to 7/group) makes definitive conclusions difficult, the authors suggest that the delayed filling of lung lobes or segments is likely a result of an increase in airway resistance brought about by narrowing of the peripheral small airways.

6.2.2 Airway Hyperresponsiveness

Airway hyperresponsiveness refers to a condition in which the conducting airways undergo enhanced bronchoconstriction in response to a variety of stimuli. Airway responsiveness is typically quantified by measuring changes in pulmonary function (e.g., FEV_1 or specific airway resistance [sRaw]) following the inhalation of an aerosolized specific (allergen) or nonspecific (e.g., methacholine) bronchoconstricting agent or another stimulus such as exercise or cold air. Asthmatics are generally more sensitive to bronchoconstricting agents than nonasthmatics, and the use of an airway challenge to inhaled bronchoconstricting agents is a diagnostic test in asthma. Standards for airway responsiveness testing have been developed for the clinical laboratory (ATS, 2000a), although variation in methodology for administering the bronchoconstricting agent may affect the results (Cockcroft et al., 2005). There is a wide range of airway responsiveness in nonasthmatic people, and responsiveness is influenced by wide range of factors, including cigarette smoke, pollutant exposures, respiratory infections, occupational exposures, and respiratory irritants. Airways hyperresponsiveness in response to O_3 exposure has not been examined widely in epidemiologic studies; such evidence is derived primarily from controlled human exposure and toxicological studies.

6.2.2.1 Controlled Human Exposures

Beyond its direct effect on lung function, O_3 exposure causes an increase in airway responsiveness in human subjects as indicated by a reduction in the concentration of specific (e.g., ragweed) and non-specific (e.g., methacholine) agents required to produce a given reduction in FEV_1 or increase in sRaw. Increased airway responsiveness is an important consequence of exposure to ambient O_3, because the airways are then predisposed to narrowing upon inhalation of a variety of ambient stimuli including specific allergens, SO_2, and cold air.

Increases in airway responsiveness have been reported for exposures to 80 ppb O_3 and above. Horstman et al. (1990) evaluated airway responsiveness to methacholine in young healthy adults (22 M) exposed to 80, 100, and 120 ppb O_3 (6.6 h, quasi continuous moderate exercise, 39 L/min). Dose-dependent decreases of 33, 47, and 55% in the cumulative dose of methacholine required to produce a 100% increase in sRaw after exposure to O_3 at 80, 100, and 120 ppb, respectively, were reported. Molfino et al. (1991) reported increased allergen-specific airway responsiveness in mild asthmatics exposed to 120 ppb O_3 (1 h resting exposure). Due to safety concerns, however, the exposures in the Molfino et al. (1991) study were not randomized with FA conducted first and O_3 exposure second. Attempts to reproduce the findings of Molfino et al. (1991) using a

randomized exposure design have not found statistically significant changes in airway responsiveness at such low levels of O_3 exposure. At a considerably higher exposure to 250 ppb O_3 (3 h, light-to-moderate intermittent exercise, 30 L/min), Jörres et al. (1996) found significant increases in specific and non-specific airway responsiveness of mild asthmatics 3 h following O_3 exposure. Kehrl et al. (1999) found increased reactivity to house dust mite antigen in mild atopic asthmatics 16-18 h after exposure to 160 ppb O_3 (7.6 h, light quasi continuous exercise, 25 L/min). Holz et al. (2002) demonstrating that repeated daily exposure to lower concentrations of 125 ppb O_3 (3 h for four consecutive days; intermittent exercise, 30 L/min) causes an increased response to allergen challenge at 20 h postexposure in allergic airway disease.

O_3 exposure of asthmatic subjects, who characteristically have increased airway responsiveness at baseline relative to healthy controls (by nearly two orders of magnitude), can cause further increases in responsiveness (Kreit et al., 1989). Similar relative changes in airway responsiveness are seen in asthmatics and healthy control subject exposed to O_3 despite their markedly different baseline airway responsiveness. Several studies (Kehrl et al., 1999; Jorres et al., 1996; Molfino et al., 1991) have suggested an increase in specific (i.e., allergen-induced) airway reactivity. An important aspect of increased airway responsiveness after O_3 exposure is that this may represent a plausible link between ambient O_3 exposure and increased respiratory symptoms in asthmatics, and increased hospital admissions and ED visits for asthma.

Changes in airway responsiveness after O_3 exposure appear to resolve more slowly than changes in FEV_1 or respiratory symptoms (Folinsbee and Hazucha, 2000). Studies suggest that O_3-induced increases in airway responsiveness usually resolve 18 to 24 h after exposure, but may persist in some individuals for longer periods (Folinsbee and Hazucha, 1989). Furthermore, in studies of repeated exposure to O_3, changes in airway responsiveness tend to be somewhat less susceptible to attenuation with consecutive exposures than changes in FEV_1 (Gong et al., 1997a; Folinsbee et al., 1994; Kulle et al., 1982; Dimeo et al., 1981). Increases in airway responsiveness do not appear to be strongly associated with decrements in lung function or increases in symptoms (Aris et al., 1995). Recently, Que et al. assessed methacholine responsiveness in healthy young adults (83M, 55 F) at one day after exposure to 220 ppb O_3 and FA for 2.25 h (alternating 15 min periods of rest and brisk treadmill walking). Increases in airways responsiveness at 1 day post-O_3 exposure were not correlated with FEV_1 responses immediately following the O_3 exposure nor with changes in epithelial permeability assessed 1 day post-O_3 exposure.

6.2.2.2 Toxicology

In addition to human subjects, a number of species, including nonhuman primates, dogs, cats, rabbits, and rodents, have been used to examine the effect of O_3 exposure on airway hyperresponsiveness. With a few exceptions, commonly used animal models have been guinea pigs, rats, or mice acutely exposed to O_3 concentrations of 1 to 3 ppm to induce airway hyperresponsiveness. These animal models are helpful for determining underlying mechanisms of general airway hyperresponsiveness and are relevant for understanding airway responses in humans. Although 1-3 ppm may seem like a high exposure concentration, based on $^{18}O_3$ (oxygen-18-labeled ozone) in the BALF of humans and rats, an exposure of 0.4 ppm O_3 in exercising humans appears roughly equivalent to an exposure of 2 ppm in resting rats (Hatch et al., 1994).

A limited number of studies have observed airway hyperresponsiveness in rodents and guinea pigs after exposure to less than 0.3 ppm O_3. As previously reported in the 2006 O_3 AQCD, one study demonstrated that a very low concentration of O_3 (0.05 ppm for 4 h) induced airway hyperresponsiveness in some of the nine strains of rats tested (Depuydt et al., 1999). This effect occurred at a concentration of O_3 that was much lower than has been reported to induce airway hyperresponsiveness in any other species. Similar to ozone's effects on other endpoints, these observations suggest a genetic component plays an important role in O_3-induced airway hyperresponsiveness in this species and warrants verification in other species. More recently, Chhabra and colleagues (2010) demonstrated that exposure of ovalbumin (OVA)-sensitized guinea pigs to 0.12 ppm for 2 h/day for 4 weeks produced specific airway hyperresponsiveness to an inhaled OVA challenge. Interestingly, in this study , dietary supplementation of the guinea pigs with vitamins C and E ameliorated a portion of the airway hyperresponsiveness as well as indices of inflammation and oxidative stress. Larsen and colleagues did an O_3 concentration-response study in mice sensitized by 10 daily inhalation treatments with an OVA aerosol (Larsen et al., 2010). Although airway responsiveness to methacholine was increased in non-sensitized animals exposed to a single 3-h exposure to 0.5, but not 0.1 or 0.25, ppm O_3, airway hyperresponsiveness was observed after exposure to 0.1 and 0.25 ppm O_3 in OVA-sensitized mice. Shore and colleagues (Johnston et al., 2005b) have also demonstrated O_3-induced airway hyperresponsiveness in mice after exposure to 0.3 ppm O_3 for 3 hours. Mice that were exposed to the same concentration of O_3 for 72 hours showed no evidence of airway hyperresponsiveness, indicating attenuation of this effect. Thus, recent toxicological studies have demonstrated that O_3-induced airway hyperresponsiveness occurs in guinea pigs and mice after either acute or repeated exposure to relevant concentrations of O_3.

The mechanisms by which O_3 enhances the airway responsiveness to either specific (e.g., OVA) or non-specific (e.g., methacholine) bronchoprovocation are not clear, but appear to be associated with complex cellular and biochemical changes in the conducting airways. Considerable research effort has been directed towards exploring the causes of O_3-induced airway hyperresponsiveness, but the majority of such studies have been conducted at high concentrations of O_3. It is clear that inflammation plays a key role in O_3-induced airway hyperresponsiveness, although the precise mediators and cells that are involved have not been identified at relevant concentrations of O_3. Because inflammation is likely to play a role in O_3-induced airway hyperresponsiveness, the mechanism for this response may be multifactorial, involving the presence of cytokines, prostanoids, or neuropeptides; activation of macrophages, eosinophils, or mast cells; and epithelial damage that increases direct access of mediators to the smooth muscle or receptors in the airways that are responsible for reflex bronchoconstriction. Johnston et al. (2005b) demonstrated that airway hyperresponsiveness occurred in both wild type and IL-6 knockout mice exposed to 0.3 ppm O_3 despite reduction in markers of lung injury and inflammation in O_3-exposed IL-6 knockout mice. This same group of investigators has demonstrated the involvement of natural killer T cells, obesity, CXCR2, leptin, and IL-17 in O_3-induced airway hyperresponsiveness at exposure concentrations of 1-3 ppm O_3 (Garantziotis et al., 2010; Voynow et al., 2009; Pichavant et al., 2008; Williams et al., 2007b; Lu et al., 2006; Johnston et al., 2005a; Shore et al., 2003). A recent study demonstrated a role for mindin, an extracellular matrix protein, in the AHR response resulting from acute exposure to 1 ppm O_3 (Frush et al., In Press). Thus, a number of potential mediators and cells may play a role in O_3-induced airway hyperresponsiveness; mechanistic studies are discussed in greater detail in Chapter 5.

In order to evaluate the ability of O_3 to enhance specific and non-specific airway responsiveness, it is important to take into account the phenomenon of attenuation in ozone's effects. Several studies have clearly demonstrated that some effects caused by acute exposure are absent after repeated exposures to O_3. The ability of the pulmonary system to adapt to repeated insults to O_3 is complex, however, and experimental findings for attenuation to O_3-induced airway hyperresponsiveness are inconsistent. As described above, airway hyperresponsiveness was observed in mice after a 3-h exposure but not in mice exposed continuously for 72 hours to 0.3 ppm (Johnston et al., 2005b). However, the Chhabra study demonstrated O_3-induced airway hyperresponsiveness in guinea pigs exposed for 2 h/day for 10 days (Chhabra et al., 2010). Besides the obvious species disparity, these studies differ in that the mice were exposed continuously for 72 hours, whereas the guinea pigs were exposed intermittently over 10 days, suggesting that attenuation might be lost with periods of rest in between O_3 exposures.

6.2.3 Pulmonary Inflammation, Injury and Oxidative Stress

In addition to physiological pulmonary responses, respiratory symptoms, and airway hyperresponsiveness, O_3 exposure has been shown to result in increased epithelial permeability and respiratory tract inflammation. In general, inflammation can be considered as the host response to injury and the induction of inflammation as evidence that injury has occurred. Inflammation induced by exposure of humans to O_3 can have several potential outcomes: (1) inflammation induced by a single exposure (or several exposures over the course of a summer) can resolve entirely; (2) continued acute inflammation can evolve into a chronic inflammatory state; (3) continued inflammation can alter the structure and function of other pulmonary tissue, leading to diseases such as fibrosis; (4) inflammation can alter the body's host defense response to inhaled microorganisms, particularly in potentially susceptible populations such as the very young and old; and (5) inflammation can alter the lung's response to other agents such as allergens or toxins. Except for outcome (1), the possible chronic responses have only been directly observed in animals exposed to O_3. It is also possible that the profile of response can be altered in persons with preexisting pulmonary disease (e.g. asthma, COPD) or smokers. Oxidative stress has been shown to play a key role in initiating and sustaining O_3-induced inflammation. Secondary oxidation products formed as a result of reactions between O_3 and components of the ELF can increase the expression of cytokines, chemokines, and adhesion molecules and enhance airway epithelium permeability (Sections 5.3.3. and 5.3.4.).

6.2.3.1 Controlled Human Exposures

As reported in studies reviewed in the 1996 and 2006 O_3 AQCDs, acute O_3 exposure initiates an acute inflammatory response throughout the respiratory tract which has been observed to persist for at least 18-24 hours postexposure. A meta-analysis of 21 studies (Mudway and Kelly, 2004a) showed that neutrophils (PMN) influx in healthy subjects was linearly associated ($p<0.01$) with total O_3 dose (i.e., the product of O_3 concentration, exposure duration, and V_E). As with FEV_1 responses to O_3, within individual inflammatory responses to O_3 are generally reproducible and correlated between repeat exposures (Holz et al., 1999). Some individuals also appear to be intrinsically more susceptible to increased inflammatory responses to O_3 exposure (Holz et al., 2005).

The presence of PMNs in the lung has long been accepted as a hallmark of inflammation and is an important indicator that O_3 causes inflammation in the lungs. Neutrophilic inflammation of tissues indicates activation of the innate immune system and requires a complex series of events which are normally followed by processes that clear the

evidence of acute inflammation. Inflammatory effects have been assessed in vivo by lavage (proximal airway and bronchoalveolar), bronchial biopsy, and more recently, induced sputum. A single acute exposure (1-4 hours) of humans to moderate concentrations of O_3 (0.2-0.6 ppm) while exercising at moderate to heavy intensities results in a number of cellular and biochemical changes in the lung, including an inflammatory response characterized by increased numbers of PMNs, increased permeability of the epithelial lining of the respiratory tract, cell damage, and production of proinflammatory cytokines and prostaglandins (U.S. EPA, 2006b). These changes also occur in humans exposed to 80 and 100 ppb O_3 for 6-8 hours (Alexis et al., 2010; Peden et al., 1997; Devlin et al., 1991). Soluble mediators of inflammation such as the cytokines (e.g., IL-6, IL-8) and arachidonic acid metabolites (e.g., prostaglandin [PG]E_2, $PGF_{2\alpha}$, thromboxane, and leukotrienes [LTs] such as LTB_4) have been measured in the BALF of humans exposed to O_3. In addition to their role in inflammation, many of these compounds have bronchoconstrictive properties and may be involved in increased airway responsiveness following O_3 exposure. The possible relationship between repetitive bouts of acute inflammation in humans caused by O_3 and the development of chronic respiratory disease is unknown.

Studies reviewed in the 2006 O_3 AQCD reported that inflammatory responses do not appear to be correlated with lung function responses in either asthmatic or healthy subjects. In healthy adults (14 M, 6 F) and asthmatic (12 M, 6 F) volunteers exposed to 200 ppb O_3 (4 h with moderate quasi continuous exercise, V_E = 44 L/min), percent PMN and total protein in BAL fluids were significantly increased in the asthmatics relative to the healthy controls. Spirometric measures of lung function were significantly decreased following the O_3 exposure in both groups, but were not significantly different between the asthmatic and healthy subjects. Effects of O_3 on PMN and total protein were not correlated with changes in FEV_1 or FVC (Balmes et al., 1997; Balmes et al., 1996). Devlin et al. (1991) exposed healthy adults (18 M) to 80 and 100 ppb O_3 (6.6 h with moderate quasi continuous exercise, 40 L/min). In BAL fluid collected 18 h after exposure to 100 ppb O_3, significant increases in PMNs, protein, PGE2, fibronectin, IL-6, lactate dehydrogenase, and α-1 antitrypsin compared to FA. Similar but smaller increases in all mediators were found after exposure to 80 ppb O_3 except for protein and fibronectin. Changes in BAL markers were not correlated with changes in FEV_1. Holz et al. (1999) examined inflammatory responses in healthy (n=21) and asthmatic (n=15) subjects exposed to 125 and 250 ppb O_3 (3 h, light intermittent exercise, 26 L/min). Significantly increased percent PMN in sputum due to O_3 exposure was observed in both asthmatics and healthy subjects following the 250 ppb exposure. At the lower, 125 ppb exposure, only the asthmatic group experienced statistically significantly increases in the percent PMN. Significant decrements in FEV_1 were only found following exposure to 250 ppb; these changes in FEV_1 did not differ significantly between the asthmatic and

healthy groups, nor were changes in FEV_1 correlated with changes in PMN levels. In contrast to these earlier findings, Vagaggini et al. (2010) recently reported a significant (r=0.61, p=0.015) correlation between changes in FEV_1 and changes in sputum neutrophils in mild-to-moderate asthmatics (n=23; 33 ± 11 years) exposed to 300 ppb O_3 for 2 hours with moderate exercise.

The time course of the inflammatory response to O_3 in humans has not been fully characterized. Different markers exhibit peak responses at different times. Studies in which lavages were performed 1 hour after O_3 exposure (1 h at 0.4 ppm or 4 h at 0.2 ppm) have demonstrated that the inflammatory responses are quickly initiated (Torres et al., 1997; Devlin et al., 1996; Schelegle et al., 1991). Inflammatory mediators and cytokines such as IL-8, IL-6, and PGE_2 are greater at 1 h than at 18 h post-O_3 exposure (Torres et al., 1997; Devlin et al., 1996). However, IL-8 still remained elevated at 18 h post-O_3 exposure (4 h at 0.2 ppm O_3 versus FA) in healthy subjects (Balmes et al., 1996). Schelegle et al. (1991) found increased PMNs in the "proximal airway" lavage at 1, 6, and 24 hours after O_3 exposure (4 h at 0.2 ppm O_3), with a peak response at 6 hours. However, at 18-24 hours after O_3 exposure, PMNs remain elevated relative to 1 hour postexposure (Torres et al., 1997; Schelegle et al., 1991).

Alexis et al. (2010) recently reported that a 6.6-hour exposure with moderate exercise to 80 ppb O_3 caused increased sputum neutrophil levels at 18 hours postexposure in young healthy adults (n=15; 24 ± 1 years). In a prior study, Alexis et al. (2009) found genotype effects on inflammatory responses but not lung function responses to a 2 h-exposure to 400 ppb O_3. At 4 h post O_3 exposure, both GSTM1 genotypes had significant increases in sputum neutrophils with a tendency for a greater increase in GSTM1-sufficient than null individuals. At 24 h postexposure, neutrophils had returned to baseline levels in the GSTM1-sufficient individuals. In the GSTM1-null subjects, however, neutrophil levels increased further from 4 h to 24 h and were significantly greater than both baseline levels and 24 h levels in GSTM1-sufficient individuals. Alexis et al. (2009) found that GSTM1-sufficient individuals (n=19; 24 ± 3 years) had a decrease in macrophage levels at 4--24 hours postexposure to 400 ppb O_3 for 2 h with exercise. These studies also provide evidence for activation of innate immunity and antigen presentation, as discussed in Section 5.3.6. Effects of the exposure apart from O_3 cannot be ruled out in the Alexis et al. (2010; 2009) studies, however, since no FA exposure was conducted.

Kim et al. (2011) has more recently shown a significant ($p < 0.001$) increase in sputum neutrophil levels following a 6.6-hour exposure to 60 ppb O_3 relative to FA in young healthy adults (13 F, 11 M; 25.0 ± 0.5 years). There was no significant effect of GSTM1 genotype (half GSTM1-null) on the inflammatory responses observed in these

individuals. Previously, inflammatory responses had only been evaluated down to a level of 80 ppb O_3.

Inflammatory responses to O_3 exposure have also been studied in asthmatic subjects (Peden et al., 1997; Scannell et al., 1996; Basha et al., 1994). In these studies, asthmatics showed significantly more neutrophils in BALF (18 hours postexposure) than did 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 (twofold increase), as well as neutrophilic inflammation (threefold increase). In a study of subjects with intermittent asthma exposed to 0.4 ppm O_3 for 2 hours, increases in eosinophil cationic protein, neutrophil elastase and IL-8 were found to be significantly increased 16 hours postexposure and comparable in induced sputum and BALF (Hiltermann et al., 1999). Scannell et al. (1996) also reported that IL-8 tends to be higher in the BALF of asthmatics compared to nonasthmatics following O_3 exposure, suggesting a possible mediator for the significantly increased neutrophilic inflammation in those subjects. Bosson et al. (2003) found significantly greater epithelial expression of IL-5, IL-8, granulocyte-macrophage colony-stimulating factor and epithelial cell-derived neutrophil-activating peptide-78 in asthmatics compared to healthy subjects following exposure to 0.2 ppm O_3 for 2 h. In contrast, Stenfors et al. (2002) did not detect a difference in the O_3-induced increases in neutrophil numbers between 15 mild asthmatic and 15 healthy subjects by bronchial wash at the 6 h postexposure time point. However, the asthmatics were on average 5 years older than the healthy subjects in this study, and it is not yet known how age affects inflammatory responses. It is also possible that the time course of neutrophil influx differs between healthy and asthmatic individuals. Differences between asthmatics and healthy subjects in ozone-mediated activation of innate and adaptive immune responses have been observed in two studies (Hernandez et al., 2010; Bosson et al., 2003), as discussed in Sections 6.2.5.4 and 5.4.2.2.

Vagaggini et al. (2002) investigated the effect of prior allergen challenge on responses in mild asthmatics exposed for 2 h to 0.27 ppm O_3 or filtered air. At 6 h postexposure, eosinophil numbers in induced sputum were found to be significantly greater after O_3 than after air exposures. Studies such as this suggest that the time course of eosinophil and neutrophil influx following O_3 exposure can occur at 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 O_3. For example, in an *in vitro* study of primary human nasal epithelial cells and BEAS-2B cell line, cytokine production induced by rhinovirus infection was enhanced synergistically by concurrent exposure to O_3 at 0.2 ppm for 3 hours (Spannhake et al., 2002).

Markers from BALF following both 2 hours (Devlin et al., 1997) and 4 hours (Jorres et al., 2000; Christian et al., 1998) repeated O_3 exposures (up to 5 days) indicate that there is ongoing cellular damage irrespective of the attenuation of some cellular inflammatory responses of the airways, pulmonary function, and symptom responses. Devlin et al. (1997) found that several indicators of inflammation (e.g., PMN, IL-6, PGE_2, fibronectin) were attenuated after 5 days of exposure (i.e., values were not different from FA). However, other markers (LDH, IL-8, total protein, epithelial cells) did not show attenuation, suggesting that tissue damage probably continues to occur during repeated exposure. Some cellular responses did not return to baseline levels for more than 10-20 days following O_3 exposure. Christian et al. (1998) showed decreased numbers of neutrophils and a decrease in IL-6 levels in healthy adults after 4 days of exposure versus the single exposure to 0.2 ppm O_3 for 4 h. Jörres et al. (2000) also found both functional and BALF cellular responses to O_3 were abolished at 24 hours postexposure following the fourth exposure day. However, levels of total protein, IL-6, IL-8, reduced glutathione and ortho-tyrosine was still increased significantly. In addition, visual scores (bronchoscopy) for bronchitis and erythema and the numbers of neutrophils in bronchial mucosal biopsies were increased. Results indicate that, despite an attention of some markers of inflammation in BALF and pulmonary function decrements, inflammation within the airways persists following repeated exposure to O_3. The continued presence of cellular injury markers indicates a persistent effect that may not necessarily be recognized due to the attenuation of spirometric and symptom responses.

A number of studies show that O_3 exposures increase epithelial cell permeability through direct (technetium-99m labeled diethylene triamine pentaacetic acid, ^{99m}Tc-DTPA, clearance) and indirect (e.g., increased BALF albumin, protein) techniques. Kehrl et al. (1987) showed increased ^{99m}Tc-DTPA clearance in healthy young adults at 75 minutes postexposure to 0.4 ppm O_3 for 2 hours. Foster and Stetkiewicz (1996) have shown that increased ^{99m}Tc-DTPA clearance persists for at least 18-20 hours post-O_3 exposure (130 minutes to average O_3 concentration of 0.24 ppm), and the effect is greater at the lung apices than at the base. Increased BALF protein, suggesting O_3-induced changes in epithelial permeability, have also been reported at 1 hour and 18 hours postexposure (Devlin et al., 1997; Balmes et al., 1996). Meta-analysis of results from 21 publications (Mudway and Kelly, 2004a), showed that increased BALF protein is associated with total inhaled O_3 dose (i.e., the product of O_3 concentration, exposure duration, and V_E).

It has been postulated that changes in permeability associated with acute inflammation may provide increased access of inhaled antigens, particles, and other inhaled substances deposited on lung surfaces to the smooth muscle, interstitial cells, and the blood. Hence, increases in epithelial permeability following O_3 exposure might lead to increases in airway responsiveness to specific and nonspecific agents. Que et al. investigated this

hypothesis in healthy young adults (83M, 55 F) exposed to 220 ppb O_3 for 2.25 h (alternating 15 min periods of rest and brisk treadmill walking). As has been observed by others for FEV_1 responses, within individual changes in permeability were correlated between sequential O_3 exposures. This indicates differences in susceptibility to epithelial damage from O_3 exposure among individuals. Increases in epithelial permeability at 1 day post-O_3 exposure were not correlated with FEV_1 responses immediately following the O_3 exposure nor with changes in airway responsiveness to methacholine in assessed 1 day post-O_3 exposure. The authors concluded that changes in FEV_1, permeability, and airway responsiveness following O_3 exposure were relatively constant over time in young healthy adults; although, these responses appear to be mediated by differing physiologic pathways.

6.2.3.2 Epidemiology

In the 2006 O_3 AQCD, epidemiologic evidence of changes in pulmonary inflammation in association with short-term ambient O_3 exposure (30-min or 1-h max) was limited to observations of increases in nasal lavage levels of inflammatory cell counts, eosinophilic cationic protein, and myeloperoxidases (U.S. EPA, 2006b). As a result of the development of less invasive methods to collect exhaled breath samples repeatedly from individuals in the field, the number of studies assessing ambient O_3-related changes in lower airway inflammation and oxidative stress in recent years has increased dramatically. Although most of the biomarkers examined in these studies were not specific to the lung, most studies collected exhaled breath, exhaled breath condensate (EBC), nasal lavage fluid, or induced sputum with the aim of monitoring inflammatory responses in airways, as opposed to monitoring systemic responses in blood. These recent studies form a larger base to establish coherence with findings from human experimental and animal toxicological studies that have measured similar or related endpoints and provide further biological plausibility for associations of ambient O_3 exposure with respiratory symptoms and lung function decrements. These biological markers also allow the assessment of short-term O_3-related acute respiratory effects in populations that are less likely to experience respiratory symptoms, including healthy populations and groups with increased outdoor exposures.

Table 6-14 Mean and upper percentile ozone concentrations in studies examining biological markers of pulmonary inflammation and oxidative stress

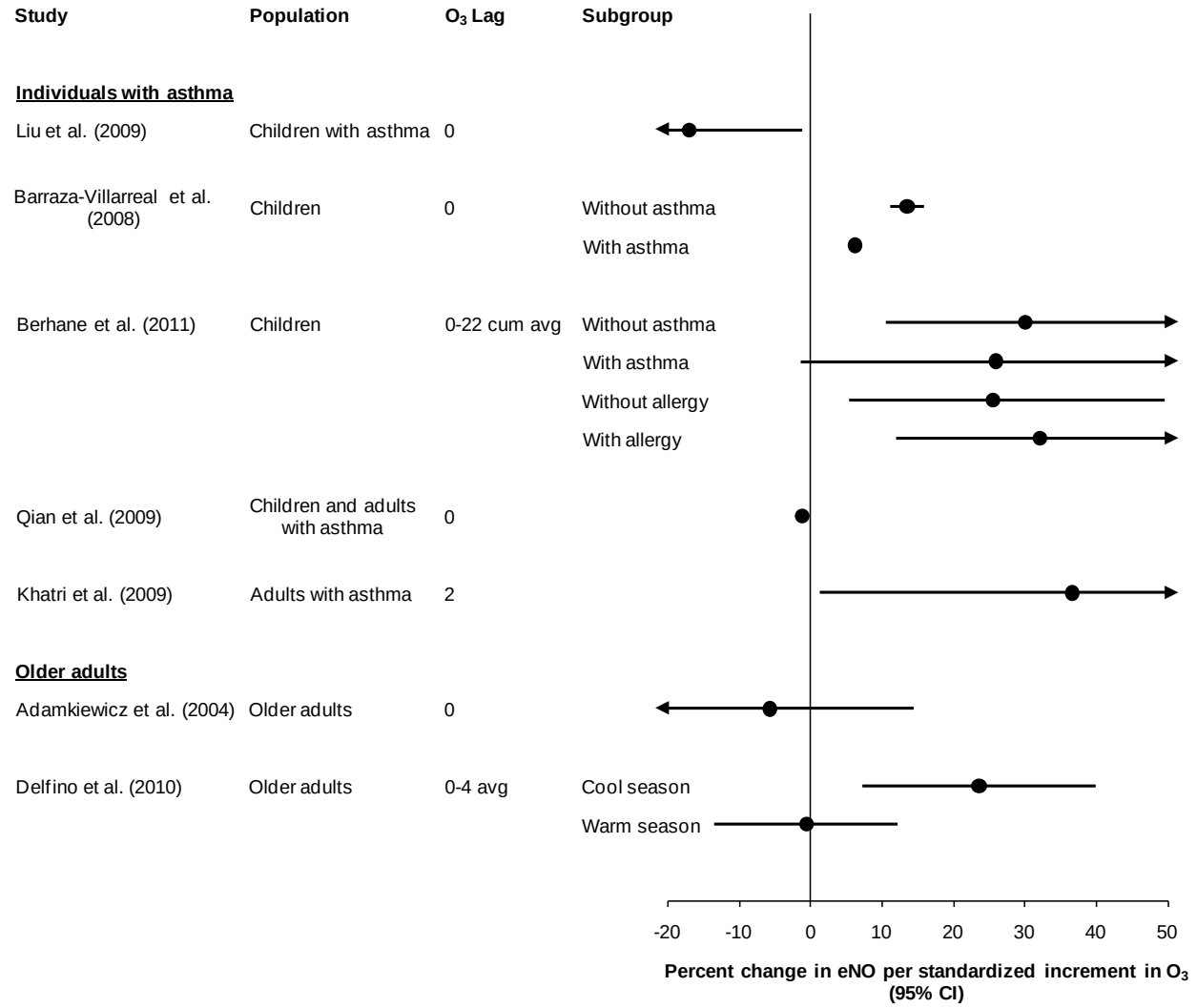
Study	Location	Years	O_3 Averaging Time	Mean/Median Concentration (ppb)	Upper Percentile Concentrations (ppb)
Qian et al. (2009)	Boston, MA; New York, NY; Denver, CO; Philadelphia, PA; San Francisco, CA; Madison, WI (SOCS)	1997-1999 All-year	8-h max	33.6	75th: 44.4, Max: 91.5
Khatri et al. (2009)	Atlanta, GA	2003, 2005, 2006 Warm season	8-h max	59[a]	Max: 73[a]
Ferdinands et al. (2008)	Atlanta, GA	2004 Warm season	1-h max	61 (median)	75th: 67
Adamkiewicz et al. (2007)	Steubenville, OH	2000 Cold season	24-h avg 1-h avg[b]	15.3 19.8	75th: 20.2, Max: 32.2 75th: 27.5, Max: 61.6
Berhane et al. (2011)	13 Southern California Communities	September 2004- June 2005	8-h avg (10:00 a.m. - 6:00 p.m.)	NR	NR
Delfino et al. (2010a)	Los Angeles, CA	2005-2007 All-year	24-h avg	Warm season: 33.3 Cool season: 20.6	Max: 76.4 Max: 44.9
Liu et al. (2009a)	Windsor, ON, Canada	2005 Cold season	24-h avg	13.0	95th: 26.5
Sienra-Monge et al. (2004)	Mexico City, Mexico	1999-2000 All-year	8-h max	66.2	Max: 142.5
Barraza-Villarreal et al. (2008)	Mexico City, Mexico	2003-2005 All-year	8-h max	31.6	Max (8-h max): 86.3
Romieu et al. (2008)	Mexico City, Mexico	2004 All-year	8-h max	31.1	75th: 38.3 Max: 60.7
Nickmilder et al. (2007)	southern Belgium	2002 Warm season	1-h max 8-h max	NR NR	Max (across 6 camps): 24.5-112.7[c] Max (across 6 camps): 18.9-81.1[c]
Chimenti et al. (2009)	Sicily, Italy	NR All-year	8-h avg (7:00 a.m.-3:00 p.m.)	Fall: 32.7 (pre-race), 35.1 (race)[c] Winter: 37.0 (pre-race), 30.8 (race)[c] Summer: 51.2 (pre-race), 46.1 (race)[c]	NR

Max = Maximum, NR = Not Reported.

[a]Individual-level exposure estimates were derived based on time spent in the vicinity of various O_3 monitors.

[b]Average O_3 oncentration in the 1 h preceding eNO collection.

[c]Concentrations converted from µg/m^3 to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).



Results are presented first for children with asthma followed by results for adults with asthma and older adults. Effect estimates are from single-pollutant models and are standardized to a 30-ppb increase for 8-h max or 8-h avg ozone exposures and a 20-ppb increase for 24-h avg ozone exposures.

Figure 6-10 Percent change in exhaled nitric oxide (eNO) per standardized increment in ambient ozone exposure in studies of individuals with and without asthma.

Table 6-15 Additional characteristics and quantitative data for studies represented in Figure 6-10

Study	Location/ Population	O_3 Lag	O_3 Averaging Time	Subgroup	Standardized Percent Change (95% CI)[a]
Studies in individuals with asthma					
Liu et al. (2009a)	Windsor, ON, Canada Children with asthma	0	24-h avg		-17.0 (-30.3, -1.1)
Barraza-Villarreal et al. (2008)	Mexico City, Mexico Children	0	8-h max	Without asthma With asthma	13.5 (11.2, 15.8) 6.2 (6.0, 6.5)
Berhane et al. (2011)	12 Southern California communities Children	0-22 cum avg	8-h avg (10:00 a.m.-6:00 p.m.)	Without asthma With asthma Without allergy With allergy	30.1 (10.6, 53.2) 26.0 (-1.4, 60.9) 25.5 (5.3, 49.6) 32.1 (12.0, 55.9)
Qian et al. (2009)	6 U.S. communities Children and adults with asthma	0	8-h max		-1.2 (-1.7, -0.64)
Khatri et al. (2009)	Atlanta, GA Adults with asthma	2	8-h max		36.6 (1.2, 71.9)
Studies in older adults					
Adamkiewicz et al. (2007)	Steubenville, Ohio Older adults	0	24-h avg		-5.7 (-25.9, 14.5)
Delfino et al. (2010a)	Los Angeles, CA Older adults	0-4 avg	24-h avg	Cool season Warm season	23.6 (7.3, 39.9) -0.58 (-13.4, 12.3)

[a]Effect estimates are standardized to a 30-ppb increase for 8-h max or 8-h avg O_3 and a 20-ppb increase for 24-h avg O_3.

Table 6-16 Associations between short-term ambient ozone exposure and biological markers of pulmonary inflammation and oxidative stress

Study	Location/ Population	O_3 Lag	O_3 Averaging Time	Biological Marker	Subgroup	Effect Estimate (95% CI)[a]
Liu et al. (2009a)	Windsor, ON, Canada Children with asthma	0	24-h avg	EBC 8-isoprostane (% change) EBC TBARS (% change)		10.2 (-9.2, 33.5) 7.2 (-18.3, 40.7)
Romieu et al. (2008)	Mexico City, Mexico Children with asthma	0	8-h max	EBC MDA[b]		1.3 (1.0, 1.7)
Barraza-Villarreal et al. (2008)	Mexico City, Mexico Children	0	8-h max	Nasal lavage IL-8 (pg/ml) EBC pH	Without asthma With asthma Without asthma With asthma	1.6 (1.4, 1.8) 1.6 (1.4, 1.9) -0.10 (-0.27, 0.08)[c] -0.10 (-0.20, 0.01)[c]
Sienra-Monge et al. (2004)	Mexico City, Mexico Children with asthma	0-2 avg	8-h max	Nasal lavage IL-8[b] Nasal lavage IL-6[b] Nasal lavage Uric acid[b] Nasal lavage GSx[b]	Placebo Antioxidant Placebo Antioxidant Placebo Antioxidant Placebo Antioxidant	1.4 (1.0, 2.0) 1.0 (0.70, 1.5) 1.5 (1.2, 2.0) 1.0 (0.76, 1.4) 0.88 (0.70, 1.1) 1.1 (0.84, 1.5) 0.90 (0.82, 0.99) 0.91 (0.83, 0.98)
Khatri et al. (2009)	Atlanta, GA Adults with asthma	2	8-h max	Blood eosinophils (% change)		2.4 (0.62, 4.2)
Ferdinands et al. (2008)	Atlanta, GA Children exercising outdoors	0	1-h max	EBC pH		2.5 (-0.20, 5.1)[c]

EBC = exhaled breath condensate, TBARS = thiobarbituric acid reactive substances, MDA = malondialdehyde, IL-8 = interleukin 8, IL-6 = interleukin 6, Antioxidant=group supplemented with vitamins C and E, GSx = glutathione.

[a]Effect estimates are standardized to a 40-, 30- and 20-ppb increase for 1-h max, 8-h max, and 24-h avg O3, respectively

[b]Models analyzed log-transformed biological markers. Therefore, effect estimates represent the ratio of the geometric means of biological markers for a standardized increase in O_3 exposure. An estimate less than 1 indicates a decrease in pulmonary inflammation or oxidative stress for an increase in O_3 exposure, and an estimate greater than 1 indicates an increase in pulmonary inflammation or oxidative stress for an increase in O_3 exposure.

[c]Negative and positive effect estimates indicate increases and decreases in pulmonary inflammation, respectively.

Despite the strengths of biomarker studies, it is important to note that research in this field continues to develop, and several uncertainties are recognized that may limit the interpretations of associations between ambient O_3 exposure and changes in biomarker levels. Current areas of development include examination of the clinical relevance of the observed magnitudes of changes in biological markers of pulmonary inflammation (Murugan et al., 2009; Duramad et al., 2007), characterization of the time course of changes between biomarker levels and other endpoints of respiratory morbidity, development of standardized methodologies for collection, improvement of the sensitivity and specificity of assay methods, and characterization of subject factors (e.g., asthma severity and recent medication use) that contribute to inter-individual variability. These sources of uncertainty may contribute to differences in findings among studies.

In recent epidemiologic studies, the biomarker most frequently measured was exhaled nitric oxide (eNO), likely related to its ease of collection in the field and automated measurement. Other biological media analyzed included EBC, induced sputum, and nasal lavage fluid, all of which are hypothesized to contain aerosolized particles and/or cells from fluid lining the lower and upper airways (Balbi et al., 2007; Howarth et al., 2005; Hunt, 2002). These fluids contain cytokines, cells, and markers of oxidative stress that mediate inflammatory responses. In particular, several of the cytokines, cells, and markers of oxidative stress examined in epidemiologic studies also have been examined in controlled human exposure and toxicological studies.Table 6-14 presents the characteristics and ambient O_3 concentration data from recent studies assessing associations between O_3 exposure and biological markers of pulmonary inflammation and oxidative stress. Many recent studies reported positive associations between short-term ambient O_3 exposure and increases in pulmonary inflammation and oxidative stress, in particular, studies of children with asthma conducted in Mexico City (Figure 6-10 and Tables 6-15 and 6-16).

Populations with Asthma

Exhaled Nitric Oxide

Nitric oxide or eNO has not been examined in controlled human exposure or toxicological studies of O_3 exposure. However, several lines of evidence support its analysis as an indicator of pulmonary inflammation in epidemiologic studies. Inducible nitric oxide synthase can be activated by pro-inflammatory cytokines, and NO can be produced by cells such as neutrophils, eosinophils, and epithelial cells in the lung during an inflammatory response (Barnes and Liew, 1995). Additional support is provided by observations of higher eNO in individuals with asthma, and increases in the levels during acute exacerbations (Jones et al., 2001; Kharitonov and Barnes, 2000).

As indicated in Figure 6-10 and Table 6-15, several studies found that short-term ambient O_3 exposure (8-h max or avg) was associated with increases in eNO in children with asthma. Liu et al. (2009a) (described in Section 6.2.1.2) reported O_3-associated decreases in eNO; however, this study was restricted to winter months. In this study, results for EBC levels of TBARS and 8-isoprostane as well as lung function did not provide strong evidence of O_3 effects on airway oxidative stress.

The two studies that compared children with and without asthma did not find larger O_3-associated increases in eNO in children with asthma (Figure 6-10 and Table 6-15). Among children in Southern California, Berhane et al. (2011) examined a 0-22 day cumulative average of 8-h avg (10:00 a.m.-6:00 p.m.) O_3 and estimated similar effects for children with and without asthma and children with and without allergy. Among children in Mexico City, Barraza-Villarreal et al. (2008) examined lag 0 of 8-h max O_3 and estimated larger effects for children without asthma.

In the two studies that included adults with asthma, ambient O_3 exposure was associated with both decreases and increases in eNO (Khatri et al., 2009; Qian et al., 2009). In the multicity salmeterol (β-2 adrenergic agonist) trial (Boston, MA; New York, NY; Denver, CO; Philadelphia, PA; San Francisco, CA; and Madison, WI), eNO was collected every 2-4 weeks over a 16-week period from 119 subjects with persistent asthma, 87% of whom were 20-65 years of age (Qian et al., 2009). Among all subjects, lag 0 of 8-h max O_3 was associated with a decrease in eNO as were exposures lagged 1 to 3 days and averaged over 5 days. Results did not vary among the salmeterol, CS, and placebo groups, indicating that the counterintuitive findings for O_3 were not simply due to the reduction of inflammatory responses by medication use. The authors suggested that at higher O_3 exposures, O_3 may rapidly react with NO in airways to form reactive nitrogen species such as peroxynitrite. However, in the other study of adults with asthma, ambient concentrations of 8-h max O_3 were higher, and a positive association was found with eNO (Khatri et al., 2009). In this study conducted during a summer season in Atlanta, GA, a 30-ppb increase in lag 2 of 8-h max O_3 was associated with a 36.6% increase in eNO (95% CI: 1.2, 71.9). These findings should be interpreted with caution as they were based on a single eNO measurement per subject and were not adjusted for any meteorological factors.

Other biological markers of pulmonary inflammation and oxidative stress

As indicated in Table 6-16, studies have found associations between short-term ambient O_3 exposure and changes in the levels of proinflammatory cytokines and cells, indicators of oxidative stress, and antioxidants. Importantly, any particular endpoint was examined only in one to two studies, and the evidence in individuals with asthma is derived primarily from studies conducted in Mexico City (Romieu et al., 2009; Barraza-Villarreal

et al., 2008; Romieu et al., 2008; Sienra-Monge et al., 2004). Despite the limited evidence, the epidemiologic observations are well-supported by controlled human exposure and toxicological studies that have measured analogous endpoints.

Several of the modes of action of O_3 are mediated by secondary oxidation products produced in the airways by O_3 (Section 5.3.3). Reactive oxygen species (ROS) are involved in the regulation of inflammation via regulation of the expression of cytokines and activity of inflammatory cells in airways (Heidenfelder et al., 2009). In controlled human exposure and toxicological studies, prostaglandins have been frequently measured to indicate O_3-induced increases in oxidative stress (Sections 5.3.3 and 6.2.3.1). Prostaglandins are produced by the peroxidation of arachidonic acid in cell membranes (Morrow et al., 1990). Romieu et al. (2008) analyzed biweekly samples of EBC malondialdehyde (MDA), a thiobarbituric acid reactive substance, which like prostaglandins, is derived from oxidative degradation of lipids (Janero, 1990). The ratio of the geometric means of MDA was 1.3 (1.0, 1.7) per a 30-ppb increase in lag 0 of 8-h max O_3. Similar results were reported for lags 1 and 0-1 average exposures. An important limitation of the study was that 25% of EBC samples had nondetectable levels of MDA. Thus, the random assignment of concentrations between 0 and 4.1 nmol may have contributed random measurement error to the estimated O_3 effects. Because MDA represents less than 1% of lipid peroxides and is present at low concentrations, its reliability as a marker of oxidative stress in vivo has been questioned. However, Romieu et al. (2008) pointed to their observations of statistically significant associations of EBC MDA levels with nasal lavage IL-8 levels to support its analysis as a biologically-relevant indicator of pulmonary inflammation.

Uric acid and glutathione are ROS scavengers that are present in the airway ELF. While the roles of these markers in the inflammatory cascade of asthma are not well characterized, they are observed to be consumed in response to short-term O_3 exposure in controlled human exposure and animal studies (Section 5.3.3). Results from an epidemiologic study also indicate that ambient O_3 exposure may stimulate an antioxidant response. In a panel study with three measurements of nasal lavage at 3-week intervals, Sienra-Monge et al. (2004) found O_3-associated decreases in nasal lavage levels of uric acid and glutathione in children with asthma not supplemented with antioxidant vitamins (Table 6-16). The magnitude of association was similar for O_3 exposures lagged 2 or 3 days and averaged over 3 days.

Both controlled human exposure and toxicological studies find O_3-induced increases in the cytokines IL-6 and IL-8 (Sections 5.3.3, 6.2.3.1, and 6.3.3.3), which are involved in initiating an influx of neutrophils, a hallmark of inflammation induced by short-term O_3 exposure. Recent epidemiologic studies produced similar findings. Barraza-Villarreal

et al. (2008) observed that a 30-ppb increase in lag 0 of 8-h max O_3 was associated with a 1.61 pg/ml increase (95% CI: 1.4, 1.8) in IL-8. In another study of children with asthma in Mexico City, Sienra-Monge et al. (2004) found that lags 2, 3, and 0-2 avg of 8-h max O_3 were associated with increases in nasal lavage levels of IL-6 and IL-8 (placebo group), with the largest effects estimated for lag 0-2 average exposure (Table 6-16).

Neutrophil influx has been a prominent characterisitc of O_3-induced inflammation; however, controlled human exposure studies also have found O_3-induced increases in eosinophils in adults with asthma (Section 6.2.3.1). Eosinophils are believed to be the main effector cells that initiate and sustain inflammation in asthma and allergy (Schmekel et al., 2001). Consistent with these findings, in a cross-sectional study of adults with asthma in Atlanta, GA, a 30-ppb increase in lag 0 of 8-h max O_3 was associated with a 2.4% increase (0.62, 4.2) in blood eosinophils (Khatri et al., 2009). These results were not adjusted for meteorological factors.

The pH of EBC also was analyzed as an indicator of pulmonary inflammation. EBC pH is thought to reflect the proton-buffering capacity of ammonium in airways. It has been widely used in the clinical assessment of asthma, is consistently lower in subjects with asthma, decreases upon acute asthma exacerbation (on the order of 2 units), and is negatively correlated with airway levels of proinflammatory cytokines (Carpagnano et al., 2005; Kostikas et al., 2002; Hunt et al., 2000). In addition to finding O_3-associated increases in eNO and nasal lavage IL-8, Barraza-Villarreal et al. (2008) found small O_3-associated decreases in EBC pH (Table 6-16).

The prominent influences of ROS and antioxidants in mediating the effects of O_3 provide biological plausibility for the effect modification by antioxidant supplementation. The modulation of O_3-associated lung function by antioxidant capacity has been described in controlled human exposure and epidemiologic studies (Sections 6.2.1.1 and 6.2.1.2). Epidemiologic studies also found that higher levels of dietary or supplemented antioxidants attenuated inflammation and oxidative stress. Sienra-Monge et al. (2004) conducted a 12 week-trial with daily vitamin C and E supplements. In the antioxidant group, the ratios of the geometric means of nasal lavage IL-6 and IL-8 per 30-ppb increases in lag 0-2 avg of 8-h max O_3 were 1.0, reflecting no increases with increases in O_3 exposure (Table 6-16). Effect modification by antioxidant supplementation was not consistent for uric acid and glutathione (Table 6-16). Ozone was associated with increases in uric acid in the antioxidant group and decreases in the placebo group across O_3 lags of exposure. Associations with glutathione were similar in both groups. Therefore, the results do not clearly delineate the interactions among inhaled O_3, endogenous antioxidants, and dietary supplementations of antioxidants. In another cohort of children with asthma in Mexico City, a diet high in fruits and vegetables was found to

protect against O_3-related increases in nasal lavage IL-8 (Romieu et al., 2009). At high ambient O_3 levels (≥ 38 ppb, 8-h max), a 1-unit increase in FVI was associated with a 0.219 pg/ml decrease (95% CI: -0.38, -0.05) in IL-8. The protective effect was diminished by about 49% at O_3 levels of 25 ppb or lower. Results from these two studies indicate that augmenting the circulating levels of antioxidants, through diet or vitamin supplements, may reduce nasal inflammation associated with high ambient O_3 exposures.

Clinical significance of ozone-associated changes in pulmonary inflammation and oxidative stress in children with asthma

While the results of epidemiologic studies in children with asthma were consistent with the known modes of action of O_3 in consuming antioxidants and inducing oxidative stress and pulmonary inflammation (Section 5.3.3), the clinical significance of these changes has not been well-characterized. The levels of several of the biological markers such as eNO, EBC pH, and MDA have been shown to differ between subjects with and without asthma and change acutely during an acute asthma exacerbation (Corradi et al., 2003; Hunt et al., 2000); however, the magnitudes of change for these conditions are not well-defined. Several studies conducted in individuals with asthma found large O_3-associated increases in eNO; effect estimates ranged between a 6 and 36% increase per standardized increment in ambient O_3 concentration[1] (Figure 6-10 and Table 6-15). Standardized increments in ambient O_3 exposure were associated with smaller (1-2%) increases in interleukins or indicators of oxidative stress (Khatri et al., 2009; Barraza-Villarreal et al., 2008) (Romieu et al., 2008; Sienra-Monge et al., 2004).

Some studies permitted the evaluation of the potential clinical relevance of these changes in eNO through the concurrent assessment of respiratory symptoms. Among children with asthma in Mexico City, O_3 exposure was associated with increases in eNO and nasal lavage IL-8 and concurrently assessed cough but not wheeze (Barraza-Villarreal et al., 2008). Among adults with asthma in Atlanta, O_3 was associated with increases in eNO, blood eosinophils, and a decrease in quality of life score, which incorporates indices for symptoms, mood, and activity limitations (Khatri et al., 2009). These findings suggest that the more subtle O_3-associated increases in biological markers of airway inflammation may be sufficient to result in respiratory symptoms or activity limitations.

Children without Asthma

Recent studies found that short-term O_3 exposure (8-h max or avg) was associated with indicators of airway inflammation in children without asthma (Berhane et al., 2011; Barraza-Villarreal et al., 2008) (Figure 6-10 and Tables 6-15 and 6-16). In the panel

[1] Effect estimates were standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max, and 24-h avg O_3.

study of children in Mexico City, O_3 exposure was associated with a larger increase in eNO in the children without asthma than with asthma (13.5% versus 6.2% increase per 30-ppb increase in lag 0 of 8-h max O_3). Ozone was associated with similar magnitudes of changes in IL-8 and EBC pH in children with and without asthma. A distinguishing feature of this study was that most of the children without asthma were atopic (72%) as indicated by positive skin prick tests, which may have contributed to the similar effects of O_3 exposure observed in children with and without asthma.

However, the Southern California Children's Health Study estimated similar effects for 8-h avg (10:00 a.m.-6:00 p.m.) ambient O_3 exposure on eNO in children with and without respiratory allergy (Berhane et al., 2011). Results from this large study (n = 2240 children) provided evidence that ambient O_3 exposure increases airway inflammation in healthy children. In comparison with other studies, this analysis from the Children's Health Study provided detailed information on differences in association among various lags of 8-h avg (10:00 a.m.-6:00 p.m.) O_3 exposure. Consistent with other studies examining pulmonary inflammation and oxidative stress, Berhane et al. (2011) found that relatively shorter lags of exposure, including 1 to 5 days, were associated with increases in eNO. However, in an examination of several types of lag-based models, including unconstrained lag models, polynomial distributed lag models, spline-based distributed lag models, and cumulative lag models, investigators found that a 23-day cumulative lag model best fit the data. Among the studies evaluated in the current assessment, Berhane et al. (2011) was unique in evaluating and finding larger effects for cumulative average O_3 exposures over multiple weeks (e.g., 13-30 days). O_3 exposures averaged over the several hours preceding eNO collection were not significantly associated with eNO. The mechanism for the effects of O_3 peaking with a 23-day cumulative lag of exposure is not known.

Populations with Increased Outdoor Exposures

In a limited number of available studies, ambient O_3 exposure was not consistently associated with pulmonary inflammation in populations with increased outdoor exposures. Important limitations of these studies include small numbers of subjects and repeated measurements. In a cross-sectional study of children at camps in south Belgium, although O_3 was not associated with lung function, an association was found for eNO (Nickmilder et al., 2007). Children at camps with lag 0 1-h max O_3 concentrations above 85.2 ppb had greater increases in intraday eNO compared with children at camps with O_3 concentrations below 51 ppb. A benchmark dose analysis indicated that the threshold for an O_3-induced increase of 4.3 ppb eNO (their definition of increased pulmonary inflammation) was 68.6 ppb for 1-h max O_3 and 56.3 ppb for 8-hr max O_3. While these results provide additional evidence for O_3-associated increases in airway inflammation in

healthy children, they should be interpreted with caution since they were not adjusted for any potential confounding factors.

Recent studies examined associations of O_3 exposure with biological markers of airway inflammation in populations exercising outdoors. In a panel study of 16 adolescent long-distance runners in Atlanta, GA, lags 0, 1, and 2 of 1-h max O_3 were associated with increases in EBC pH, indicating O_3-associated decreases in pulmonary inflammation (Ferdinands et al., 2008). Among 9 adult male runners in Sicily, Italy examined 3 days before and 20 hours after 3 races in fall, winter, and summer, weekly average O_3 concentrations (8-h avg, 7:00 a.m.-3:00 p.m.) were positively correlated with apoptosis of airway cells (Spearman's $r = 0.76$, $p < 0.0005$) and bronchial epithelial cell differential counts (Spearman's $r = 0.467$, $p < 0.05$) but not with neutrophil or macrophage cell counts or levels of the proinflammatory cytokines TNF-α and IL-8 (Chimenti et al., 2009). Although this study provides evidence for some new endpoints, the implications of the findings are limited since they were not based on a rigorous statistical analysis.

Older Adults

Two panel studies examining O_3-associated changes in eNO in older adults produced contrasting findings (Figure 6-10 and Table 6-15). Both studies were similar in that outdoor O_3 was monitored by investigators in the vicinity of subjects' residences, and cool season-specific results were presented. However, several differences were noteworthy, including geographic location, inclusion of healthy subjects, and lags of O_3 exposure examined. Delfino et al. (2010a) followed 60 elderly subjects with coronary artery disease in the Los Angeles, CA area for two 6-week periods, one in the warm season and one in the cool season, although the exact months were not specified. Multiday averages of O_3 (3- to 9-day) were associated with increases in eNO, with effect estimates increasing with increasing number of averaging days. In contrast with most other studies, a strong positive effect was estimated for the cooler season (4.06 ppb [95% CI: 1.25, 6.87]) increase in eNO per 20-ppb increase in lag 0-4 of 24-h avg O_3), whereas no association was observed for the warm season (-0.01 ppb change in eNO [95% CI: -2.31, 2.11]). Despite these unusual findings for the cool season, they were similar to findings from another study of Los Angeles area adults with asthma that found O_3 effects (i.e., decrease in indoor activity) during the fall season (Eiswerth et al., 2005).

Adamkiewicz et al. (2004) did not find a positive association between O_3 exposure and eNO in a group of older adults (ages 54-91 years) comprising healthy subjects and those with asthma or COPD. The study was conducted in Steubenville, OH between September and December, and as was observed in most other studies conducted during winter months, O_3 (concurrent 1 hour and 24 hours preceding eNO collection) was associated

with decreases in eNO, indicating a decrease in pulmonary inflammation (Figure 6-10 and Table 6-16).

Confounding in Epidemiologic Studies of Pulmonary Inflammation and Oxidative Stress

Except where noted in the preceding text, most epidemiologic studies of pulmonary inflammation and oxidative stress accounted for the potential for confounding by meteorological factors. Ambient O_3 exposure was associated with pulmonary inflammation or oxidative stress in models that adjusted for temperature and/or humidity (Delfino et al., 2010a; Barraza-Villarreal et al., 2008; Romieu et al., 2008). Most studies conducted over multiple seasons adjusted for season or time trend. Sienra-Monge et al. (2004) and Berhane et al. (2011) did not adjust for temperature in their final results after finding that the inclusion of temperature did not change results.

Although information is limited to a small number of studies conducted in Mexico City, the evidence does not indicate the confounding of O_3 associations by $PM_{2.5}$ or PM_{10} exposure. In these studies, which analyzed 8-h averages for both O_3 and PM and reported moderate correlations between pollutants (r=0.46-0.54), robust associations were found for O_3 (Barraza-Villarreal et al., 2008; Romieu et al., 2008; Sienra-Monge et al., 2004). Only Romieu et al. (2008) provided quantitative results. Lag 0 of 8-h max O_3 was associated with the same magnitude of increase in MDA with and without lag 0 of 8-h max $PM_{2.5}$ in the model (ratio of geometric means per 30-ppb increase: 1.3 [95% CI: 1.0, 1.7]). In the copollutant model, the effect estimate for $PM_{2.5}$ was cut in half.

Summary of Epidemiologic Studies of Pulmonary Inflammation and Oxidative Stress

Many recent epidemiologic studies reported positive associations between short-term ambient O_3 exposure and increases in pulmonary inflammation and oxidative stress, particularly, studies of children with asthma in Mexico City. By also finding that O_3-associated increases in pulmonary inflammation were attenuated with higher antioxidant intake, these studies, as a whole, provided evidence that inhaled O_3 may be an important source of ROS in airways and/or may increase airway inflammation via oxidative stress-mediated mechanisms. Studies also indicated that ambient O_3 exposure may increase airway inflammation in healthy children (Berhane et al., 2011; Nickmilder et al., 2007). The limited available evidence in subjects exercising outdoors and older adults was inconclusive. Temperature and humidity were not found to confound O_3 associations, and in the few studies that evaluated copollutant models, O_3 effect estimates were robust to

inclusion of $PM_{2.5}$ or PM_{10} (Barraza-Villarreal et al., 2008; Romieu et al., 2008; Sienra-Monge et al., 2004).

Most studies examined associations with daily 8-h max or daytime 8-h avg O_3 exposures, although associations were observed for 1-h max (Nickmilder et al., 2007) and 24-h avg O_3 exposures (Delfino et al., 2010a). Collectively, studies examined associations with single-day O_3 exposures lagged from 0 to 5 days, and exposures averaged over 2 to 9 days. Lag 0 of 8-h max O_3 exposure was most frequently examined and consistently associated with increased airway inflammation and oxidative stress. However, in the few studies that examined multiple lags of exposure, multiday cumulative O_3 exposures, primarily based on 8-h max or 8-h avg, were associated with greater increases in airway inflammation and oxidative stress (Berhane et al., 2011; Delfino et al., 2010a; Sienra-Monge et al., 2004). These findings for longer lags of exposure are supported by controlled human exposure studies that similarly have found that indicators of airway inflammation remain elevated following exposures to O_3 repeated over multiple days (Section 6.2.3.1).

Several epidemiologic studies simultaneously examined associations of ambient O_3 exposure with biological markers of airway inflammation and oxidative stress, lung function, and respiratory symptoms. In most cases, the results differed between the various biomarkers and lung function. Whether evaluated at the same or different lags of O_3 exposure, associations generally were stronger for biological markers of airway inflammation than for lung function (Barraza-Villarreal et al., 2008; Nickmilder et al., 2007). Controlled human exposure studies also have demonstrated a lack of correlation between inflammatory and spirometric responses induced by O_3 exposure. Studies have suggested that O_3-related respiratory morbidity may occur via multiple mechanisms with varying time courses of action, and the examination of a limited number of O_3 exposure lags in these aforementioned studies may explain some of the inconsistencies in associations of O_3 with different respiratory health endpoints.

The clinical significance of changes in biological markers of airway inflammation and oxidative stress are not well-characterized. However, the simultaneous examination of associations of O_3 with respiratory symptoms has permitted the assessment of the clinical significance of the changes observed in biomarkers. In subjects with asthma, ambient O_3 exposure was associated with increases in eNO and IL-6 that were accompanied by a concomitant increase in cough (Barraza-Villarreal et al., 2008) and increases in eNO and blood eosinophils that were accompanied by a decrease in quality of life score (Khatri et al., 2009). These findings support clinically-important increases in O_3-associated airway inflammation in individuals with asthma. Similar data are limited to assess the clinical

significance of changes in other biological markers of airway inflammation and oxidative stress and in other populations.

6.2.3.3 Toxicology

The 2006 O_3 AQCD states that the "extensive human clinical and animal toxicological evidence, together with the limited available epidemiologic evidence, is clearly indicative of a causal role for O_3 in inflammatory responses in the airways" (U.S. EPA, 2006b). Airway ciliated epithelial cells and Type 1 cells are the most O_3-sensitive cells and are initial targets of O_3. These cells are damaged by O_3 and produce a number of proinflammatory mediators (e.g., interleukins [IL-6, IL-8], PGE2) capable of initiating a cascade of events leading to PMN influx into the lung, activation of alveolar macrophages, inflammation, and increased permeability across the epithelial barrier. One critical aspect of inflammation is the potential for metaplasia and alterations in pulmonary morphology. Studies have observed increased thickness of the alveolar septa, presumably due to increased cellularity after acute exposure to O_3. Epithelial hyperplasia starts early in exposure and increases in magnitude for several weeks, after which it plateaus until exposure ceases. When exposure persists for a month and longer, excess collagen and interstitial fibrosis are observed. This response, discussed in Chapter 7, continues to increase in magnitude throughout exposure and can even continue to increase after exposure ends (Last et al., 1984). Previously published toxicological studies of the ability of O_3 to cause inflammation, injury, and morphological changes are described in Table 6-5 on p. 6-25 and Tables 6-10 and 6-11 beginning on p. 6-61 of the 1996 O_3 AQCD, and Tables AX5-8 and AX5-9, beginning on p. AX5-17 of the 2006 O_3 AQCD. Numerous recent in vitro and in vivo studies add to this very large body of evidence for O_3-induced inflammation and injury, and provide new information regarding the underlying mechanisms (Bauer et al., 2011; Aibo et al., 2010; Farraj et al., 2010; Garantziotis et al., 2010; Hicks et al., 2010b; Castagna et al., 2009; Damera et al., 2009; Oslund et al., 2009; Vancza et al., 2009; Voynow et al., 2009; Fakhrzadeh et al., 2008; Han et al., 2008; Inoue et al., 2008; Oslund et al., 2008; Carey et al., 2007; Cho et al., 2007; Dahl et al., 2007; Johnston et al., 2007; Kooter et al., 2007; Wagner et al., 2007; Wang et al., 2007; Yoon et al., 2007; Huffman et al., 2006; Johnston et al., 2006; Kenyon et al., 2006; Manzer et al., 2006; Plopper et al., 2006; Jang et al., 2005; Janic et al., 2005; Johnston et al., 2005a; Johnston et al., 2005b; Oyarzún et al., 2005; Servais et al., 2005; Frush et al., In Press).

A number of species, including dogs, rabbits, guinea pigs, rats, and mice have been used as models to study the pulmonary effects of O_3, but the similarity of non-human primates to humans makes them an attractive model in which to study the pulmonary response to

O_3. As reviewed in the 1996 and 2006 O_3 AQCDs, several pulmonary effects, including inflammation, changes in morphometry, and airway hyperresponsiveness, have been observed in macaque and rhesus monkeys after acute exposure to O_3 (Table 6-17 presents a highlight of these studies). Increases in inflammatory cells were observed after a single 8-hr exposure of adult rhesus monkeys to 1 ppm O_3 (Hyde et al., 1992). Inflammation was linked to morphometric changes, such as increases in necrotic cells, smooth muscle, fibroblasts, and nonciliated bronchiolar cells, which were observed in the trachea, bronchi, or respiratory bronchioles. Effects have also been observed after short-term repeated exposure to O_3 at concentrations that are more relevant to ambient O_3 levels. Morphometry changes in the lung, nose, and vocal cords were observed after exposure to 0.15 ppm O_3 for 8-h/day for 6 days (Harkema et al., 1993; Dimitriadis, 1992; Harkema et al., 1987a). Since 2006, however, only one study has been published regarding acute exposure of non-human primates to O_3 (a number of recent chronic studies in non-human primates are described in Chapter 7). In this study, a single 6-h exposure of adult male cynomolgus monkeys to 1 ppm O_3 induced significant increases in inflammatory and injury markers, including BAL neutrophils, total protein, alkaline phosphatase, IL-6, IL-8, and G-CSF (Hicks et al., 2010b). Gene expression analysis confirmed the increases in the pro-inflammatory cytokine IL-8, which had been previously described in O_3 exposed rhesus monkeys (Chang et al., 1998). The anti-inflammatory cytokine IL-10 was also elevated, but the fold changes in IL-10 and G-CSF were relatively low and highly variable. The single exposure also caused necrosis and sloughing of the epithelial lining of the most distal portions of the terminal bronchioles and the respiratory bronchioles. Bronchiolitis, alveolitis, parenchymal and centriacinar inflammation were also observed. A second exposure protocol (two exposures with a 2-week inter-exposure interval) resulted in similar inflammatory responses, with the exception of total protein and alkaline phosphatase levels which were attenuated, indicating that attenuation of some but not all lavage parameters occurred upon repeated exposure of non-human primates to O_3 (Hicks et al., 2010b). This variability in adaptation is similar to the findings of earlier reports in rodents (Wiester et al., 1996b) and non-human primates (Tyler et al., 1988). Table 6-17 describes morphometric studies conducted in non-human primates exposed to O_3.

Table 6-17 Morphometric observations in non-human primates after acute O_3 exposure

Reference	O_3 concentration	Exposure duration	Species, Sex, Age	Observation
Harkema et al. (1993)	0.15	8 h/day for 6 days	Macaca radiata	Several fold increase in thickness of surface epithelium in respiratory bronchioles
Harkema et al. (1987a; 1987b) Dimitriadis (1992)	0.15 0.3	8 h/day for 6 days	Macaca radiata, M, F 2-6 years old	Ciliated cell necrosis, shortened cilia, and increased mucous cells in the respiratory epithelium of nose after 0.15 ppm; changes in nonciliated cells, intraepithelial leukocytes, and mucous cells in the transitional epithelium
Leonard et al. (1991)	0.25	8 h/day for 7 days	Macaca radiata	The O_3 exposure level is not clear – the abstract states 0.64 ppm, but the text mentions only 0.25 ppm. Morphometric changes in vocal cord mucosa: disruption and hyperplasia of stratified squamous epithelium; epithelial and connective tissue thickness increased
Chang et al. (1998)	0.96	8 h	Rhesus, M	Increase in IL-8 in airway epithelium correlated with PMN influx
Hyde et al. (1992)	0.96	8 h	Rhesus, M 2-8.5 years old	Increased PMNs; morphometric changes in trachea, conducting airways, respiratory bronchioles
Hicks et al. (2010a)	1.0	6 h	Cynomolgus, M 5-7 kg	Increase in PMNs and IL-8 in lavage fluid

Confirmation of pulmonary changes observed in non-human primates, at near ambient O_3concentrations, has been done in a large number of studies in guinea pigs and rodents (see 1996 and 2006 O_3 AQCDs) (U.S. EPA, 2006b, 1996a). Mechanistic studies completed more recently have extended these findings. Exposure of adult BALB/c mice to 0.1 ppm O_3 for 4 hours increased BAL levels of keratinocyte chemoattractant (KC; IL-8 homologue) (~ sixfold), IL-6 (~12-fold), and TNF-α (~ twofold) (Damera et al., 2010). Additionally, O_3 increased BAL neutrophils by 21% without changes in other cell types. A trend of increased neutrophils with increased O_3 concentration (0.12-2 ppm) was observed in BALB/c mice exposed for 3 hours (Jang et al., 2005). Although alterations in the epithelium of the airways were not evident in 129J mice after 4 hours of exposure to 0.2 ppm O_3 (Plopper et al., 2006), detachment of the bronchiolar epithelium was observed in SD rats after 5 days or 60 days of exposure to 0.25 ppm O_3 (Oyarzún et al., 2005). Subacute (65 hours) exposure to 0.3 ppm O_3 induced pulmonary inflammation, cytokine induction, and enhanced vascular permeability in wild type mice of a mixed background (129/Ola and C57BL/6) and these effects were exacerbated in metallothionein I/II knockout mice (Inoue et al., 2008). Three hours or 72 hours of exposure to 0.3 ppm O_3 resulted in similar levels of IL-6 expression in the lungs of C57BL/6 mice (Johnston et al., 2005b), along with increases in BAL protein, sTNFR1, and sTNFR2. Increased neutrophils were observed only after the 72-h exposure, and neither exposure resulted in detectable levels of IL-6 or KC protein. Levels of BAL

protein, sTNFR1, and sTNFR2 were higher in the 72-h exposure group than in the 3-h exposure group. In another study, the same subacute (72 hours) exposure protocol elicited increases in BALF protein, IP-10, sTNFR1, macrophages, neutrophils, and IL-6, IL-1α, and IL-1β expression (Johnston et al., 2007). Yoon et al. (2007) exposed C57BL/6J mice continuously to 0.3 ppm O_3 for 6, 24, 48, or 72 hours, and observed elevated levels of KC, MIP-2, metalloproteinases, and inflammatory cells in the lungs at various time points. A similar exposure protocol using C3H/HeJ and C3H/OuJ mice demonstrated elevations in protein, PMNs, and KC, which were predominantly TLR 4 pathway dependent based on their prominence in the TLR 4 sufficient C3H/OuJ strain (Bauer et al., 2011). C3H/OuJ mice also had elevated levels of the heat-shock protein HSP70, and further experiments in HSP70 deficient mice indicated a role for this particular pathway in O_3-related injury, discussed in more detail in Chapter 5.

As reviewed in the 2006 O_3 AQCD, the time course for changes in BAL depends on the parameters being studied. Similarly, after exposing adult C57BL mice to 0.5 ppm O_3 for 3 hours, Han et al. (2008) observed early (5 hours postexposure) increases in BAL TNF-α and IL-1β, which diminished by 24 hours postexposure. Total BAL protein was elevated at 24 hours, but there were only minimal or negligible changes in LDH, total cells, or PMNs. Ozone increased BAL mucin levels (with statistical significance by 24 hours postexposure), and significantly elevated surfactant protein D at both time points. Prior intratracheal (IT) exposure to multiwall carbon nanotubes enhanced most of these effects, but the majority of responses to the combined exposure were not greater than those to nanotubes alone. Ozone exposure did not induce markers of oxidative stress in lung tissue, BAL, or serum. Consistent with this study, Aibo et al. (2010) did not detect changes in BAL inflammatory cell numbers in the same mouse strain after a 6-h exposure to 0.25 or 0.5 ppm. The majority of inflammatory cytokines (pulmonary or circulating) were not significantly changed (as assessed 9 hours post O_3 exposure).

Animal toxicology studies have also examined susceptibility factors and the findings complement research in both controlled human exposure and epidemiologic studies. In a study examining age, strain, and gender as factors for susceptibility to O_3 in mice, increased BAL neutrophils were observed in all 8 strains of neonates and adults but statistical significance was found in only 4 strains of neonates and 2 strains of adults at 24 hours after exposure to 0.8 ppm O_3 for 5 hours (Vancza et al., 2009). Lung injury, as measured by BAL protein, was significantly increased in 5 and 8 strains of neonates and adults, respectively. Interestingly, the observed age-dependent differences in response to O_3 occurred in only certain strains. For example, the fold-increase in neutrophils was significantly higher, in neonates compared to adults, in the SJL and C3H/HeJ strains and lower in BALB/c mice. Measurement of ^{18}O determined that the observed strain- and age-dependent differences were not due to absorbed O_3 dose. Subanalysis of the adult

mice demonstrated that gender also played a small, but statistically significant, role in the effect of O_3 on BAL neutrophils and protein. These findings suggest that the response to O_3, in mice, may consist of a complex interaction of age, gender, and genetic factors.

A study assessing NQO1 as a susceptibility factor was conducted by Voynow et al. (2009). Specific effects of this gene on O_3 responses are discussed in Chapter 8; only ozone's effects in wild type C57BL/6 mice are described here. Exposure to 1 ppm for 3 hours increased BAL total cells, neutrophils, and KC; these responses were greatest at 24 hours postexposure. F2-isoprostane (8-isoprostane), a marker of oxidative stress, was also elevated by O_3, peaking at 48 hours postexposure.

Atopic asthma appears to be a risk factor for more severe O_3 induced airway inflammation in humans (Balmes et al., 1997; Scannell et al., 1996), and allergic animal models are often used to investigate the effects of O_3 on this susceptible population. Farraj et al. (2010) exposed allergen-sensitized adult male BALB/c mice to 0.5 ppm O_3 for 5 hours once per week for 4 weeks. Ovalbumin-sensitized mice exposed to O_3 had significantly increased BAL eosinophils by 85% and neutrophils by 103% relative to OVA sensitized mice exposed to air, but these changes were not evident upon histopathological evaluation of the lung, and no O_3 induced lesions were evident in the nasal passages. Ozone increased BAL levels of N-acetyl-glucosaminidase (NAG; a marker of injury) and protein. DEP co-exposure (2.0 mg/m^3, nose only) inhibited these responses. These pro-inflammatory effects in an allergic mouse model have also been observed in rats. Wagner et al. (2007) exposed the relatively O_3-resistant Brown Norway rat strain to 1 ppm O_3 after sensitizing and challenging with OVA. Rats were exposed for 2 days, and airway inflammation was assessed one day later. Filtered air for controls contained less than 0.02 ppm O_3. Histopathology indicated O_3 induced site-specific lung lesions in the centriacinar regions, characterized by wall thickening partly due to inflammatory cells influx. BAL neutrophils were elevated by O_3 in allergic rats, and modestly increased in non-allergic animals (not significant). A slight (but not significant) increase in macrophages was observed, but eosinophil numbers were not affected by O_3. Soluble mediators of inflammation (Cys-LT, MCP-1, and IL-6) were elevated by O_3 in allergic animals but not non-allergic rats. Treatment with γT, which neutralizes oxidized lipid radicals and protects lipids and proteins from nitrosative damage, did not alter the morphologic character or severity of the centriacinar lesions caused by O_3, nor did it reduce neutrophil influx. It did, however, significantly reduce O_3-induced soluble inflammatory mediators in allergic rats. The effects of O_3 in animal models of allergic asthma are discussed in section 6.2.6.

In summary, a large number of toxicology studies have demonstrated that acute exposure to O_3 produces injury and inflammation in the mammalian lung, supporting the

observations in controlled human exposure studies (Section 6.2.3.1). These acute changes, both in inflammation and morphology, provide a modicum of evidence for long term sequelae of exposure to O_3. Related alterations resulting from long term exposure, such as fibrotic changes, are discussed in Chapter 7.

Mechanisms of Injury

Since O_3 has been well established as a causative agent of airway inflammation and injury, which may contribute to functional changes observed in human subjects, the majority of recent research has focused on the underlying mechanisms. A brief description of some of the recent contributions to this area of research is provided here; more detailed descriptions of the mechanisms behind O_3-mediated injury and inflammation can be found in the mode of action chapter (Chapter 5). There are several signaling pathways responsive to changes in oxidation status, which tend to be influenced at different levels in different host backgrounds. The molecular mechanisms of TNF receptor-mediated lung injury induced by O_3 and associated signaling pathways (NF-κB, MAPK/AP-1) have been examined (Fakhrzadeh et al., 2008; Cho et al., 2007), along with the changes in gene expression which characterize O_3-induced stress and inflammation (Wang et al., 2007). Other contributors to injury and inflammation include the IL-1 and neurokinin receptors (Oslund et al., 2008; Johnston et al., 2007), calcitonin gene-related peptide receptor activation (Oslund et al., 2009), CXCR2, a receptor for neutrophil chemokines (Johnston et al., 2005a), mindin, an extracellular matrix protein (Frush et al., In Press), and NQO1 (Voynow et al., 2009), an enzyme involved in oxidative stress. Studies indicate a role for oxidative stress in mediating inflammation (Wagner et al., 2007; Jang et al., 2005). Protective roles have been identified for nitric oxide synthase (Kenyon et al., 2006), metallothionein (Inoue et al., 2008), matrix metalloproteinases (Yoon et al., 2007), Clara cell secretory protein (Plopper et al., 2006), and the recognition of oxidized lipids by alveolar macrophages (Dahl et al., 2007).

6.2.4 Respiratory Symptoms and Medication Use

Controlled human exposure and toxicological studies have described the modes of action through which short-term O_3 exposure may lead to increases in respiratory symptoms by demonstrating O_3-induced increases in airway hyperresponsiveness, bronchoconstriction (Section 6.2.2), and pulmonary inflammation (Sections 6.2.3.1 and 6.2.3.3). While epidemiologic studies have not widely examined associations between ambient O_3 exposure and airway hyperresponsiveness, they have found O_3-associated increases in pulmonary inflammation and oxidative stress (Section 6.3.2.2). In addition to decreases

in lung function, controlled human exposure studies clearly demonstrate increases in subjective respiratory symptoms including cough, pain on deep inspiration, and shortness of breath (described in detail in Section 6.2.1.1). Similar to lung function responses, these respiratory symptoms increase with exposure concentration, activity level of the exposed individual, and duration of exposure (McDonnell et al., 1999). Increases in subjective respiratory symptoms have been reported following 5.6 and 6.6 h of exposure to 60 ppb O_3. However, the severity of respiratory symptoms following 6.6 h of exposure to 80 ppb O_3 during moderate exercise is roughly 2-3 times greater than that at 60 ppb O_3 (Adams, 2006a). These findings integrated across disciplines provide biological plausibility for epidemiologic associations between increases in short-term ambient O_3 exposure and increases in respiratory symptoms.

In epidemiologic studies, respiratory symptom data typically are collected by having subjects or their parents record symptoms such as wheeze, cough, and shortness of breath and medication use in a diary without direct supervision by study staff. Several limitations of symptom reports are well-recognized: recall error if not recorded daily, differences among subjects in the interpretation of symptoms, biased reporting between participants with and without asthma, and occurrence in a smaller percentage of the population compared with changes in lung function and biological markers of pulmonary inflammation. Nonetheless, symptom diaries remain a convenient and useful tool to collect individual-level data from a large number of subjects and allow the modeling of associations between daily changes in O_3 exposure and daily changes in respiratory morbidity. Importantly, most of the limitations described above are sources of random measurement error that can bias effect estimates to the null or increase the uncertainty around effect estimates. Furthermore, because respiratory symptoms are associated with limitations in activity and function and are the primary reason for using medication and seeking medical care, they provide an assessment of the clinical and public health significance of ambient O_3 exposure.

Most studies have been conducted in individuals with asthma, and as was concluded in previous O_3 AQCD, the collective body of epidemiologic evidence strongly supports associations between increases in short-term ambient O_3 exposure and increases in respiratory symptoms in children with asthma (U.S. EPA, 2006b, 1996a) (Figure 6-11 and Table 6-19). Evidence also indicates that O_3 exposure likely is associated with increased use of asthma medication (Figure 6-12 and Table 6-20). Studies also find O_3 exposure to be associated with respiratory symptoms in adults with asthma. The effects of O_3 exposure on respiratory symptoms in healthy populations are not as clearly indicated (Figure 6-13 and Table 6-23)

6.2.4.1 Children with Asthma

Respiratory Symptoms

Table 6-18 presents the characteristics and ambient O_3 concentration data from studies assessing associations of short-term O_3 exposure with respiratory symptoms and medication use in children with asthma. The strong evidence for associations between ambient O_3 exposure and respiratory symptoms among children with asthma is derived mostly from several single-region or single-city studies (Figure 6-11 and Table 6-19). Most studies of children with asthma examined 1-h max, 8-h max, or 8-h average O_3 exposures. In U.S. multicity studies, O_3 was associated with both increases and decreases in respiratory symptoms among children with asthma (O'Connor et al., 2008; Schildcrout et al., 2006; Mortimer et al., 2002). In the NCICAS cohort (described in Section 6.2.1.2), a 30-ppb increase in lag 1-4 avg of 8-h avg (10:00 a.m.-6:00 p.m.) O_3 was associated with an increase in morning asthma symptoms with an OR (95% CI) of 1.35 (95% CI: 1.04, 1.69) (Mortimer et al., 2002). This association did not change (OR: 1.37 [95% CI: 1.02, 1.84]) in an analysis restricted to O_3 concentrations below 80 ppb. Odds ratios for lags 2 and 4 of O_3 exposure were similar in magntiude. In the ICAS cohort (described in Section 6.2.1.2), associations of 19-day avg of 24-h avg O_3 with wheeze and nighttime asthma were positive and negative, respectively (O'Connor et al., 2008). NCICAS was conducted during the warm season, and symptom data were collected daily (Mortimer et al., 2002; Mortimer et al., 2000), whereas in ICAS, every 2 months, parents reported the number of days with respiratory symptoms over the previous 2 weeks (O'Connor et al., 2008). Because of the two-week symptom reporting period, ICAS investigators were precluded from examining associations with single-day and shorter-duration O_3 exposure periods.

Evidence of O_3-associated respiratory symptoms also was weak in another recent U.S. multicity study (with cities in common with NCICAS and ICAS, Table 6-18) of 990 children with asthma (Schildcrout et al., 2006). As part of the Childhood Asthma Management Program, symptom data were collected daily, and analyses were restricted to peak O_3 periods between May and September. In meta-analyses that combined city-specific estimates, a 40-ppb increase in lag 0 of 1-h max O_3 was associated with any asthma symptom with an OR (95% CI) of 1.08 (0.89, 1.31). Odds ratios for lags 1 and 2 and the 3-day sum of O_3 were near 1.0. In this study, data were available from an average of 12 subjects per day per city, and fewer data were collected in summer months. Because O_3 analyses were restricted to summer months, the fewer number of observations reduced the power to detect associations for O_3 relative to other pollutants, which were analyzed using year-round data.

Table 6-18 Mean and upper percentile ozone concentrations in epidemiologic studies examining respiratory symptoms, medication use, and activity levels in children with asthma

Study	Location	Years/Season	O_3 Averaging Time	Mean/Median Concentration (ppb)	Upper Percentile Concentrations (ppb)
Mortimer et al. (2000) Mortimer et al. (2002)	Bronx, East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI, Cleveland, OH; Chicago, IL; St. Louis, MO (NCICAS)	1993 Warm season	8-h avg (10:00 a.m.-6:00 p.m.)	48	NR
O'Connor et al. (2008)	Boston, MA; Bronx, Manhattan NY; Chicago, IL; Dallas, TX, Seattle, WA; Tucson, AZ (ICAS)	1998-2001 All-year	24-h avg	NR	NR
Schildcrout et al. (2006)	Albuquerque, NM; Baltimore, MD; Boston, MA; Denver, CO; San Diego, CA; Seattle, WA; St. Louis, MO; Toronto, ON, Canada (CAMP)	1994-1995 Warm season	1-h max	Range in medians across cities: 43.0-65.8	Range in 90th across cities: 61.5-94.7
Gent et al. (2003)	CT, southern MA	2001 April-September	1-h max 8-h rolling avg	58.6 51.3	Max: 125.5 Max: 99.6
Thurston et al. (1997)	Connecticut River Valley, CT	1991-1993 Warm season	1-h max	83.6	Max: 160
Rabinovitch et al. (2004)	Denver, CO	1999-2002 Cold season	1-h max	28.2	Max: 70.0
Mann et al. (2010)	Fresno/Clovia, California	2000-2005 All-year	8-h max	49.4 (median)	75th: 69.5, Max: 120.0
Ostro et al. (2001)	Los Angeles, CA	1993 August-October	1-h max	Los Angeles: 59.5 Pasadena: 95.8	Max: 130 Max: 220
Delfino et al. (2003)	Los Angeles, CA	1999-2000 Cold season	1-h max 8-h max	25.4 17.1	90th: 38.0, Max: 52 90th: 26.1, Max: 37
Romieu et al. (1996)	northern Mexico City, Mexico	April-July 1991 November 1991-February 1992	1-h max	190	Max: 370
Romieu et al. (1997)	southern Mexico City, Mexico	April-July 1991 November 1991-February 1992	1-h max	196	Max: 390
Romieu et al. (2006)	Mexico City, Mexico	1998-2000 All-year	1-h max 8-h max	102 69	Max: 309 Max: 184
Escamilla-Nunez et al. (2008)	Mexico City, Mexico	2003-2005 All-year	1-h max 8-h max	86.5 31.6	Max: 86.3 (8-h max)
Gielen et al. (1997)	Amsterdam, Netherlands	1995 Warm season	8-h max	34.2	Max: 56.5
Just et al. (2002)	Paris, France	1996 April-June	24-h avg	30.0	Max: 61.7
Jalaludin et al. (2004)	Sydney, Australia	1994 All-year	15-h avg (6:00 a.m.-9:00 p.m.)	12	Max: 43

NCICAS = National Cooperative Inner-City Asthma Study, NR = Not Reported, ICAS = Inner City Asthma Study, NR = Not Reported, CAMP = Childhood Asthma Management Program, Max = Maximum.

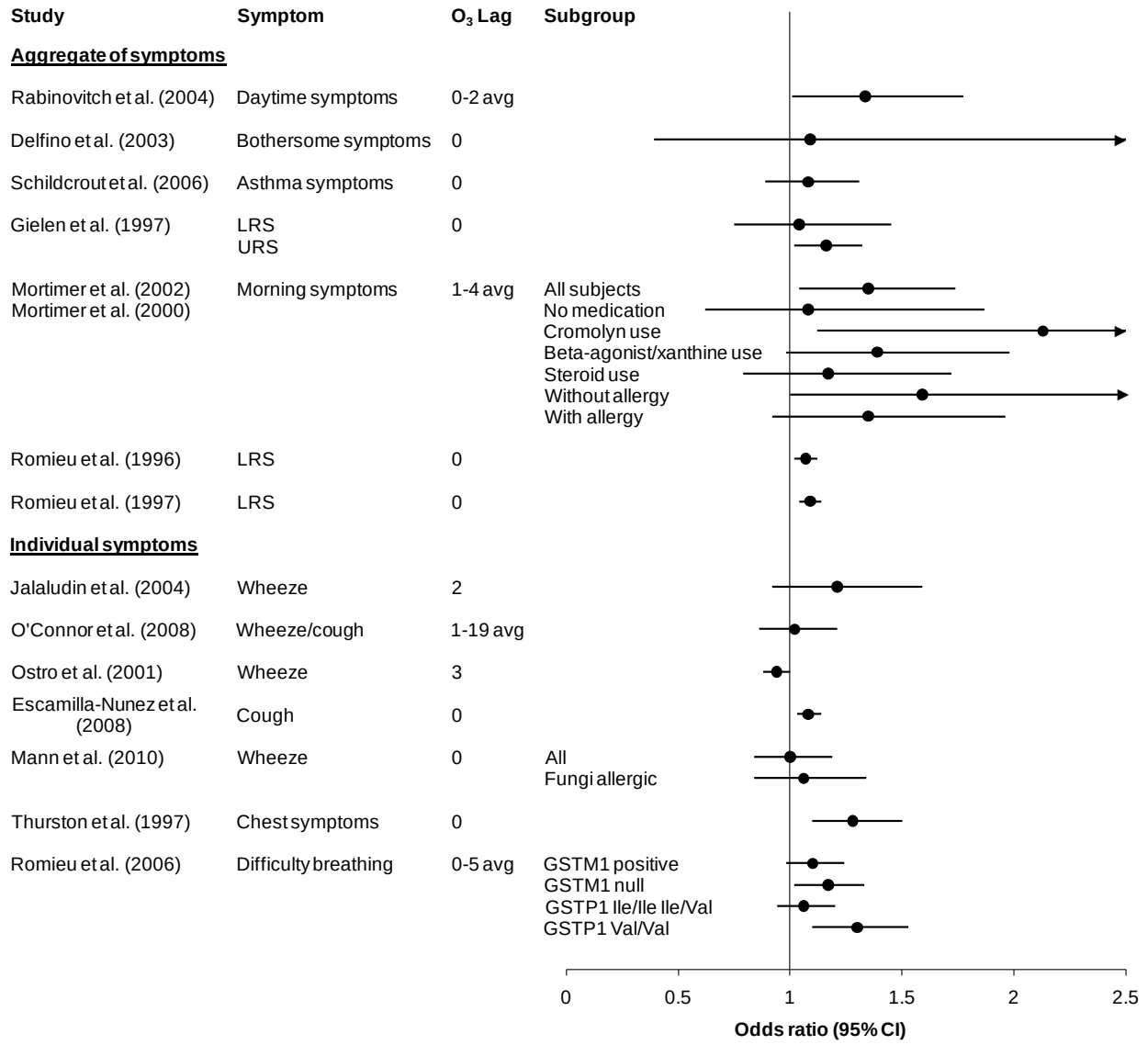


Figure 6-11 Associations of ambient ozone exposure with respiratory symptoms in children with asthma. Results are presented first for aggregate indices of symptoms then for individual symptoms. Within each category, results generally are organized in order of increasing mean ambient O_3 concentration. LRS = lower respiratory symptoms, URS = upper respiratory symptoms. Effect estimates are from single-pollutant models and are standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max or 8-h avg, and 15-h avg or 24-h avg ozone exposures, respectively.

Table 6-19 Additional characteristics and quantitative data for studies presented in Figure 6-11

Study	Location/ Population	O_3 Lag	O_3 Averaging Time	Symptom	Subgroup	Odds Ratio (95% CI)[a]
Studies examining aggregates of symptoms						
Rabinovitch et al. (2004)	Denver, CO Children with asthma	0-2 avg	1-h max	Daytime symptoms		1.34 (1.01, 1.77)
Delfino et al. (2003)	Los Angeles, CA Children with asthma	0	1-h max	Bothersome symptoms		1.09 (0.39, 3.03)
Schildcrout et al. (2006)	8 U.S. communities Children with asthma	0	1-h max	Asthma symptoms		1.08 (0.89, 1.31)
Gielen et al. (1997)	Amsterdam, Netherlands Children with asthma	0	8-h max	LRS URS		1.04 (0.75, 1.45) 1.16 (1.02, 1.32)
Mortimer et al. (2002) Mortimer et al. (2000)	8 U.S. communities Children with asthma	1-4 avg	8-h avg (10:00 a.m.-6:00 p.m.)	Morning symptoms	All subjects No medication use Cromolyn use β-agonist/xanthine use Steroid use Without allergy With allergy	1.35 (1.04, 1.74) 1.08 (0.62, 1.87 2.13 (1.12, 4.04) 1.39 (0.98, 1.98) 1.17 (0.79, 1.72) 1.59 (1.00, 2.52) 1.35 (0.92, 1.96)
Romieu et al. (1996)	northern Mexico City, Mexico Children with asthma	0	1-h max	LRS		1.07 (1.02, 1.12)
Romieu et al. (1997)	southern Mexico City, Mexico Children with asthma	0	1-h max	LRS		1.09 (1.04, 1.14)
Studies examining individual symptoms						
Jalaludin et al. (2004)	Sydney, Australia Children with asthma	2	15-h avg (6:00 a.m.-9:00 p.m.)	Wheeze		1.21 (0.92, 1.59)
O'Connor et al. (2008)	7 U.S. communities Children with asthma	1-19 avg	24-h avg	Wheeze/cough		1.02 (0.86, 1.21)
Ostro et al. (2001)	Los Angeles, CA Children with asthma	3	1-h max	Wheeze		0.94 (0.88, 1.00)
Escamilla-Nunez et al. (2008)	Mexico City, Mexico Children with asthma	0	1-h max	Wheeze		1.08 (1.03, 1.14)
Mann et al. (2010)	Fresno/Clovia, California Children with asthma	0	8-h max	Wheeze	All Fungi allergic	1.00 (0.84, 1.19) 1.06 (0.84, 1.34)
Thurston et al. (1997)	CT River Valley, CT Children with asthma	0	1-h max	Chest symptoms		1.28 (1.10, 1.50)
Romieu et al. (2006)	Mexico City, Mexico Children with asthma	0-5 avg	1-h max	Difficulty breathing	GSTM1 sufficient GSTM1 null GSTP1 Ile/Ile Ile/Val GSTP1 Val/Val	1.10 (0.98, 1.24) 1.17 (1.02, 1.33) 1.06 (0.94, 1.20) 1.30 (1.10, 1.53)

LRS = Lower respiratory symptoms, URS = Upper respiratory symptoms.
[a]Effect estimates are standardized to a 40, 30, and 20 ppb increase for 1-h max, 8-h max or 8-h avg, and 15-h avg or 24-h avg O_3, respectively.

Several longitudinal studies conducted in multiple cohorts of children with asthma in Mexico City, Mexico examined 1-h max O_3 exposures and found associations with increases in respiratory symptoms (Escamilla-Nuñez et al., 2008; Romieu et al., 2006; Romieu et al., 1997; Romieu et al., 1996). Recent studies expanded on earlier evidence

by indicating associations with multiday averages of O_3 exposure. Both Romieu et al. (1996) and Romieu et al. (1997) found that among single-day 1-h max O_3 exposures lagged 0 to 2 days, lag 0 had the greatest estimated effect on respiratory symptoms. Romieu et al. (2006) and Escamilla-Nunez et al. (2008) found that the magnitudes of association of ambient 1-h max O_3 exposure with respiratory symptoms and medication use increased with increasing number of days over which O_3 exposure was averaged.

Studies of children with asthma also identified factors that may contribute to heterogeneity in symptom responses to ambient O_3 exposure. Multiple studies, all of which examined 8-h avg (10:00 a.m.-6:00 p.m.) or 8-h max O_3 exposures, found larger associations among subjects taking asthma medication; however, the medications varied among studies. Consistent with findings for lung function, in the NCICAS multicity cohort, larger associations for morning symptoms were observed in children taking cromolyn (used to treat asthma with allergy) or beta-agonists/xanthines than in children taking no medication. Odds ratios did not differ as much between children taking steroids and children taking no medication (Figure 6-11 and Table 6-19) (Mortimer et al., 2000). In a cohort of children with asthma in Southern New England, O_3 exposures were associated with larger increases in chest tightness among children taking maintenance medication (i.e., steroids, cromolyn, or leukotriene inhibitors).

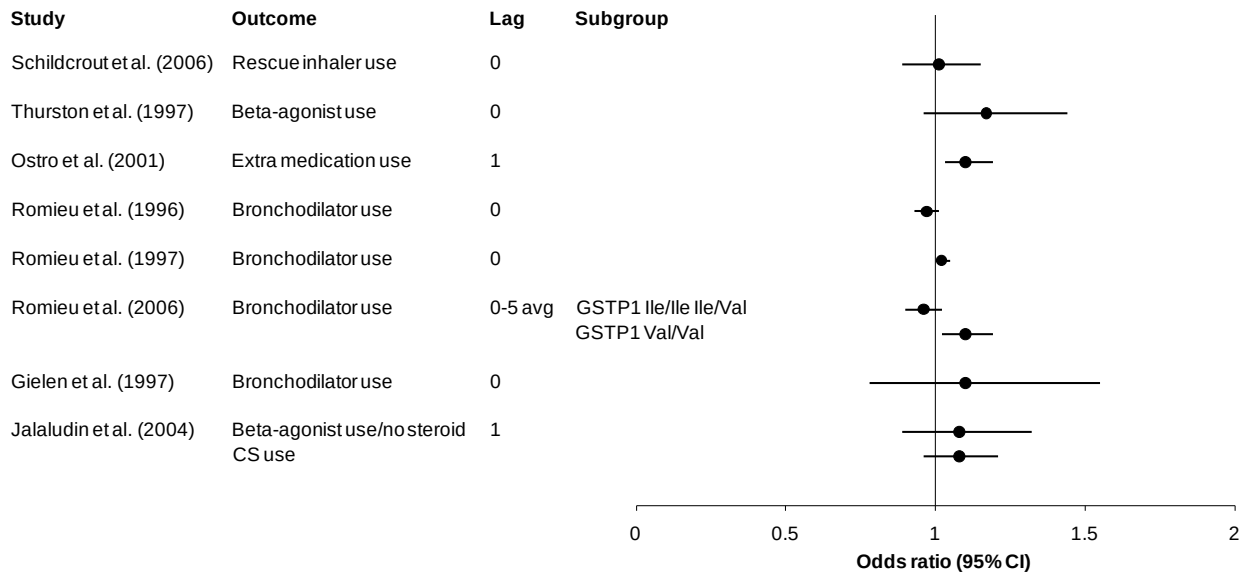
Most studies of children with asthma reported that a majority of subjects (52 to 100%) were atopic as determined by a positive skin prick test to any examined allergen; however, results did not conclusively indicate that children with asthma and atopy were more susceptible to the effects of O_3 exposure. In the multicity NCICAS cohort, Mortimer et al. (2000) found that O_3 was associated with a similar incidence of asthma symptoms among the 79% of subjects with atopy and the 21% of subjects without atopy (Figure 6-11 and Table 6-19). Odds ratios did not differ by residential levels of allergens. In a recent study of children with asthma in Fresno, CA, most associations of single- and multiday lags of 8-h max O_3 exposure (0-14 days) with wheeze were near or below 1.0 (Mann et al., 2010). The estimated effects did not differ in fungi allergic subjects, A larger association was found for cat allergic subjects; however, this finding was limited to O_3 exposure lagged 14 days. In this study, many subjects were allergic to multiple allergens; however, associations were not compared between subjects with any versus no allergic sensitization.

Although Romieu et al. (2006) did not observe differences in associations between O_3 and lung function by GST genetic polymorphisms (Section 6.2.1.2), they did observe effect modification for respiratory symptoms. Compared with GSTM1 positive subjects and GSTP1 Ile/Ile or Ile/Val subjects, larger effects were estimated for GSTM1 null subjects and for GSTP1 Val/Val subjects, respectively (Figure 6-11 and Table 6-19).

Ozone had the greatest estimated effect on difficulty breathing in children with asthma who were both GSTM1 null and GSTP1 Val/Val (OR: 1.49 [95% CI: 1.14, 1.93] per 30-ppb increase in lag 0-5 avg of 8-h max O_3). In the same cohort of children, antioxidant supplementation reduced O_3-associated increases in airway inflammation (Sienra-Monge et al., 2004). These results add to the body of epidemiologic evidence that antioxidant capacity influences risk of O_3-related respiratory morbidity. As was discussed in Section 6.2.1.2, compared with the GSTM1 genotype, evidence for effect modification by GSTP1 genetic polymorphisms is less certain. Romieu et al. (2006) found that the GSTP1 Val/Val variant was associated with a lesser O_3-associated decrement in lung function but greater risk of respiratory symptoms. Whereas some studies have reported greater risk of asthma among GSTP1 Ile/Ile or Ile/Val subjects (Mapp et al., 2002; Hemmingsen et al., 2001), others have reported greater risk among GSTP1 Val/Val subjects (Tamer et al., 2004). In Romieu et al. (2006), GSTP1 Ile/Ile was associated with greater severity of asthma, and Lee et al. (2004b) also reported greater risk of air pollution-associated asthma among GSTP1 Ile/Ile children in the Southern California Children's Health Study.

Asthma Medication Use

The 2006 O_3 AQCD concluded that ambient O_3 likely was associated with increased asthma medication use based on the positive associations found in several studies of children with asthma (Figure 6-12 and Table 6-20). Among the few newly available studies on asthma medication use, evidence generally supported the previous conclusion (Escamilla-Nuñez et al., 2008; Romieu et al., 2006). Most of these studies examined lags 0 or 1 of 1-h max O_3 exposures; however, Romieu et al. (2006) found that lag 0-5 avg of 1-h max O_3 was associated with a larger increase in bronchodilator use than were lags 1 or 0-1 avg. As compared with respiratory symptoms, effects on medication use were estimated with greater uncertainty as indicated by the wide 95% CIs. The wide 95% CIs have been attributed to a smaller number of study subjects reporting medication use and the low frequency of use over the study period. However, within most studies, findings were similar for respiratory symptoms and asthma medication use. Among recent studies, Romieu et al. (2006) and Escamilla-Nunez et al. (2008) observed O_3-associated increases in both respiratory symptoms and bronchodilator use. Schildcrout et al. (2006) did not observe O_3-associated increases in either respiratory symptoms or rescue inhaler use. In contrast, Romieu et al. (1996) and Rabinovitch et al. (2004) observed that O_3 was positively associated with daytime respiratory symptoms but not with bronchodilator use.



CS = corticosteroid. Results are presented in increasing order of ambient ozone concentration. Effect estimates are from single-pollutant models and are standardized to a 40- and 30-ppb increase for 1-h max and 8-h max ozone, respectively

Figure 6-12 Associations of ambient ozone exposure with asthma medication use.

Table 6-20 Additional characteristics and quantitative data for studies presented in Figure 6-12

Study	Location/ Population	O_3 Lag	O_3 Averaging Time	Medication	Subgroup	Odds Ratio (95% CI)[a]
Schildcrout et al. (2006)	8 U.S. communities Children with asthma	0	1-h max	Rescue inhaler use		1.01 (0.89, 1.15)
Thurston et al. (1997)	CT River Valley, CT Asthmatic campers	0	1-h max	Beta-agonist use		1.17 (0.96, 1.44)
Ostro et al. (2001)	Los Angeles, CA Children with asthma	1	1-h max	Extra medication use		1.10 (1.03, 1.19)
Romieu et al. (1996)	northern Mexico City, Mexico Children with asthma	0	1-h max	Bronchodilator use		0.97 (0.93, 1.01)
Romieu et al. (1997)	southern Mexico City, Mexico Children with asthma	0	1-h max	Bronchodilator use		1.02 (1.00, 1.05)
Romieu et al. (2006)	Mexico City, Mexico Children with asthma	0-5 avg	1-h max	Bronchodilator use	GSTP1 Ile/Ile Ile/Val GSTP1 Val/Val	0.96 (0.90, 1.02) 1.10 (1.02, 1.19)
Gielen et al. (1997)	Amsterdam, Netherlands Children with asthma	0	8-h max	Bronchodilator use		1.10 (0.78, 1.55)
Jalaludin et al. (2004)	Sydney, Australia Children with asthma	1	1-h max	Beta-agonist use/no steroid ICS use		1.08 (0.89, 1.32) 1.08 (0.96, 1.21)

CS= Corticosteroid.
[a]Effect estimates are standardized to a 40- and 30-ppb increase for 1-h max and 8-h max O_3, respectively.

Changes in Activity

While investigation has been limited, evidence has not consistently indicated associations between O_3 exposure and diminished activity level in children with asthma (O'Connor et al., 2008; Delfino et al., 2003). These studies have examined a range of O_3 averaging times and lags of exposure. In the large ICAS cohort, O'Connor et al. (O'Connor et al., 2008) found that a 20-ppb increase in lag 1-19 avg of 24-h O_3 ambeint was associated with a 10% lower odds (95% CI: -26, 10) of slow play. In a small (n = 22) panel study conducted in children with asthma in Los Angeles CA, Delfino et al. (2003) found that a 40-ppb increase in lag 0 of 1-h max O_3 was associated with an increase in symptoms that interfered with daily activity with an OR (95% CI) of 7.41 (1.18, 43.2). Several studies reported increases in school absenteeism in children with asthma in association with long lags of O_3 exposure (14-day and 30-day distributed lags or 19-day avg) (O'Connor et al., 2008; Gilliland et al., 2001; Chen et al., 2000). Whereas Chen et al. (2000) and O'Connor et al. (2008) examined absences for any reason, Gilliland et al. (2001) found associations with absences for respiratory illnesses. Despite this evidence, several limitations have been noted, including the uncertain biological relevance of long lag periods of O_3 exposure and the potential for residual seasonal confounding when examining long lag periods of exposure. In analyses of single-day lags, Gilliland et al. (2001) found that 8-h avg (10:00 a.m.-6:00 p.m.) O_3 exposure was associated with increases in respiratory-related absences from lag day 1 to lag day 5, indicating an effect of exposures with shorter lag periods.

6.2.4.2 Adults with Respiratory Disease

Characteristics and ambient O_3 concentration data from studies of adults with respiratory disease are presented in Table 6-21. In this relatively small body of literature, several studies found ambient O_3 exposure (1-h max or 8-h max) to be associated with increases respiratory symptoms and decreases in activity levels in adults with asthma (Khatri et al., 2009; Feo Brito et al., 2007; Eiswerth et al., 2005; Ross et al., 2002). In a recent panel study of adults with COPD, investigators found lag 1 of 8-h max O_3 to be associated with increased odds of dyspnea and sputum changes but decreased odds of nasal discharge, wheeze, or upper respiratory symptoms (Peacock et al., 2011).

In a panel study of children and adults with asthma, lag 1-3 avg of 8-h max O_3 exposure was associated with increases in morning and evening symptom scores and frequency of asthma medication use (Ross et al., 2002). During one pollen season (May-June 2000 or 2001), Feo Brito et al. (2007) specifically followed a group of 137 adults who had asthma and pollen allergy in central Spain. In the industrial Puertollano, a 40-ppb increase in lag

3 of 1-h max O_3 was associated with a 14.3% increase (95% CI: 3.6, 26.0) in the number of subjects reporting respiratory symptoms, adjusting only for time trend. There was a much weaker association in the less industrialized Ciudad Real with lower ambient air pollution concentrations and a narrower range of ambient O_3 concentrations (2.3% [95% CI: -14, 21%] per 40-ppb increase in lag 4 of 1-h max O_3). Park et al. (2005a) followed adults with asthma in Korea during a period that included dust storms and found that a 20-ppb increase in lag 0 of 24-h avg O_3 was associated with an increased odds of night symptoms (OR: 1.11 [95% CI: 0.96, 1.29]) but not cough (OR: 1.00 [95% CI: 0.94, 1.06]) or rescue inhaler use (OR: 0.99 [95% CI: 0.94, 1.05]).

Table 6-21 Mean and upper percentile ozone concentrations in epidemiologic studies examining respiratory symptoms and medication use in adults with respiratory disease

Study	Location	Years/Season	O_3 Averaging Time	Mean/Median Concentration (ppb)	Upper Percentile Concentrations (ppb)
Khatri et al. (2009)	Atlanta, GA	2003, 2005, 2006 Warm season	8-h max	59[a]	Max: 73[a]
Ross et al. (2002)	East Moline, IL	April-October 1994	8-h avg	41.5	Max: 78.3
Eiswerth et al. (2005)	Glendora, CA	1983 Cold season	1-h max	NR	NR
Peacock et al. (2011)	London, England	1995-1997 All-year	8-h max	15.5	Autumn/Winter Max: 32 Spring/Summer Max: 74
Feo Brito et al. (2007)	Ciudad Real and Puertollano, Spain	2000-2001 Warm season	1-h max	65.9 (Ciudad Real)[b] 56.8 (Puertollano)[b]	Max; 101.5[b] (Ciudad Real); 70.5[b] (Puertollano)
Wiwatanadate et al. (2011)	Chiang Mai, Thailand	August 2005-June 2006	24-h avg	17.5	90th: 26.82 Max: 34.65
Park et al. (2005a)	Incheon, Korea	March-June 2002	24-h avg	Dust event days: 23.6 Control days: 25.1	NR

NR = Not Reported, Max = Maximum.
[a]Individual-level exposure estimates were derived based on time spent in the vicinity of various O_3 monitors.
[b]Concentrations converted from µg/m^3 to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

Studies also indicated that ambient O_3 exposure may result in decreases in activity levels in adults with asthma. Notably, although conducted over single seasons, these studies did not consider confounding by meteorological factors. In a cross-sectional summer study in Atlanta, GA (described in Section 6.2.1.2), Khatri et al. (2009) observed that a 30-ppb increase in lag 2 of 8-h max O_3 was associated with a 0.69-point decrease (95% CI: -1.28, -0.11) in the Juniper quality of life score, which incorporates indices for symptoms, mood, and activity limitations (7-point scale). In a fall study conducted in the Los Angeles, CA area, Eiswerth et al. (2005) examined the activities of 64 individuals with asthma (age 16 years and older). A 40-ppb increase in 1-h max O_3 was associated with a 0.24% (95% CI: 0.08, 0.40%) lower probability of participation in indoor activities. The association with outdoor activities was positive but not statistically significant. Although

the authors acknowledged that their findings were unexpected and may have been influenced by lack of control for potential confounders, they interpreted the decrease in indoor activities as rest replacing chores. In contrast, in a panel study of individuals with asthma (ages 13-78 years) in Thailand, O_3 exposure was associated with a lower odds of symptoms that interfered with activities (OR: 0.74 [95% CI: 0.57, 0.96] per 20-ppb increase in lag 4 of 24-h avg O_3) (Wiwatanadate and Liwsrisakun, 2011).

6.2.4.3 Populations not Restricted to Individuals with Asthma

Characteristics and ambient O_3 concentration data from studies of populations not restricted to individuals with asthma are presented in Table 6-22. In contrast with findings for lung function (Section 6.2.1.2), epidemiologic studies do not provide consistent evidence of associations between short-term ambient O_3 exposure and increases in respiratory symptoms in children without asthma (Figure 6-13 and Table 6-23).

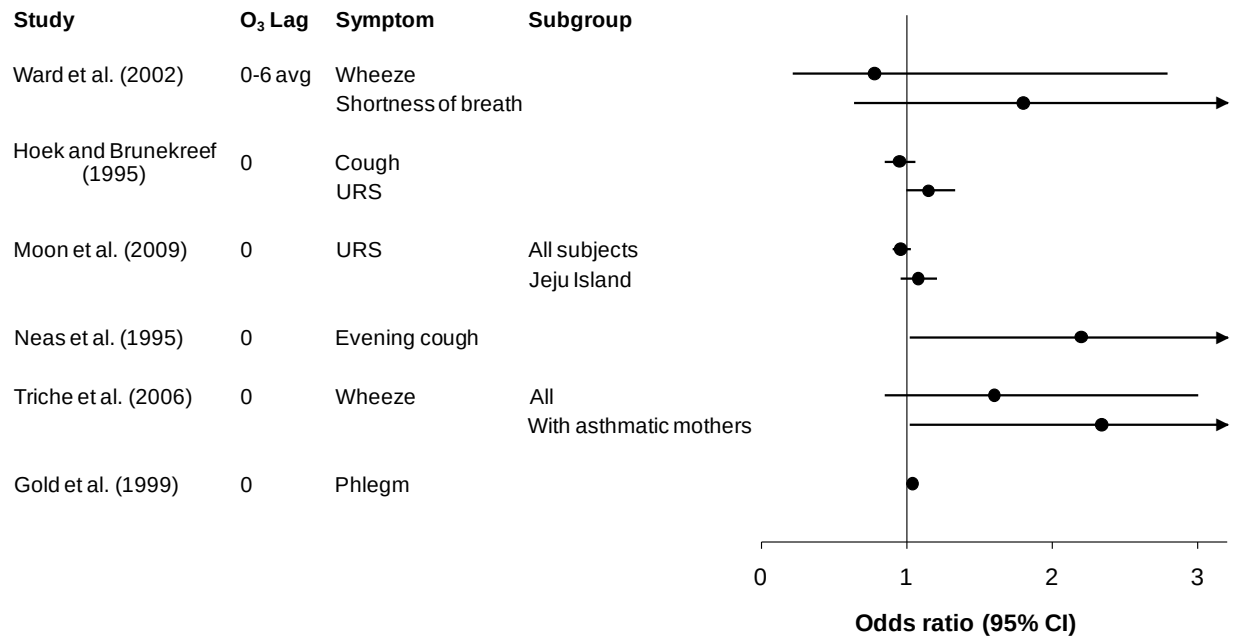
Table 6-22 Mean and upper percentile ozone concentrations in epidemiologic studies examining respiratory symptoms in populations not restricted to individuals with asthma

Study	Location	Years/Season	O_3 Averaging Time	Mean/Median Concentration (ppb)	Upper Percentile Concentrations (ppb)
Apte et al. (2008)	Multiple U.S. cities (NR)	1994-1998 Winter or summer	Workday avg (8:00 a.m. - 5:00 p.m.) 24-h avg	34.2[a] 25.5[a]	Max: 86.2[a] Max: 67.3[a]
Neas et al. (1995)	Uniontown, PA	June-August 1990	12-h avg (8:00 a.m.-8:00 p.m.)	37.2	Max: 44.9
Triche et al. (2006)	Southwestern VA	1995-1996 Warm season	1-h max 8-h max 24-h avg	60.8 54.5 35.2	75th: 70.0, Max: 95.0 75th: 64.1, Max: 87.6 75th: 40.6, Max: 56.6
Linn et al. (1996)	Rubidoux, Upland, Torrence, CA	1992-1993, 1993-1994 Fall and spring	24-h avg	23	Max: 53
Gold et al. (1999)	Mexico City, Mexico	1991 Winter, spring, fall	24-h avg	52.0	Max: 103
Ward et al. (2002)	Birmingham and Sandwell, England	1997 Winter and summer	24-h avg	Winter median: 13.0 Summer median: 22.0	Winter Max: 33 Summer Max: 41
Hoek and Brunekreef (1995)	Deurne and Enkhuizen, Netherlands	1989 March-July	1-h max	Deurne: 57 Enkhuizen: 59	Max: 107 Max: 114
Moon et al. (2009)	4 cities, South Korea	April-May 2003	8-h avg (10:00 a.m.-6:00 p.m.)	NR	NR
Rodriguez et al. (2007)	Perth, Australia	1996-2003 All-year	1-h max 24-h avg	33 28	Max: 95 Max: 74

NR = Not Reported, Max = Maximum.
[a]Concentrations converted from µg/m^3 to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

Among healthy children in Uniontown, PA, Neas et al. (1995) found a stronger association between O_3 exposure and evening cough using ambient concentrations weighted by time spent outdoors (OR: 2.20 [95% CI: 1.02, 4.75] per 30-ppb increase in lag 0 of 12-h avg [8:00 a.m.-8:00 p.m.]) than using unweighted concentrations (OR: 1.36 [95% CI: 0.86, 2.13] per 30-ppb increase in lag 0 of 12-h avg [8:00 a.m.-8:00 p.m.]). Several other panel studies of school-aged children, in which asthma prevalence ranged between 0 to 50%, reported null or negative associations between various averaging times and lags of ambient O_3 exposure and respiratory symptoms (Moon et al., 2009; Rodriguez et al., 2007; Ward et al., 2002; Linn et al., 1996; Hoek and Brunekreef, 1995). For example, a large study of 696 children in four regions in South Korea, Moon et al. (2009) observed that among all subjects, ORs of lag 0 8-h avg O_3 with most respiratory symptoms were close to 1.0. In city-specific analyses, O_3 exposure was only consistently associated with increases in URS (runny nose or sneezing), with the largest magnitude of association observed in Jeju island (OR: 1.08 [95% CI: 0.96, 1.21] per a 30-ppb increase in lag 0 8-h avg O_3). Consistent with other studies conducted in Mexico City, Gold et al. (1999) reported a positive association between lag 1 of 24-h avg O_3 exposure and phlegm in children; however, investigators acknowledged being unable to distinguish between the effects of the highly-correlated O_3 and PM_{10} (r = 0.75).

In a recent study, O_3 exposure was associated with increased odds of respiratory symptoms in a group of infants who have mothers with asthma (Triche et al., 2006). Triche et al. (2006) followed 691 infants in southwestern VA \for 83 days between June and August of 1995 and/or 1996 and found that a 20-ppb increase in lag 0 of 24-h avg O_3 was associated with odds ratios (95% CI) of 2.34 (1.02, 5.37) for wheeze and of 3.63 (1.81, 7.28) for difficulty breathing among the 61 infants who had mothers with asthma. Investigators estimated smaller magnitudes of association for 1-h and 8-h max O_3 exposures. Smaller, statistically nonsignificant associations also were found in analyses that included all subjects (Figure 6-13 and Table 6-23). While these results suggested that children with mothers with asthma may be at greater risk of O_3-related respiratory morbidity, the authors acknowledged that mothers with asthma may be more likely to report symptoms in their children and that transient wheeze, which is common in infants, may not predict respiratory morbidity later in life. In a study of children with parental history of asthma with follow-up to an older age (5 years), ambient O_3 exposure was not associated with increases in respiratory symptoms (Rodriguez et al., 2007).



LRS = lower respiratory symptoms, URS = Upper respiratory symptoms. Effect estimates are from single-pollutant models and are standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max or 12-h avg, and 24-h avg ozone exposures, respectively.

Figure 6-13 Associations of ambient ozone exposure with respiratory symptoms in studies not restricted to children with asthma.

Table 6-23 Additional characteristics and quantitative data for studies presented in Figure 6-13

Study	Location/ Population	O_3 Lag	O_3 Averaging Time	Symptom	Subgroup	Odds Ratio (95% CI)[a]
Ward et al. (2002)	Birmingham and Sandwell, England Children	0-6 avg	24-h avg	Wheeze Shortness of breath		0.78 (0.22, 2.79) 1.80 (0.64, 5.06)
Hoek and Brunekreef (1995)	Enkhuizen, Netherlands Children	0	1-h max	Cough URS		0.95 (0.71, 1.25) 1.15 (1.00, 1.33)
Moon et al. (2009)	4 cities, South Korea Children	0	24-h avg	URS	All subjects Jeju Island	0.96 (0.90, 1.03) 1.08 (0.96, 1.21)
Neas et al. (1995)	Uniontown, PA Healthy children	0	12-h avg (8:00 a.m.-8:00 p.m.)	Evening cough		2.20 (1.02, 4.75)[b]
Triche et al. (2006)	southwestern VA Infants	0	8-h max	Wheeze	All subjects Maternal asthma	1.60 (0.85, 3.00) 2.34 (1.02, 5.37)
Gold et al. (1999)	Mexico City, Mexico Children	1	24-h avg	Phlegm		1.04 (1.00, 1.07)

LRS = Lower respiratory symptoms, URS = Upper respiratory symptoms

[a]Effect estimates are standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max or 12-h avg, and 24-h avg O_3, respectively.

[b]O_3 exposures were weighted by the proportion of time spent outdoors.

A recent cross-sectional study examined 4,200 adult workers from 100 office buildings across the U.S. and found that a range of ambient O_3 exposure metrics, including the 24-h, workday (8:00 a.m.-5:00 p.m.), and late workday (3:00 p.m.-6:00 p.m.) averages, were associated with increases in building-related URS (nasal congestion or sore throat) and LRS (wheeze, shortness of breath, or chest tightness) (Apte et al., 2008). Investigators suggested that the findings may have been attributable to formaldehyde and organic acids produced from O_3-initiated reactions within buildings; however, additional data on indoor levels of volatile organic compounds, indoor O_3, and infiltration rates is warranted to characterize whether the observed associations were attributable to the formation of these secondary species by ambient O_3 penetrating indoors

6.2.4.4 Confounding in Epidemiologic Studies of Respiratory Symptoms and Medication Use

Epidemiologic studies did not indicate that associaitons between short-term O_3 exposure and respiratory symptoms were confounded by meteorological factors. Except where specified in the text, associations between ambient O_3 exposure and respiratory symptoms or medication use were found after adjusting for temperature in models. Some studies additionally included humidity in models (Triche et al., 2006; Ross et al., 2002) or found no independent association with respiratory symptoms (Thurston et al., 1997).

Several studies that examined populations with a high prevalence of atopy found O_3-associated increases in respiratory symptoms and asthma medication use in copollutant models that included daily pollen counts (Just et al., 2002; Ross et al., 2002; Gielen et al., 1997). Gielen et al. (1997) and Ross et al. (2002) specifically reported a high prevalence of grass pollen allergy in their study populations (52% and 38%, respectively). Ross et al. (2002) found similar associations of O_3 with morning symptoms and asthma medication use in a single-pollutant model (e.g., 0.21-point [95% CI: 0.12, 0.30] increase in symptom score per 30-ppb increase in lag 1-3 avg of 8-h max O_3) and in a copollutant model with daily pollen counts (e.g., 0.20-point [95% CI: 0.11, 0.29] increase in symptom score per 30-ppb increase in lag 1-3 avg of 8-h max O_3). Feo Brito et al. (2007) specifically followed a group of adults in central Spain, all of whom had both asthma and pollen allergy. In one city, O_3 was associated with an increase in the number of subjects reporting symptoms. A smaller, statistically nonsignificant effect estimate was obtained for pollen. Conversely, in another city, pollen was associated with an increased incidence of respiratory symptoms, whereas O_3 was not. While copollutant modeling was not conducted, in both locations, O_3 and pollen concentrations were weakly correlated, indicating that the findings for O_3 were not likely confounded by pollen. Rather, the

results suggested that O_3 and pollen may have independent effects that vary between locations, depending on the mix of airborne pollutants.

Table 6-24 Associations between short-term ozone exposure and respiratory symptoms in single- and copollutant models

Study	Location/ Population	O_3 Exposure Data	Symptom	O_3-associated OR in Single-Pollutant Model (95% CI)[a]	O_3-associated OR in Copollutant Model (95% CI)[a]
Mortimer et al. (2002)	Bronx, East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI, Cleveland, OH; Chicago, IL; St. Louis, MO (NCICAS) Children with asthma	8-h avg (10:00 a.m.-6:00 p.m.) Lag 1-4 avg	Morning symptoms	8 cities with SO_2 data 1.35 (1.04, 1.69) 7 ciites with NO_2 data 1.25 (0.94, 1.67) 3 cities with PM_{10} data 1.21 (0.61, 2.41)	with lag 1-2 avg, 3-h avg SO_2 1.23 (0.94, 1.61) with lag 1-6 avg, 24-h avg NO_2 1.14 (0.85, 1.55) with lag 1-2 avg, 24-h avg PM_{10} 1.08 (0.49, 2.39)
Thurston et al. (1997)	CT River Valley Children with asthma attending summer camp	1-h max Lag 0	Chest symptoms	1.21 (1.12, 1.31)[b]	with lag 0, 12-h avg sulfate 1.19 (1.06, 1.35)[b]
Romieu et al. (1996)	Mexico City, Mexico Children with asthma	1-h max Lag 0	LRS	1.07 (1.02, 1.12)	with lag 0, 24-h avg $PM_{2.5}$ 1.06 (1.02, 1.10)
Romieu et al. (1997)	Mexico City, Mexico Children with asthma	1-h max Lag 0	LRS	1.09 (1.04, 1.14)	with lag 0, 24-h avg PM_{10} 1.09 (1.01, 1.19)

LRS = Lower respiratory symptoms.

[a]Effect estimates are standardized to a 40- and 30-ppb increase for 1-h max and 8-h avg O_3, respectively.

[b]Temperature not included in models.

Robust associations between O_3 exposure and respiratory symptoms also were observed in copollutant models that included $PM_{2.5}$, PM_{10}, sulfate, SO_2, or NO_2 (Table 6-24). Information on confounding in asthma medication use associations was more limited. The association between O_3 and bronchodilator use did not change in Gent et al. (2003) after adjusting for $PM_{2.5}$ but decreased in magnitude in Thurston et al. (1997) after adjusting for 12-h avg sulfate. For respiratory symptoms and medication use, copollutant associations remained robust after adjusting for O_3. Notably, studies examined different averaging times for O_3 (1-h max or 8-h avg) and co-pollutants (3-h to 24-h avg) and reported a range of correlations with co-pollutants. Two studies conducted concurrently in two regions of Mexico City examined lag 0 exposures of 1-h max O_3 and 24-h avg PM_{10} or $PM_{2.5}$ and found robust associations with respiratory symptoms for both O_3 and co-pollutants (Romieu et al., 1997; Romieu et al., 1996). Romieu et al. (1997) reported a moderate correlation between 1-h max O_3 and 24-h avg PM_{10} (r = 0.47). Thurston et al. (1997) and Gent et al. (2003) found 1-h max O_3 concentrations to be highly correlated with 12-h avg sulfate (r=0.74) and 24-h avg $PM_{2.5}$ (r=0.77), respectively, thus the copollutant results should be interpreted with caution. The association between O_3 exposure and respiratory symptoms observed in NCICAS was robust in two-pollutant

models with SO_2, NO_2, and or PM_{10}; however, the interpretation is complicated because of the different averaging times and lags of exposure examined for O_3 and co-pollutants (Mortimer et al., 2002) (Table 6-24). Also difficult are interpretations of the robust associations observed between ambient O_3 exposure and respiratory symptoms after adjusting for multiple pollutants (i.e., $PM_{2.5}$ plus NO_2 or $PM_{10-2.5}$) (Escamilla-Nuñez et al., 2008; Triche et al., 2006).

6.2.4.5 Summary of Epidemiologic Studies of Respiratory Symptoms and Asthma Medication Use

With a majority of investigation focused on individuals with asthma, the collective epidemiologic evidence clearly demonstrates that short-term ambient O_3 exposure is associated with increases in respiratory symptoms and asthma medication use in children with asthma. In a smaller body of literature, several studies find associations in adults with asthma. In comparison, evidence has not consistently indicated that short-term O_3 exposure is associated with reduced activity levels in children or adults with asthma. Although O_3 exposure has been associated with school absenteeism among children with asthma, only Gilliland et al. (2001) examined absences specifically for respiratory causes and found associations with O_3 exposure lag periods shorter than 14 days. Epidemiologic studies do not provide consistent evidence of association between short-term ambient O_3 exposure and respiratory symptoms in children without asthma.

Collectively, epidemiologic studies most frequently examined 1-h max and 8-h max or avg O_3 exposures, and the few studies that examined both averaging times found similar magnitudes of associations with respriatory symptoms (Triche et al., 2006; Delfino et al., 2003; Gent et al., 2003). Several studies found increases in respiratory symptoms with O_3 exposures averaged over 12 to 24 hours (Triche et al., 2006; Jalaludin et al., 2004; Gold et al., 1999; Neas et al., 1999). Epidemiologic studies examined associations of respiratory symptoms with single-day O_3 concentrations lagged from 0 to 5 days as well concentrations averaged over 2 to 19 days. While O_3 exposures lagged 0 or 1 days were consistently associated with respiratory symptoms, several studies that examined a range of exposure lags found larger effect estimates for multiday averages (3- to 6-days) of O_3 exposure (Escamilla-Nuñez et al., 2008; Romieu et al., 2006; Rabinovitch et al., 2004; Just et al., 2002; Mortimer et al., 2002; Ross et al., 2002). These epidemiologic findings are in contrast with those from controlled human exposure studies that find attenuated symptom responses with O_3 exposures repeated over several days (Section 6.2.1.1). The epidemiologic findings for lagged O_3 exposures or those accumulated over several days are well-supported by the action of O_3 to sensitize bronchial smooth muscle to hyperreactivity, thus acting as a primer for subsequent exposure to antigens such as

allergens (Section 5.3.5). In several of the studies of individuals with asthma, the prevalence of atopy was high (50-100%), and sensitization of airways provides a biologically plausible mode of action by which lagged or multiday average O_3 exposures are associated with increases in respiratory symptoms in these studies of individuals with asthma.

Epidemiologic evidence did not indicate that associations between short-term O_3 exposure and respiratory symptoms were confounded by temperature or pollen. In the limited analysis of confounding by co-pollutants (primarily PM), robust associations with respiratory symptoms were observed for O_3; however, disentangling the independent effects of O_3 exposure in many studies is complicated due to the high correlations observed between O_3 and PM, different averaging times and lags of exposure examined for co-pollutants, and the multiple co-pollutants included in models. Nonetheless, the consistency of association among individuals with asthma with and without adjustment for copollutant exposures combined with evidence from controlled human exposure studies for the direct effect of O_3 exposure provide substantial evidence for the independent effects of ambient O_3 exposure on increases in respiratory symptoms

6.2.5 Lung Host Defenses

The mammalian respiratory tract has a number of closely integrated defense mechanisms that, when functioning normally, provide protection from the adverse effects of a wide variety of inhaled particles and microbes. For simplicity, these interrelated defenses can be divided into two major parts: (1) nonspecific (transport, phagocytosis, and bactericidal activity) and (2) specific (immunologic) defense mechanisms. A variety of sensitive and reliable methods have been used to assess the effects of O_3 on these components of the lung's defense system to provide a better understanding of the health effects associated with the inhalation of this pollutant. The previous O_3 AQCD states that animal toxicological studies provide extensive evidence that acute O_3 exposures as low as 0.08 to 0.5 ppm can cause increases in susceptibility to infectious diseases due to modulation of lung host defenses. Tables 6-6 through 6-9, beginning on p. 6-41 of the 1996 O_3 AQCD (U.S. EPA, 1996a), and Table AX5-7, beginning on p. AX5-8 of the 2006 O_3 AQCD (U.S. EPA, 2006b), present studies on the effects of O_3 on host defense mechanisms. This section discusses the various components of host defenses, such as the mucociliary escalator, the phagocytic, bactericidal, and regulatory role of the alveolar macrophages (AMs), the adaptive immune system, and integrated mechanisms that are studied by investigating the host's response to experimental pulmonary infections.

6.2.5.1 Mucociliary Clearance

The mucociliary system is one of the lung's primary defense mechanisms. It protects the conducting airways by trapping and quickly removing material that has been deposited or is being cleared from the alveolar region by migrating alveolar macrophages. Ciliary movement directs particles trapped on the overlying mucous layer toward the pharynx, where the mucus is swallowed or expectorated.

The effectiveness of mucociliary clearance can be determined by measuring such biological activities as the rate of transport of deposited particles; the frequency of ciliary beating; structural integrity of the ciliated cells; and the size, number, and distribution of mucus-secreting cells. Once this defense mechanism has been altered, a buildup of both viable and nonviable inhaled substances can occur on the epithelium and may jeopardize the health of the host, depending on the nature of the uncleared substance. Impaired mucociliary clearance can result in an unwanted accumulation of cellular secretions, increased infections, chronic bronchitis, and complications associated with chronic obstructive pulmonary disease. A number of previous studies with various animal species have examined the effect of O_3 exposure on mucociliary clearance and reported morphological damage to the cells of the tracheobronchial tree from acute and sub-chronic exposure to O_3 0.2 ppm and higher. The cilia were either completely absent or had become noticeably shorter or blunt. After placing these animals in a clean-air environment, the structurally damaged cilia regenerated and appeared normal (U.S. EPA, 1986). Based on such morphological observations, related effects such as ciliostasis, increased mucus secretions, and a slowing of mucociliary transport rates might be expected. However, no measurable changes in ciliary beating activity have been reported due to O_3 exposure alone. Essentially no data are available on the effects of prolonged exposure to O_3 on ciliary functional activity or on mucociliary transport rates measured in the intact animal. In general, functional studies of mucociliary transport have observed a delay in particle clearance soon after acute exposure. Decreased clearance is more evident at higher doses (1 ppm), and there is some evidence of tolerance/adaptation for these effects (U.S. EPA, 1986). However, no recent studies have evaluated the effects of O_3 on mucociliary clearance.

6.2.5.2 Alveolobronchiolar Transport Mechanism

In addition to the transport of particles deposited on the mucous surface layer of the conducting airways, particles deposited in the deep lung may be removed either up the respiratory tract or through interstitial pathways to the lymphatic system. The pivotal mechanism of alveolobronchiolar transport involves the movement of AMs with

phagocytized particles to the bottom of the mucociliary escalator. Failure of the AMs to phagocytize and sequester the deposited particles from the vulnerable respiratory membrane can lead to particle entry into the interstitial spaces. Once lodged in the interstitium, particle removal is more difficult and, depending on the toxic or infectious nature of the particle, its interstitial location may allow the particle to set up a focus for pathologic processes. Although some studies show reduced early (tracheobronchial) clearance after O_3 exposure, late (alveolar) clearance of deposited material is accelerated, presumably due to macrophage influx (which in itself can be damaging due to proteases and oxidative reactions in these cells). In an important older study investigating the effects of longer term O_3 exposure on alveolobronchiolar clearance, rats were exposed to an urban pattern of O_3 (continuous 0.06 ppm, 7 days/week with a slow rise to a peak of 0.25 ppm and subsequent decrease to 0.06 ppm over a 9 h period for 5 days/week) for 6 weeks and were exposed 3 days later to chrysotile asbestos, which can cause pulmonary fibrosis and neoplasia (Pinkerton et al., 1989). After 30 days, the lungs of the O_3-exposed animals had twice the number and mass of asbestos fibers as the air-exposed rats. New evaluations of O_3 effects on alveolar clearance have not been performed.

6.2.5.3 Alveolar Macrophages

Within the gaseous exchange region of the lung, the first line of defense against microorganisms and nonviable particles that reach the alveolar surface is the AM. This resident phagocyte is responsible for a variety of activities, including the detoxification and removal of inhaled particles, maintenance of pulmonary sterility via destruction of microorganisms, and interaction with lymphocytes for immunologic protection. Under normal conditions, AMs seek out particles deposited on the alveolar surface and ingest them, thereby sequestering the particles from the vulnerable respiratory membrane. To adequately fulfill their defense function, the AMs must maintain active mobility, a high degree of phagocytic activity, and an optimally functioning biochemical and enzyme system for bactericidal activity and degradation of ingested material. As discussed in previous AQCDs, short periods of O_3 exposure can cause a reduction in the number of free AMs available for pulmonary defense, and these AMs are more fragile, less phagocytic, and have decreased lysosomal enzyme activities required for killing pathogens. For example, in results from earlier work in rabbits, a 2-h exposure to 0.1 ppm O_3 inhibited phagocytosis and a 3-h exposure to 0.25 ppm decreased lysosomal enzyme activities (Driscoll et al., 1987; Hurst et al., 1970). Similarly, AMs from rats exposed to 0.1 ppm O_3 for 1 or 3 weeks exhibited reduced hydrogen peroxide production (Cohen et al., 2002). A controlled human exposure study reported decrements in the ability of alveolar macrophages to phagocytize yeast following exposure of healthy volunteers to

80 to 100 ppb O_3 for 6.6-h during moderate exercise (Devlin et al., 1991). Although the percentage of phagocytosis-capable macrophages was unchanged by O_3 exposure, the number of yeast engulfed was reduced when phagocytosis was complement-dependent. However, there was no difference in the ability of macrophages to produce superoxide anion after O_3 exposure. These results are consistent with those from another controlled human exposure study in which no changes in the level of lysosomal enzymes or superoxide anion production were observed in macrophages lavaged from healthy human subjects exposed to 400 ppb O_3 for 2 h with heavy intermittent exercise (Koren et al., 1989). More recently, Lay et al. (2007) observed no difference in phagocytic activity or oxidative burst capacity in macrophages or monocytes from sputum or blood collected from healthy volunteers after a 2-hour exposure to 400 ppb O_3 with moderate intermittent exercise. However, another study found that oxidative burst and phagocytic activity in macrophages increased in GSTM1 null subjects compared to GSTM1 positive subjects, who had relatively unchanged macrophage function parameters after an O_3 exposure identical to that of Lay et al. described above (Alexis et al., 2009). Collectively, these studies demonstrate that O_3 can affect multiple steps or aspects required for proper macrophage function, but any concentration-response relationship appears complex and genotype may be a consideration. A few other recent studies have evaluated ozone's effects on macrophage function, but these are of questionable relevance due to the use of in vitro exposure systems and amphibian animal models (Mikerov et al., 2008b; Dohm et al., 2005; Klestadt et al., 2005).

6.2.5.4 Infection and Adaptive Immunity

General Effects on the Immune System

The effects of O_3 on the immune system are complex and dependent on the exposure regimen and the observation period. According to toxicological studies it appears that the T-cell-dependent functions of the immune system are more affected than B-cell-dependent functions (U.S. EPA, 2006b). Generally, there is an early immunosuppressive effect that subsides with continued O_3 exposure, resulting in either a return to normal responses or an enhancement of immune responses. However, this is not always the case as Aranyi (1983) showed decreased T-cell mitogen reactions in mice after subchronic (90-day) exposure to 0.1 ppm O_3. Earlier studies report changes in cell populations in lymphatic tissues (U.S. EPA, 2006b). A more recent study in mice demonstrated that numbers of certain T cell subsets in the spleen were reduced after exposure to 0.6 ppm O_3 (10h/day x 15d) (Feng et al., 2006).

The inflammatory effects of O_3 involve the innate immune system, and as such can affect adaptive (or acquired) immunity via alterations in antigen presentation and costimulation by innate immune cells such as macrophages and dendritic cells. Several recent controlled human exposure studies demonstrate increased expression of molecules involved in antigen presentation or costimulation. Lay et al. (2007) collected sputum monocytes from healthy volunteers exposed to 400 ppb O_3 for 2 h with moderate intermittent exercise and detected increases in HLA-DR, used to present antigen to T cells, and CD86, a costimulatory marker necessary for T cell activation. Upregulation of HLA-DR was also observed by Alexis et al. (2009) in sputum dendritic cells and macrophages from GSTM1 null subjects exposed to 400 ppb O_3 for 2 h with moderate intermittent exercise. On airway monocytes from healthy volunteers 24 hours after exposure to 80 ppb O3 for 6.6 h with moderate intermittent exercise, HLA-DR, CD86, and CD14 (a molecule involved in bacterial endotoxin reacitivity) were increased, whereas CD80, a costimulatory molecule of more heterogeneous function, was decreased (Alexis et al., 2010). Patterns of expression on macrophages were similar, except that HLA-DR was found to be significantly decreased after O_3 exposure and CD86 was not significantly altered. An increase in IL-12p70, a macrophage and dendritic cell product that activates T cells, was correlated with increased numbers of dendritic cells. It should be noted that these results are reported as comparisons to baseline as there was no clean air control (Alexis et al., 2010; Alexis et al., 2009). Another controlled human exposure study reported no increase in IL-12p70 in sputum from healthy, atopic, or atopic asthmatic subjects following a 2-hour exposure to 400 ppb O_3 with intermittent moderate exercise (Hernandez et al., 2010). Levels of HLA-DR, CD14 and CD86 were not increased on macrophages collected from any of these subjects. It is difficult to compare these results to those of Lay et al. (2007) and Alexis et al. (2010) due to differences in O_3 concentration, cell type examined, and timing of postexposure analysis.

Although no controlled human exposure studies have examined the effects of O_3 on the ability to mount antigen-specific responses, upregulation of markers associated with innate immune activation and antigen presentation could potentially enhance adaptive immunity and increase immunologic responses to antigen. While this may bolster defenses against infection, it also may enhance allergic responses (Section 6.2.6).

In animal models, O_3 has been found to alter responses to antigenic stimulation. For example, antibody responses to a T-cell-dependent antigen were suppressed after a 56-day exposure of mice to 0.8 ppm O_3, and a 14-day exposure to 0.5 ppm O_3 decreased the antiviral antibody response following influenza virus infection (Jakab and Hmieleski, 1988); the latter impairment may pave the way for lowered resistance to reinfection. The immune response is highly influenced by the temporal relationship between O_3 exposure and antigenic stimulation. When O_3 exposure preceded *Listeria* infection, there were no

effects on delayed-type hypersensitivity or splenic lymphoproliferative responses; however, when O_3 exposure occurred during or after *Listeria* infection was initiated, these immune responses were suppressed (Van Loveren et al., 1988). In another study, a reduction in mitogen activated T-cell proliferation was observed after exposure to 0.6 ppm for 15 days, and could be ameliorated by antioxidant supplementation. Antigen-specific proliferation decreased by 60%, indicating attenuation of the acquired immunity needed for subsequent memory responses (Feng et al., 2006). O_3 exposure also skewed the ex-vivo cytokine responses elicited by non-specific stimulation toward inflammation, decreasing IL-2 and increasing IFN-γ. Modest decreases in immune function assessed in the offspring of O_3-exposed dams (mice) were observed by Sharkhuu et al. (2011). The ability to mount delayed-type hypersensitivity responses was significantly suppressed in 42 day-old offspring when dams were exposed to 0.8 or 1.2 ppm O_3, but not 0.4 ppm, from gestational day 9-18. Humoral responses to immunization with sheep red blood cells were unaffected, as were other immune parameters such as splenic populations of CD45+ T cells, iNKT cells, and levels of IFN-γ, IL-4, and IL-17 in the BALF. Generally, continuous exposure to O_3 impairs immune responses for the first several days of exposure, followed by an adaptation to O_3 that allows a return of normal immune responses. Most species show little effect of O_3 exposures prior to immunization, but show a suppression of responses to antigen in O_3 exposures post-immunization.

Microbial Infection

Bacterial infection

A relatively large body of evidence shows that O_3 increases susceptibility to bacterial infections. The majority of studies in this area were conducted before the 1996 O_3 AQCD was published and many are included in Table 6-9 on p. 6-53 of that document. Known contributing factors are impaired mucociliary streaming, altered chemotaxis/motility, defective phagocytosis of bacteria, decreased production of lysosomal enzymes or superoxide radicals by alveolar macrophages, and decreased IFN-γ levels. In animal models of bacterial infection, exposure to 0.08 ppm O_3 increases streptococcus-induced mortality, regardless of whether O_3 exposure precedes or follows infection (Miller et al., 1978; Coffin and Gardner, 1972; Coffin et al., 1967). Increases in mortality are due to the infectious agent, thereby reflecting functional impairment of host defenses. Exercise and copollutants can enhance ozone's effects in infectivity models. Although both mice and rats exhibit impaired bactericidal macrophage activity after O_3 exposure, mortality due to infection is only observed in mice. Additionally, although mice and humans share many host defense mechanisms, there is little compelling evidence from epidemiologic studies (Section 6.2.7.3).

Viral infection

Only a few studies, described in previous AQCDs, have examined the effects of O_3 exposure on the outcome of viral respiratory infection (see Table 6-9 on p. 6-53 of the 1996 O_3 AQCD. Some studies show increased mortality, while others show diminished severity and increased survival time. There is little to no evidence from studies of animals or humans to suggest that O_3 increases the incidence of respiratory viral infection in humans. In human volunteers infected with rhinovirus prior to O_3 exposure (0.3 ppm for 5 consecutive days), no effect on viral titers, IFN-γ production, or blood lymphocyte proliferative responses to viral antigen was observed (Henderson et al., 1988). In vitro cell culture studies of human bronchial epithelial cells indicate O_3-induced exacerbation of human rhinovirus infection (Spannhake et al., 2002), but this is of limited relevance. Newer studies on the interactions of O_3 and viral infections have not been published. Natural killer (NK) cells, which destroy virally infected cells and tumors in the lung, appear to be inhibited by higher concentrations of O_3 and either unaffected or stimulated at lower concentrations. Several studies show decreases in NK cell activity following acute exposures ranging from 0.8 to 1 ppm (Gilmour and Jakab, 1991; Van Loveren et al., 1990; Burleson et al., 1989). However, Van Loveren et al. (1990) showed that a 1-week exposure to 0.2 or 0.4 ppm O_3 increased NK cell activity, and an urban pattern of exposure (base of 0.06 ppm with peaks of 0.25 ppm) had no effect on NK cell activity after 1, 3, 13, 52, or 78 weeks of exposure (Selgrade et al., 1990). A more recent study demonstrated a 35% reduction in NK cell activity after exposure of mice to 0.6 ppm O_3 (10h/day x 15d) (Feng et al., 2006). The defective IL-2 production demonstrated in this study may impair NK cell activation. Alternatively, NK cell surface charge may be altered by ROS, decreasing their adherence to target cells (Nakamura and Matsunaga, 1998).

Summary: Infections

Taken as a whole, the data clearly indicate that an acute O_3 exposure impairs the host defense capability of both humans and animals, primarily by depressing alveolar macrophage function and perhaps also by decreasing mucociliary clearance of inhaled particles and microorganisms. This suggests that humans exposed to O_3 could be predisposed to bacterial infections in the lower respiratory tract. The seriousness of such infections may depend on how quickly bacteria develop virulence factors and how rapidly PMNs are mobilized to compensate for the deficit in alveolar macrophage function. To date, a limited number of epidemiologic studies have examined associations between O_3 exposure and HA/ED for respiratory infection, pneumonia, or influenza. Results have been mixed, and in some cases conflicting (see Sections 6.2.7.2 and 6.2.7.3). With the exception of influenza, it is difficult to ascertain whether cases of respiratory infection or pneumonia are of viral or bacterial etiology. A study that

examined the association between O_3 exposure and respiratory hospital admissions in response to an increase in influenza intensity did observe an increase in respiratory hospital admissions (Wong et al., 2009), but information from toxicological studies of O_3 and viral infections is ambiguous.

6.2.6 Allergic and Asthma-Related Responses

Effects resulting from combined exposures to O_3 and allergens have been studied in a variety of animal species, generally as models of experimental asthma. Pulmonary function and airways hyperresponsiveness in animal models of asthma are discussed in Sections 6.2.1.7 and 6.2.2.2. Previous evidence indicates that O_3 exposure skews immune responses toward an allergic phenotype. For example, Gershwin et al. (1981) reported that O_3 (0.8 and 0.5 ppm for 4 days) exposure caused a 34-fold increase in the number of IgE (allergic antibody)-containing cells in the lungs of mice. In general, the number of IgE-containing cells correlated positively with levels of anaphylactic sensitivity. In humans, allergic rhinoconjunctivitis symptoms are associated with increases in ambient O_3 concentrations (Riediker et al., 2001). Recent controlled human exposure studies have observed O_3-induced changes indicating allergic skewing. Airway eosinophils, which participate in allergic disease and inflammation, were observed to increase in atopic, mildly asthmatic volunteers 18 h following a 7.6-hour exposure to 160 ppb O_3 with light intermittent exercise (Peden et al., 1997). No increase in airway eosinophils was observed 4 h after exposure of healthy, atopic, or atopic asthmatic subjects to 400 ppb O_3 for 2 h with moderate intermittent exercise (Hernandez et al., 2010). However, atopic subjects did exhibit increased IL-5, a cytokine involved in eosinophil recruitment and activation, suggesting that perhaps these two studies observed the same effect at different time points. Several epidemiologic studies discussed in Section 7.2.5 describe an association between eosinophils and long-term O_3 exposure, consistent with chronic exposure studies in non-human primates. Hernandez et al. (2010) also observed increased expression of high and low affinity IgE receptors on sputum macrophages from atopic asthmatics, which may enhance IgE-dependent inflammation. Sputum levels of IL-4 and IL-13, both pro-allergic cytokines that aid in the production of IgE,were unaltered in any group. The lack of increase in IL-4 levels in sputum reported by Hernandez et al., along with increased IL-5, is consistent with results from Bosson et al. (2003), in which IL-5 (but not IL-4 levels) increased in bronchial epithelial biopsy specimens following exposure of mild atopic asthmatics to 200 ppb O_3 for 2 h with moderate intermittent exercise. IL-5 was not elevated in specimens obtained from healthy (non-asthmatic) O_3-exposed subjects. Collectively, findings from these studies suggest that O_3 can induce or enhance certain components of allergic inflammation in atopic and atopic asthmatic individuals.

Ozone enhances inflammatory and allergic responses to allergen challenge in sensitized animals. Short-term exposure (2 days) to 1 ppm O_3 exacerbated allergic rhinitis and lower airway allergic inflammation in Brown Norway rats, a rat strain that is comparatively less sensitive to O_3 than other rats or humans (Wagner et al., 2009; Wagner et al., 2007). OVA-sensitized rats were intranasally challenged with OVA on days 1 and 2, and exposed to 0 or 1 ppm O_3 (8 h/day) on days 4 and 5. Analysis at day 6 indicated that O_3 exposure enhanced intraepithelial mucosubstances in the nose and airways, induced cys-LTs, MCP-1, and IL-6 production in BALF, and upregulated expression of the proallergic cytokines IL-5 and IL-13. These changes were not evident in non-allergic controls. All of these responses were blunted by gamma-tocopherol (γT; vitamin E) therapy. γT neutralizes oxidized lipid radicals, and protects lipids and proteins from nitrosative damage from NO-derived metabolites. Farraj et al. (2010) exposed allergen-sensitized adult male BALB/c mice to 0.5 ppm O_3 for 5 hours once per week for 4 weeks. Ozone exposure and O_3/DEP (2.0 mg/m^3) co-exposure of OVA-sensitized mice elicited significantly greater serum IgE levels than in DEP-exposed OVA-sensitized mice (98% and 89% increases, respectively). Ozone slightly enhanced levels of BAL IL-5, but despite increases in IgE, caused a significant decrease in BAL IL-4 levels. IL-10, IL-13, and IFN-γ levels were unaffected. Lung resistance and elastance were unaffected in allergen sensitized mice exposed solely to 0.5 ppm O_3 once a week for 4 weeks (Farraj et al., 2010). However, co-exposure to O_3 and diesel exhaust particles increased lung resistance.

In addition to exacerbating existing allergic responses, O_3 can also act as an adjuvant to produce sensitization in the respiratory tract. In a model of murine asthma, using OVA free of detectable endotoxin, inclusion of 1 ppm O_3 during the initial exposures to OVA (2 h, days 1 and 6) enhanced the inflammatory and allergic responses to subsequent allergen challenge (Hollingsworth et al., 2010). Compared to air exposed animals, O_3 exposed mice exhibited significantly higher levels of total cells, macrophages, eosinophils, and PMNs in BALF, and increased total serum IgE. Pro-allergic cytokines IL-4, and IL-5 were also significantly elevated, along with pleiotropic Th2 cytokine IL-9 (associated with bronchial hyperresponsiveness) and pro-inflammatory IL-17, produced by activated T cells. Based on lower inflammatory, IgE, and cytokine responses in Toll-like receptor 4 deficient mice, the effects of O_3 seem to be dependent on TLR 4 signaling, as are a number of other biological responses to O_3 according to studies by Hollingsworth et al. (2004), Kleeberger et al.(2000) and Garanziotis et al. (2010). The involvement of TLR 4, along with its endogenous ligand, hyaluronan, in O_3-induced responses described in these studies has been corroborated by a controlled human exposure study by Hernandez et al. (2010), who found increased TLR 4 expression and elevated levels of hyaluronic acid in atopic and atopic asthmatic volunteers exposed to 400 ppb O_3. This pathway is discussed in more detail in Chapter 5. Examination of dendritic cells (DCs)

from the draining thoracic lymph nodes indicated that O_3 did not enhance the migration of DCs from the lungs to the lymph nodes, nor did it alter the expression of functional DC markers such as CD40, MHC class II, or CD83. However, O_3 did increase expression of CD86, which is generally associated with Th2 responses and is detected at higher levels on DCs from allergic asthmatics compared to those from healthy donors (Chen et al., 2006b). Increased CD86 has also been observed on airway cells collected from human subjects following exposure to O_3 in studies by Lay et al. (2007) and Alexis et al. (2009), but not Hernandez et al. (2010) (study details described in Section 6.2.5.4).

Ozone exposure during gestation has modest effects on allergy and asthma related endpoints in adult offspring. When dams were exposed to 1.2 ppm O_3 (but not 0.8 ppm) from gestational day 9-18, some allergic and inflammatory responses to OVA sensitization and challenge were reduced compared to air exposed controls. This included IgE levels and eosinophils, and was only true of mice that were immunized early in life (PND 3) as opposed to later (PND 42), perhaps due to the proximity of O_3 and antigen exposure. The effects of gestational O_3 exposure on immune function have not been widely studied, and although reductions in allergic endpoints are not generally observed in association with O_3, other parameters of immune function were found to be reduced, so a more global immunosuppression may underlie these effects.

In addition to ozone's pro-allergic effects, it could also make airborne allergens more allergenic. When combined with NO_2, O_3 has been shown to enhance nitration of common protein allergens, which may increase their allergenicity (Franze et al., 2005).

6.2.7 Hospital Admissions, Emergency Department Visits, and Physicians Visits

6.2.7.1 Summary of Findings from 2006 Ozone AQCD

The 2006 O_3 AQCD evaluated numerous respiratory ED visits and hospital admissions studies, which consisted primarily of time-series studies conducted in the U.S., Canada, Europe, South America, Australia and Asia. Upon collectively evaluating the scientific evidence, the 2006 O_3 AQCD concluded that "the overall evidence supports a causal relationship between acute ambient O_3 exposures and increased respiratory morbidity resulting in increased ED visits and [hospital admissions] during the warm season" (U.S. EPA, 2006b). This conclusion is "strongly supported by the human clinical, animal toxicologic[al], and epidemiologic evidence for [O_3-induced] lung function decrements, increased respiratory symptoms, airway inflammation, and airway hyperreactivity" (U.S. EPA, 2006b).

Since the completion of the 2006 O_3 AQCD, relatively fewer studies conducted in the U.S., Canada, and Europe have examined the association between short-term exposure to ambient O_3 and respiratory hospital admissions and ED visits with a growing number of studies having been conducted in Asia. This section focuses primarily on multicity studies because they examine the effect of O_3 on respiratory-related hospital admissions and ED visits over a large geographic area using a consistent statistical methodology. Single-city studies that encompass a large number of hospital admissions or ED visits, or included a long study-duration were also evaluated because these studies have more power to detect whether an association exists between short-term O_3 exposure and respiratory hospital admissions and ED visits compared to smaller single-city studies. Additional single-city studies were also evaluated within this section, if they were conducted in locations not represented by the larger single-city and multicity studies, or examined population-specific characteristics not included in the larger studies that may modify the association between short-term O_3 exposure and respiratory-related hospital admissions or ED visits. The remaining single-city studies identified were not evaluated in this section due to factors such as inadequate study design or insufficient sample size.

It should be mentioned that when examining the association between short-term O_3 exposure and respiratory health effects that require medical attention, it is important to distinguish between hospital admissions and ED visits. This is because it is likely that a small percentage of respiratory ED visits will be admitted to the hospital; therefore, respiratory ED visits may represent potentially less serious, but more common outcomes. As a result, in the following sections respiratory hospital admission and ED visit studies are evaluated individually. Additionally, within each section, results are presented as either a collection of respiratory diagnoses or as individual diseases (e.g., asthma, COPD, pneumonia and other respiratory infections) in order to evaluate the potential effect of short-term O_3 exposure on each respiratory-related outcome. The ICD codes (i.e., ICD-9 or ICD-10) that encompass each of these endpoints are presented in Table 6-25 along with the air quality characteristics of the city, or across all cities, included in each study evaluated in this section.

Table 6-25 Mean and upper percentile concentrations of respiratory-related hospital admission and emergency department visit studies evaluated

Study	Location	Type of Visit (ICD9/10)	Averaging Time	Mean Concentration (ppb)[a]	Upper Percentile Concentrations (ppb)[a]
Katsouyanni et al. (2009)[b,c]	90 U.S. cities (NMMAPS)[d] 32 European cities (APHEA)[d] 12 Canadian cities	Hospital Admissions: NMMAPS: All respiratory (460-519) APHEA: All respiratory (460-519) 12 Canadian cities: All respiratory (460-519)[e]	1-h max	NMMAPS: 50th: 34.9-60.0 APHEA: 50th: 11.0-38.1 12 Canadian cities: 50th: 6.7-8.3	NMMAPS: 75th: 46.8-68.8 APHEA: 75th: 15.3-49.4 12 Canadian cities: 75th: 8.9-12.4
Cakmak et al. (2006b)	10 Canadian cities	Hospital Admissions: All respiratory (466, 480-486, 490, 491, 492, 493, 494, 496)	24-h avg	17.4	Max: 38.0-79.0
Biggeri et al. (2005)[c]	4 Italian cities[f]	Hospital Admissions: All respiratory (460-519)	8-h max	Warm season (May-September): 5.7-60.0	95th: 86.1-90.0 Max: 107.5-115.1
Dales et al. (2006)	11 Canadian cities	Hospital Admissions: Respiratory disorders (486, 768.9, 769, 770.8, 786, 799.0, 799.1)	24-h avg	17.0	95th: 24.9-46.0
Lin et al. (2008a)	11 New York regions	Hospital Admissions: Respiratory diseases (466, 490-493, 496)	8-h max[g]	44.1	75th: 54.0 Max: 217.0
Wong et al. (2009)[c]	Hong Kong	Hospital Admissions: All respiratory (460-519)	8-h max[g]	18.8	75th: 25.9 Max: 100.3
Medina-Ramon et al. (2006)[h]	36 U.S. cities	Hospital Admissions: COPD (490-496, excluding 493) Pneumonia (480-487)	8-h max	Warm (May-September): 45.8 Cool (October-April): 27.6	NR
Yang et al. (2005b)	Vancouver, Canada	Hospital Admissions: COPD (490-492, 494, 496)	24-h avg	All year: 14.1 Winter (January-March): 13.2 Spring (April-June): 19.4 Summer (July-September): 13.8 Fall (October-December): 10.0	Max: 38.6
Zanobetti and Schwartz (2006)[b]	Boston, MA	Hospital Admissions: Pneumonia (480-487)	24-h avg	22.4	75th: 31.0 95th: 47.6
Silverman and Ito (2010)[b]	New York, NY	Hospital Admissions: Asthma (493)	8-h max	Warm (April-August):41.0	75th: 53 90th: 68
Stieb et al. (2009)	7 Canadian cities	Emergency Department Visits: Asthma (493) COPD (490-492, 494-496) Respiratory infection (464, 466, 480-487)	24-h avg	18.4	75th: 19.3-28.6
Tolbert et al. (2007)	Atlanta, GA	Emergency Department Visits: All respiratory (460-465, 460.0, 466.1, 466.11, 466.19, 477, 480-486, 491, 492, 493, 496, 786.07, 786.09)	8-h max	Warm: 53.0	75th: 67.0 90th: 82.1 Max: 147.5
Darrow et al. (2011b)	Atlanta, GA	Emergency Department Visits: All respiratory (460-466, 477, 480-486, 491, 492, 493, 496, 786.09)	8-h max 1-h max 24-h avg Commute Day-time Night-time	Warm (March-October): 8-h max: 53 1-h max: 62 24-h avg: 30 Commute: 35[i] Day-time: 45[i] Night-time: 14[i]	8-h max: 75th: 67 Max: 148 1-h max: 75th: 76 Max: 180 24-h avg: 75th: 37 Max: 81 Commute: 75th: 45 Max: 106 Day-time: 75th: 58 Max: 123 Night-time: 75th: 22 Max: 64
Villeneuve et al. (2007)b	Alberta, CAN	Emergency Department Visits: Asthma (493)	8-h max	Summer (April-September): 38.0 Winter (October-March): 24.3	Summer: 75th: 46.0 Winter: 75th: 31.5
Ito et al. (2007b)	New York, NY	Emergency Department Visits: Asthma (493)	8-h max	All year: 30.4 Warm (April-September): 42.7 Cold (October-March): 18.0	All year: 95th: 68.0 Warm months: 95th: 77.0 Cold months: 95th: 33.0

Study	Location	Type of Visit (ICD9/10)	Averaging Time	Mean Concentration (ppb)[a]	Upper Percentile Concentrations (ppb)[a]
Strickland et al. (2010)	Atlanta, GA	Emergency Department Visits: Asthma (493) Wheeze (786.07 after 10/1/98, 786.09 before 10/1/98)	8-h max	All year: 45.4[j] Warm (May-October): 55.2[j] Cold (November-April): 34.5[j]	NR
Mar and Koenig et al. (2009)	Seattle, WA	Emergency Department Visits: Asthma (493-493.9)	1-h max 8-h max	Warm (May-October): 1-h max: 38.6 8-h max: 32.2	75th: 1-h max: 45.5 8-h max: 39.2
Arbex et al. (2009)	Sao Paulo, Brazil	Emergency Department Visits: COPD (J40-44)	1-h max	48.8	75th: 61.0 Max: 143.8
Orazzo et al. (2009)[c]	6 Italian cities	Emergency Department Visits: Wheezing	8-h max[k]	Summer (April-September): 21.1-44.3 Winter (October-March): 11.5-27.9	NR
Burra et al. (2009)	Toronto, Canada	Physician Visits: Asthma (493)	1-h max	33.3	95th: 66 Max: 121
Villeneuve et al. (2006b)	Toronto, Canada	Physician Visits: Allergic rhinitis (177)	8-h max	30.0	Max: 98.7
Sinclair et al. (2010)[l]	Atlanta, GA	Physician Visits: Asthma Upper respiratory infection Lower respiratory infection	8-h max	Total Study Period: All-year: 44.0 25 mo Period: All-year: 47.9 Warm: 61.2 Cold: 27.8 28 mo Period: All-year: 40.7 Warm: 51.8 Cold: 26.0	NR

[a]Some studies did not present an overall value for the mean, middle and/or upper percentiles of the O_3 distribution; as a result, the range of the mean, middle, and/or upper percentiles across all of the cities included in the study are presented.

[b]Study only presented median concentrations.

[c]Study presented concentrations as µg/m3 Concentration was converted to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

[d]A subset of the European and U.S. cities included in the mortality analyses were used in the hospital admissions analyses: 8 of the 32 European cities and 14 of 90 U.S. cities.

[e]Hospital admission data was coded using three classifications (ICD-10-CA, ICD-9, and ICD-9-CM). Attempts were made by the original investigators to convert diagnosis from ICD-10-CA back to ICD-9.

[f]Only 4 of the 8 cities included in the study collected O_3 data.

[g]O_3 measured from 10:00 a.m. to 6:00 p.m.

[h]Only 35 of the 36 cities included in the analysis had O_3 data.

[i]Commute (7:00 a.m. to 10:00 a.m., 4:00 p.m. to 7:00 p.m.); Day-time (8:00 a.m. to 7:00 p.m.); Night-time (12:00 a.m. to 6:00 a.m.).

[j]Means represent population-weighted O_3 concentrations.

[k]O_3 measured from 8:00 a.m. to 4:00 p.m.

[l]This study did not report the ICD codes used for the conditions examined. The 25-month period represents August 1998-August 2000, and the 28-month period represents September 2000-December 2002. This study defined the warm months as April – October and the cold months as November-March.

6.2.7.2 Hospital Admission Studies

Respiratory Diseases

The association between exposure to an air pollutant, such as O_3, and daily respiratory-related hospital admissions has primarily been examined using all respiratory-related hospital admissions within the range of ICD-9 codes 460-519. Newly identified studies attempt to further examine the effect of O_3 exposure on respiratory-related hospital admissions through a multicity design that examines O_3 effects across countries using a

standardized methodology; multicity studies that examine effects within one country; and multi- and single-city studies that attempt to examine potential modifiers of the O_3-respiratory-related hospital admission relationship.

The Air Pollution and Health: A European and North American Approach (APHENA) study combined data from existing multicity study databases from Canada, Europe (APHEA2) (Katsouyanni et al., 2001), and the U.S. (NMMAPS) (Samet et al., 2000) in order to "develop more reliable estimates of the potential acute effects of air pollution on human health [and] provide a common basis for [the] comparison of risks across geographic areas" (Katsouyanni et al., 2009). In an attempt to address both of these issues, the investigators conducted extensive sensitivity analyses to evaluate the robustness of the results to different model specifications (e.g., penalized splines [PS] versus natural splines [NS]) and the extent of smoothing to control for seasonal and temporal trends. The trend analyses consisted of subjecting the models to varying extent of smoothing selected either a priori (e.g., 3 df/year, 8 df/year, and 12 df/year) or by using the absolute sum of the residuals of the partial autocorrelation function (PACF). However, the investigators did not identify the model they deemed to be the most appropriate for comparing the results across study locations. As a result, when discussing the results across the three study locations below, the 8 df/year results are presented for both the PS and NS models because: (1) 8 df/year is most consistent with the extent of temporal adjustment used in previous and recent large multicity studies in the U.S. (e.g., NMMAPS); (2) the risk estimates for 8 df/year and 12 df/year are comparable for all three locations; (3) the models that used the PACF method did not report the actual degrees of freedom chosen; and (4) the 3 df/year and the PACF method resulted in negative O_3 risk estimates, which is inconsistent with the results obtained using more aggressive seasonal adjustments. Additionally, when comparing results across studies in figures, only the results from one of the spline models (e.g., NS) are presented because it has been previously demonstrated that alternative spline models result in relatively similar effect estimates (HEI, 2003). However, it should be noted that the underlying data and model specifications could result in varying degrees of bias and precision in effect estimates with different spline models (Ostro et al., 2006).

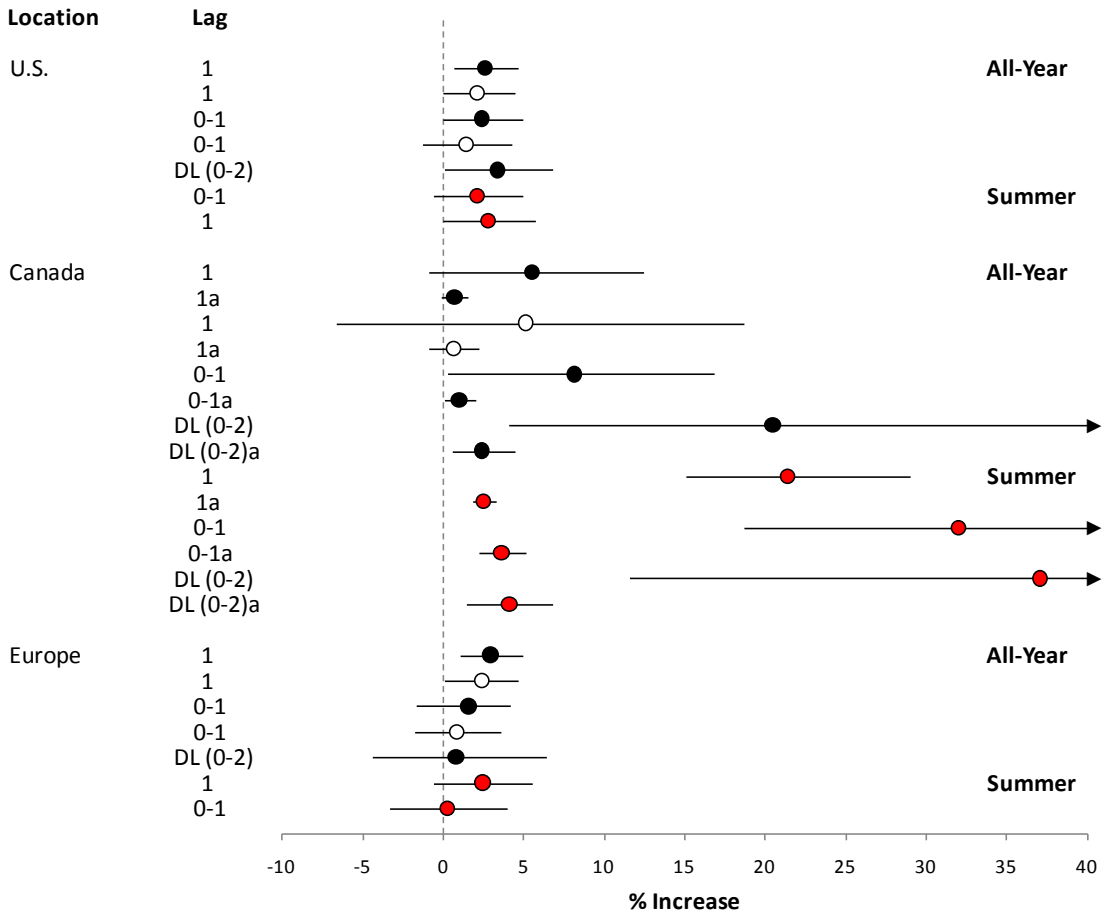
Katsouyanni et al. (2009) examined respiratory hospital admissions for people aged 65 years and older using 1-h max O_3 data. The extent of hospital admission and O_3 data varied across the 3 datasets: Canadian dataset included 12 cities with data for 3 years (1993-1996) per city; European dataset included 8 cities with each city having data for between 2 and 8 years from 1988-1997; and U.S. dataset included 14 cities with each city having data for between 4 and 10 years from 1985-1994 and 7 cities having only summer O_3 data. The investigators used a three-stage hierarchical model to account for within-city, within region, and between region variability. Results were presented individually

for each region (Figure 6-14; Table 6-26). Ozone and PM_{10} concentrations were weakly correlated in all locations in the summer (r=0.27-0.40), but not in the winter.

In the Canadian cities, using all-year data, a 40 ppb increase in 1-h max O_3 concentrations at lag 0-1 was associated with an increase in respiratory hospital admissions of 8.9% (95% CI: 0.79, 16.8%) in a PS model and 8.1% (95% CI: 0.24, 16.8%) in a NS model (Katsouyanni et al., 2009). The results were somewhat sensitive to the lag day selected, reduced when using a single-day lag (e.g., lag 1) (PS: 6.0%; NS: 5.5%) and increased when using a distributed lag model (PS: 18.6%; NS: 20.4%). When adjusting for PM_{10}, the magnitude of the effect estimate was slightly larger in the NS model (5.1% [95% CI: -6.6, 18.6%]) compared to the PS model (3.1% [95% CI: -8.3, 15.9%]); however, the copollutant analysis was only conducted using a 1-day lag. The large confidence intervals for both models could be attributed to the reduction in days included in the copollutant analyses as a result of the every-6th-day PM sampling schedule. When restricting the analysis to the summer months, stronger associations were observed between O_3 and respiratory hospital admissions across the lags examined, ranging from ~22 to 37% (the study does not specify whether these effect estimates are from a NS or PS model). Because O_3 concentrations across the cities included in the Canadian dataset (Katsouyanni et al. (2009) are low (median concentrations ranging from 6.7-8.3 ppb [Table 6-25]), the standardized increment of 40 ppb for a 1-h max increase in O_3 concentrations does not accurately reflect the observed risk of O_3-related respiratory hospital admissions. Although this increment adequately characterizes the distribution of 1-h max O_3 concentrations across the U.S. and European datasets, it misrepresents the observed O_3 concentrations in the Canadian dataset. As a result in summary figures, for comparability, effect estimates from the Canadian dataset are presented for both a 5.1 ppb increase in 1-h max O_3 concentrations (i.e., an approximate interquartile range [IQR] increase in O_3 concentrations across the Canadian cities) as well as the standardized increment used throughout the ISA.

In Europe, weaker but positive associations were also observed in year round analyses; 2.9% (95% CI: 0.63, 5.0%) in the PS model and 1.6% (95% CI: -1.7, 4.2%) in the NS model at lag 0-1 for a 40 ppb increase in 1-h max O_3 concentrations (Katsouyanni et al., 2009). Additionally, at lag 1, associations between O_3 and respiratory hospital admissions were also reduced, but in contrast to the lag 0-1 analysis, greater effects were observed in the NS model (2.9% [95% CI: 1.0, 4.9%]) compared to the PS model (1.5% [95% CI: -2.2, 5.4]). Unlike the Canadian analysis, a distributed lag model provided limited evidence of an association between O_3 and respiratory hospital admissions. To compare with the Canadian results, when adjusting for PM_{10} at lag 1, effect estimates were increased in the PS model (2.5% [95% CI: 0.39-4.8%]) and remained robust in the NS model (2.4% [95% CI: 0.08, 4.6%]). However, the European analysis also examined the

effect of adjusting for PM_{10} at lag 0-1 and found results were attenuated in both models (PS: 0.8% [95% CI: -2.3, 4.0%]; NS: 0.8% [95% CI: -1.8, 3.6%]). Unlike the Canadian and U.S. datasets, the European dataset consisted of daily PM data. The investigators did not observe stronger associations in the summer-only analyses for the European cities at lag 0-1 (PS: 0.4% [95% CI: -3.2, 4.0%]; NS: 0.2% [95% CI: -3.3, 3.9%]), but did observe some evidence for larger effects during the summer, an ~2.5% increase, at lag 1 in both models (the study does not present the extent of temporal smoothing used for these models).



Black circles = all-year results; open circles = all-year results in copollutant model with PM_{10}; and red circles = summer only results. For Canada, lag days with an "a" next to them represent the risk estimates standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in ozone concentrations.

Figure 6-14 Percent increase in respiratory hospital admissions from natural spline models for a 40 ppb increase in 1-h max ozone concentrations for each location of the APHENA study.

Table 6-26 Corresponding effect estimates for Figure 6-14

Location	Season	Lag[a]	Copollutant	% Increase (95% CI)[b]
U.S.				
	All-year	1		2.62 (0.63, 4.64)
		1	PM_{10}	2.14 (-0.08, 4.40)
		0-1		2.38 (0.00, 4.89)
		0-1	PM_{10}	1.42 (-1.33, 4.23)
		DL(0-2)		3.34 (0.02-6.78)
	Summer	0-1		2.14 (-0.63, 4.97)
		1		2.78 (-0.02, 5.71)
Canada	All-year	1		5.54 (-0.94, 12.4)
		1a		0.69 (-0.12, 1.50)a
		1	PM_{10}	5.13 (-6.62, 18.6)
		1a	PM_{10}	0.64 (-0.87, 2.20)a
		0-1		8.12 (0.24, 16.8)
		0-1a		1.00 (0.03, 2.00)a
		DL(0-2)		20.4 (4.07, 40.2)
		DL(0-2)a		2.4 (0.51, 4.40)a
	Summer	1		21.4 (15.0, 29.0)
		1a		2.50 (1.80, 3.30)a
		0-1		32.0 (18.6, 47.7)
		0-1a		3.60 (2.20, 5.10)a
		DL(0-2)		37.1 (11.5, 67.5)
		DL(0-2)a		4.1 (1.40, 6.80)a
Europe	All-year	1		2.94 (1.02, 4.89)
		1	PM_{10}	2.38 (0.08, 4.64)
		0-1		1.58 (-1.71, 4.15)
		0-1	PM_{10}	0.87 (-1.79, 3.58)
		DL(0-2)		0.79 (-4.46, 6.37)
	Summer	1		2.46 (-0.63, 5.54)
		0-1		0.24 (-3.32, 3.91)

[a]For Canada, lag days with an "a" next to them represent the risk estimates standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O_3 concentrations.

[b]Unless noted, risk estimates standardized to 40 ppb for a 1-h max increase in O_3 concentrations.

For the U.S. in year round analyses, the investigators reported a 1.4% (95% CI: -0.9, 3.9%) increase in the PS model and 2.4% (95% CI: 0.0, 4.9%) increase in the NS model in respiratory hospital admissions at lag 0-1 for a 40 ppb increase in 1-h max O_3 concentrations with similar results for both models at lag 1 (Katsouyanni et al., 2009). The distributed lag model provided results similar to those observed in the European dataset with the PS model (1.1% [95% CI: -3.0, 5.3%]), but larger effects in the NS model (3.3% [95% CI: 0.02, 6.8%]), which is consistent with the Canadian results. When adjusting for PM_{10} using the U.S. data (i.e., every-6th-day PM data), results were attenuated at lag 0-1 (PS: 0.6% [95% CI: -2.0, 3.3%]; NS: 1.4% [95% CI: -1.3, 4.2%]) which is consistent with the results presented for the European dataset. However, at lag 1, U.S. risk estimates remained robust to the inclusion of PM_{10} in copollutant models as was observed in the Canadian and European datasets. Compared to the all-year analyses, the investigators did not observe stronger associations in the summer-only analysis at either lag 0-1 (~2.2%) or lag 1 (~2.8%) in both the PS and NS models (the study does not present the extent of temporal smoothing used for these models).

Several additional multicity studies examined respiratory disease hospital admissions in Canada and Europe. Cakmak et al. (2006b) evaluated the association between ambient O_3

concentrations and respiratory hospital admissions for all ages in 10 Canadian cities from April 1993 to March 2000. The primary objective of this study was to examine the potential modification of the effect of ambient air pollution on daily respiratory hospital admissions by education and income using a time-series analysis conducted at the city-level. The authors calculated a pooled estimate across cities for each pollutant using a random effects model by first selecting the lag day with the strongest association from the city-specific models. For O_3, the mean lag day across cities that provided the strongest association and for which the pooled effect estimate was calculated was 1.2 days. In this study, all-year O_3 concentrations were used in the analysis, and additional seasonal analyses were not conducted. Cakmak et al. (2006b) reported a 4.4% increase (95% CI: 2.2, 6.5%) in respiratory hospital admissions for a 20 ppb increase in 24-h average O_3 concentrations. The investigators only examined the potential effect of confounding by other pollutants through the use of a multipollutant model (i.e., two or more additional pollutants included in the model), which is difficult to interpret due to the potential multicollinearity between pollutants. Cakmak et al. (2006b) also conducted an extensive analysis of potential modifiers, specifically sex, educational attainment, and family income, on the association between air pollution and respiratory hospital admissions. When stratifying by sex, the increase in respiratory hospital admissions due to short-term O_3 exposure were similar in males (5.2% [95% CI: 3.0, 7.3%]) and females (4.2% [95% CI: 1.8, 6.6%]). In addition, the examination of effect modification by income found no consistent trend across the quartiles of family income. However, there was evidence that individuals with an education level less than the 9th grade were disproportionately affected by O_3 exposure (4.6% [95% CI: 1.8, 7.5%]) compared to individuals that completed grades 9-13 (1.7% [95% CI: -1.9, 5.3%]), some university or trade school (1.4% [95% CI: -2.0, 5.1%]), or have a university diploma (0.66% [95% CI: -3.3, 4.7%]). The association between O_3 and individuals with an education level less than the 9th grade was the strongest association across all of the pollutants examined.

A multicity study conducted in Europe by Biggeri et al. (2005) examined the association between short-term O_3 exposure and respiratory hospital admissions for all ages in four Italian cities from 1990 to 1999. In this study, O_3 was only measured during the warm season (May-September). The authors examined associations between daily respiratory hospital admissions and short-term O_3 exposure at the city-level using a time-series analysis. Pooled estimates were calculated by combining city-specific estimates using fixed and random effects models. The investigators found no evidence of an association between O_3 exposure and respiratory hospital admissions in the warm season in both the random (0.1% [95% CI: -5.2, 5.7%]; distributed lag 0-3) and fixed effects (0.1% [95% CI: -5.2, 5.7%]; distributed lag 0-3) models for a 30 ppb increase in 8-h max O_3 concentrations.

Additional studies examined associations between short-term O_3 exposure and respiratory hospital admissions specifically in children. In a multicity study conducted in Canada, Dales et al. (2006) examined the association between all-year ambient O_3 concentrations and neonatal (ages 0-27 days) respiratory hospital admissions in 11 Canadian cities from 1986 to 2000. The investigators used a statistical analysis approach similar to Cakmak et al. (2006b) (i.e., time-series analysis to examine city-specific associations, and then a random effects model to pool estimates across cities). The authors reported that for O_3, the mean lag day across cities that provided the strongest association was 2 days. The authors reported a 5.4% (95% CI: 2.9, 8.0%) increase in neonatal respiratory hospital admissions for a 20 ppb increase in 24-h avg O_3 concentrations at lag-2 days. The results from Dales et al. (2006) provide support for the associations observed in a smaller scale study that examined O_3 exposure and pediatric respiratory hospital admissions in New York state (Lin et al., 2008a). Lin et al. (2008a) observed a positive association between O_3 and pediatric (i.e., <18 years) respiratory admissions at lag 2 (results not presented quantitatively) in a two-stage Bayesian hierarchical model analysis of 11 geographic regions of New York from 1991 to 2001.

Overall, the evidence from epidemiologic studies continues to support an association between short-term O_3 exposure and respiratory-related hospital admissions, but it remains unclear whether certain factors (individual- or population-level) modify this association. Wong et al. (2009) examined the potential modification of the relationship between ambient O_3 (along with NO_2, SO_2, and PM_{10}) and respiratory hospital admissions by influenza intensity in Hong Kong for the period 1996 – 2002. Influenza intensity was defined as a continuous variable using the proportion of weekly specimens positive for influenza A or B instead of defining influenza epidemics. This approach was used to avoid any potential bias associated with the unpredictable seasonality of influenza in Hong Kong (Wong et al., 2009). In models that examined the baseline effect (i.e., without taking into consideration influenza intensity) of short-term O_3 exposure, the authors found a 3.6% (95% CI: 1.9, 5.3%) and 3.2% (95% CI: 1.0, 5.4%) increase in respiratory hospital admissions at lag 0-1 for a 30 ppb increase in 8-h max O_3 concentrations for the all age and $\geq$ 65 age groups, respectively. When examining influenza intensity, Wong et al. (2009) reported that the association between short-term exposure to O_3 and respiratory hospital admissions was stronger with higher levels of influenza intensity: additional increase in respiratory hospital admissions above baseline of 1.4% (95% CI: 0.24, 2.6%) for all age groups and 2.4% (95% CI: 0.94, 3.8%) for those 65 and older when influenza activity increased from 0% to 10%. No difference in effects was observed when stratifying by sex.

Cause-Specific Respiratory Outcomes

In the 2006 O_3 AQCD a limited number of studies were identified that examined the effect of short-term O_3 exposure on cause-specific respiratory hospital admissions. The limited evidence "reported positive O_3 associations with… asthma and COPD, especially… during the summer or warm season" (U.S. EPA, 2006b). Of the studies evaluated since the completion of the 2006 O_3 AQCD, more have focused on identifying whether O_3 exposure is associated with specific respiratory-related hospital admissions, including COPD, pneumonia, and asthma, but the overall body of evidence remains small.

Chronic Obstructive Pulmonary Disease

Medina-Ramon et al. (2006) examined the association between short-term exposure to ambient O_3 and PM_{10} concentrations and Medicare hospital admissions among individuals $\geq$ 65 years of age for COPD in 35 cities in the U.S. for the years 1986-1999. The cities included in this analysis were selected because they monitored PM_{10} on a daily basis. In this study, city-specific results were obtained using a monthly time-stratified case-crossover analysis. A meta-analysis was then conducted using random effects models to combine the city-specific results. All cities measured O_3 from May through September, while only 16 of the cities had year-round measurements. The authors reported a 1.6% increase (95% CI: 0.48, 2.9%) in COPD admissions for lag 0-1 in the warm season for a 30 ppb increase in 8-h max O_3 concentrations. When examining single-day lags, stronger associations were observed for lag 1 (2.9% [95% CI: 1.8, 4.0%]) compared to lag 0 (-1.5% [95% CI: -2.7, -0.24%]). The authors found no evidence of associations in cool season (-1.9% [95% CI: -3.6, -0.06%]; lag 0-1) or year round (0.24% [95% CI: -0.78, 1.2%]; lag 0-1) analyses. In a copollutant model using warm season data, the association between O_3 and COPD hospital admissions was robust to the inclusion of PM_{10} in the model (results not presented quantitatively). The authors conducted additional analyses to examine potential modification of the warm season estimates for O_3 and COPD admissions by several city-level characteristics: percentage living in poverty, emphysema mortality rate (as an indication of smoking), daily summer apparent temperature, and percentage of households using central air conditioning. Of the city-level characteristics examined, stronger associations were only reported for cities with a larger variability in daily apparent summer temperature.

In a single-city study conducted in Vancouver from 1994-1998, a location with low ambient O_3 concentrations (Table 6-25), Yang et al. (2005b) examined the association between O_3 and COPD. Ozone was moderately inversely correlated with CO (r=-0.56), NO_2 (r=-0.32), and SO_2 (r=-0.34), and weakly inversely correlated with PM_{10} (r=-0.09), suggesting that the observed O_3 effect is likely not only due to a positive correlation with

other pollutants. Yang et al. (2005b) examined 1- to 7-day (e.g., (0-6 days) lagged moving averages and observed an 8.8% (95% CI: -12.5, 32.6%) increase in COPD admissions for lag 0-3 per 20 ppb increase in 24-h avg O_3 concentrations. In two-pollutant models at lag 0-3, O_3 effect estimates were robust to the inclusion of NO_2, SO_2, and PM_{10} in the model, but were increased slightly when adding CO (Figure 6-20; Table 6-28).

Pneumonia

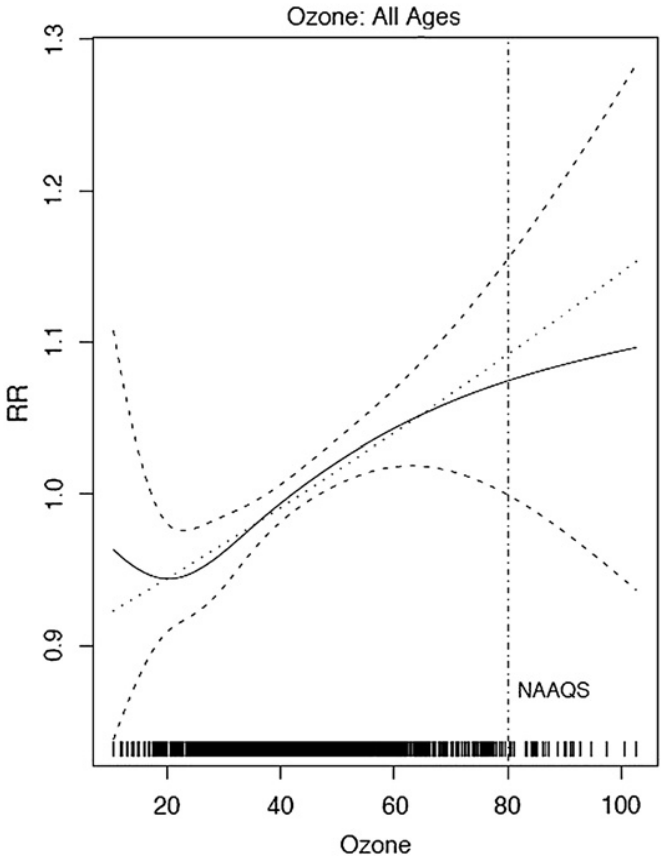
In addition to COPD, Medina-Ramon et al. (2006) examined the association between short-term exposure to ambient O_3 and PM_{10} concentrations and Medicare hospital admissions among individuals ≥ 65 years of age for pneumonia (ICD-9: 480-487). The authors reported an increase in pneumonia hospital admissions in the warm season (2.5% [95% CI: 1.6, 3.5%] for a 30 ppb increase in 8-h max O_3 concentrations; lag 0-1). Similar to the results observed for COPD hospital admissions, pneumonia hospital admissions associations were stronger at lag 1 (2.6% [95% CI: 1.8, 3.4%]) compared to lag 0 (0.06% [95% CI: -0.72, 0.78%]), and no evidence of an association was observed in the cool season or year round. In two-pollutant models, the association between O_3 exposure and pneumonia hospital admissions was robust to the inclusion of PM_{10} (results not presented quantitatively). The authors also examined potential effect modification of the warm season estimates for O_3-related pneumonia hospital admissions, as was done for COPD, by several city-level characteristics. Stronger associations were reported in cities with a lower percentage of central air conditioning use. Across the cities examined, the percentage of households having central air conditioning ranged from 6 to 93%. The authors found no evidence of effect modification of the O_3-pneumonia hospital admission relationship when examining the other city-level characteristics.

Results from a single-city study conducted in Boston did not support the results presented by Medina-Ramon et al. (2006). Zanobetti and Schwartz (2006) examined the association of O_3 and pneumonia Medicare hospital admissions for the period 1995-1999. Ozone was weakly positively correlated with $PM_{2.5}$ (r=0.20) and weakly inversely correlated with black carbon, NO_2, and CO (-0.25, -0.14, and -0.30, respectively). In an all-year analysis, the investigators reported a 3.8% (95% CI: -7.9, -0.1%) decrease in pneumonia admissions for a 20 ppb increase in 24-h average O_3 concentrations at lag 0 and a 6.0% (95% CI: -11.1, -1.4%) decrease for the average of lags 0 and 1. It should be noted that the mean daily counts of pneumonia admissions was low for this study, ~14 admissions per day compared to ~271 admissions per day for Medina-Ramon et al. (2006). However, in analyses with other pollutants Zanobetti and Schwartz (2006) did observe positive associations with pneumonia hospital admissions, indicating that the low number of daily

hospital admission counts probably did not influence the O_3-pneumonia hospital admissions association in this study. .

Asthma

There are relatively fewer studies that examined the association between short-term exposure to O_3 and asthma hospital admissions, presumably due to the limited power given the relative rarity of asthma hospital admissions compared to ED or physician visits. A study from New York City examined the association of 8-h max O_3 concentrations with severe acute asthma admissions (i.e., those admitted to the Intensive Care Unit [ICU]) during the warm season in the years 1999 through 2006 (Silverman and Ito, 2010). In this study, O_3 was moderately correlated with PM_{10} (r=0.59). When stratifying by age, the investigators reported positive associations with ICU asthma admissions for the 6- to 18-year age group (26.8% [95% CI: 1.4, 58.2%] for a 30 ppb increase in maximum 8-h avg O_3 concentrations at lag 0-1), but little evidence of associations for the other age groups examined (<6 years, 19-49, 50+, and all ages). However, positive associations were observed for each age-stratified group and all ages for non-ICU asthma admissions, but again the strongest association was reported for the 6- to 18-years age group (28.2% [95% CI: 15.3, 41.5%]; lag 0-1). In two-pollutant models, O_3 effect estimates for both non-ICU and ICU hospital admissions remained robust to adjustment for $PM_{2.5}$. In an additional analysis, using a smooth function, the authors examined whether the shape of the C-R curve for O_3 and asthma hospital admissions (i.e., both general and ICU for all ages) is linear. To account for the potential confounding effects of $PM_{2.5}$, Silverman and Ito (2010) also included a smooth function of $PM_{2.5}$ lag 0-1. When comparing the curve to a linear fit line the authors found that the linear fit is a reasonable approximation of the concentration-response relationship between O_3 and asthma hospital admissions around and below the level of the current NAAQS (Figure 6-15).



Source: Used with permission from American Academy of Allergy, Asthma & Immunology (Silverman and Ito, 2010).

The average of 0 day and 1 day lagged 8-h ozone was used in a two-pollutant model with $PM_{2.5}$ lag 0-1, adjusting for temporal trends, day of the week, and immediate and delayed weather effects. The solid lines are smoothed fit data, with long broken lines indicating 95% confidence bands. The density of lines at the bottom of the figure indicates sample size.

Figure 6-15 Estimated relative risks (RRs) of ozone-related asthma hospital admissions allowing for possible nonlinear relationships using natural splines.Averting Behavior

The studies discussed above have found consistent positive associations between short-term O_3 exposure and respiratory-related hospital admissions, however, the strength of these associations may be underestimated due to the studies not accounting for averting behavior. As discussed in Section 4.6.4, recent studies by Neidell (2009) and Neidell and Kinney (2010) conducted in Souther California demonstrate that controlling for avoidance behavior increases O_3 effect estimates for respiratory hospital admissions, specifically for children and older adults. These studies show that on days where no public alert was issued warning of high O_3 concentrations there was an increase in asthma hospital admissions. Although only a few epidemiologic studies have examined averting behavior and these studies are limited to asthma hospital admissions, they do provide preliminary evidence indicating that epidemiologic studies may underestimate

associations between O_3 exposure and health effects by not accounting for behaviorial modification when public health alerts are issued.

6.2.7.3 Emergency Department Visit Studies

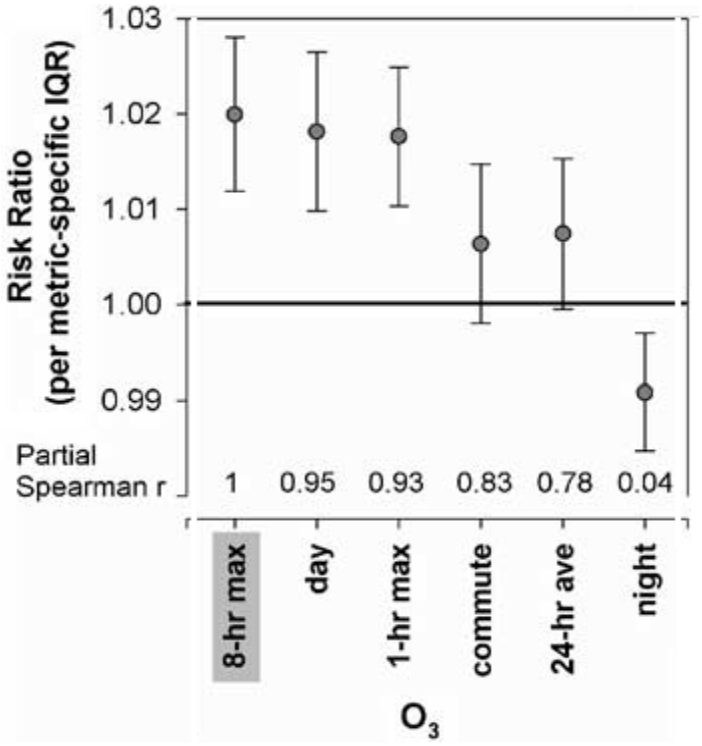
Overall, relatively fewer studies have examined the association between short-term O_3 exposure and respiratory-related ED visits, compared to hospital admissions. In the 2006 O_3 AQCD, positive, but inconsistent, associations were observed between O_3 and respiratory-related ED visits with effects generally occurring during the warm season. Since the completion of the previous AQCD, larger studies have been conducted, in terms of sample size, study duration, and in some cases multiple cities, to examine the association between O_3 and ED visits for all respiratory diseases, COPD, and asthma.

Respiratory Disease

A large single-city study conducted in Atlanta, by Tolbert et al. (2007), and subsequently reanalyzed by Darrow et al. (2011b), provides evidence for an association between short-term exposures to ambient O_3 concentrations and respiratory ED visits. Tolbert et al. (2007) examined the association between air pollution, both gaseous pollutants and PM and its components, and respiratory disease ED visits in all ages from 1993 to 2004. The correlations between O_3 and the other pollutants examined ranged from 0.2 for CO and SO_2 to 0.5-0.6 for the PM measures. Using an a priori average of lags 0-2 for each air pollutant examined, the authors reported a 3.9% (95% CI: 2.7, 5.2%) increase in respiratory ED visits for a 30 ppb increase in 8-h max O_3 concentrations during the warm season [defined as March-October in Darrow et al. (2011b)]. In copollutant models, the O_3 associations with respiratory ED visits remained robust with CO, NO_2, and PM_{10} (results not presented quantitatively).

Darrow et al. (2011b) examined the same data as Tolbert et al. (2007), but explored whether differences exist in the association between O_3 exposure and respiratory-related ED visits depending on the exposure metric used (i.e., 8-h max, 1-h max, 24-h average, commuting period [7:00 a.m. to 10:00 a.m.; 4:00 p.m. to 7:00 p.m.], day-time [8:00 a.m. to 7:00 p.m.] and night-time [12:00 a.m. to 6:00 a.m.]). To examine the association between the various O_3 exposure metrics and respiratory ED visits, the authors used a time-stratified case-crossover approach, selecting control days as those days within the same calendar month and maximum temperature as the case day. Darrow et al. (2011b) found at lag 1, the results were somewhat variable across exposure metrics. The strongest associations with respiratory ED visits were found when using the 8-h max, 1-h max, and day-time exposure metrics with weaker associations using the 24-h avg and commuting

period exposure metrics; a negative association was observed when using the night-time exposure metric (Figure 6-16).



Source: Used with permission from Nature Publishing Group (Darrow et al., 2011b).

Figure 6-16 Risk ratio for respiratory ED visits and different ozone exposure metrics in Atlanta from 1993-2004.

In an additional study conducted in 6 Italian cities, Orazzo et al. (2009) examined respiratory ED visits for ages 0-2 years in 6 Italian cities from 1996 to 2000. However, instead of identifying respiratory ED visits using the traditional approach of selecting ICD codes as was done by Tolbert et al. (2007) and Darrow et al. (2011b), Orazzo et al. (2009) used data on wheeze extracted from medical records as an indicator of lower respiratory disease. This study examined daily counts of wheeze in relation to air pollution using a time-stratified case-crossover approach in which control days were matched on day of week in the same month and year as the case day. The authors found no evidence of an association between 8-h max O_3 concentrations and respiratory ED visits in children aged 0-2 years in models that examined both single-day lags and moving averages of lags from 0-6 days in year-round and seasonal analyses (i.e., warm

and cool seasons). In all-year analyses, the percent increase in total wheeze ranged from -1.4% to -3.3% for a 0-1 to 0-6 day lag, respectively.

COPD

Stieb et al. (2009) also examined the association between short-term O_3 exposure and COPD ED visits in 7 Canadian cities. Across cities, in an all-year analysis, O_3 was found to be positively associated with COPD ED visits (4.0% [95% CI: -0.54, 8.6%] at lag 2 for a 20 ppb increase in 24-h avg O_3 concentrations). In seasonal analyses, larger effects were observed between O_3 and COPD ED visits during the warm season (i.e., April-September) 6.8% [95% CI: 0.11, 13.9%] (lag day not specified); with no associations observed in the winter season. Stieb et al. (2009) also examined associations between respiratory-related ED visits, including COPD, and air pollution at sub-daily time scales (i.e., 3-h avg of ED visits versus 3-h avg pollutant concentrations) and found no evidence of consistent associations between any pollutant and any respiratory outcome.

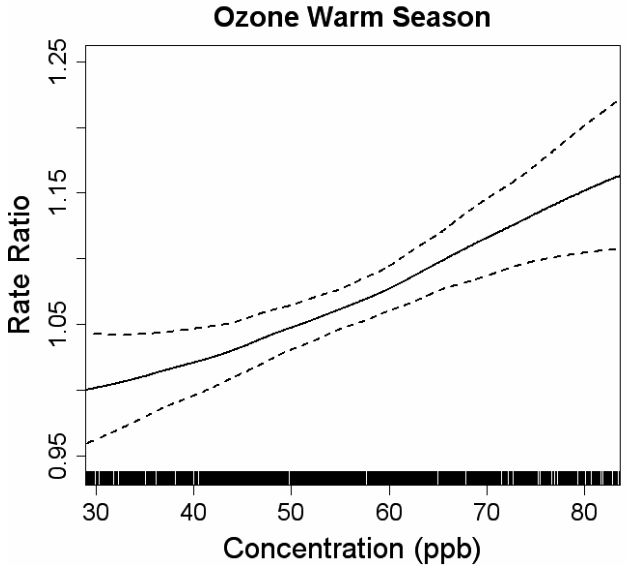
In a single-city study, Arbex et al. (2009) examined the association between COPD and several ambient air pollutants, including O_3, in Sao Paulo, Brazil for the years 2001-2003 for individuals over the age of 40. Associations between O_3 exposure and COPD ED visits were examined in both single-day lag (0-6 days) and polynomial distributed lag models (0-6 days). In all-year analyses, O_3 was not found to be associated with an increase in COPD ED visits (results not presented quantitatively). The authors also conducted stratified analyses to examine the potential modification of the air pollutant-COPD ED visits relationship by age (e.g., 40-64, >64) and sex. In these analyses O_3 was found to have an increase in COPD ED visits for women, but not for men or either of the age groups examined.

Asthma

In a study of 7 Canadian cities, Stieb et al. (2009) also examined the association between exposure to air pollution (i.e., CO, NO_2, O_3, SO_2, PM_{10}, $PM_{2.5}$, and O_3) and asthma ED visits. Associations between short-term O_3 exposure and asthma ED visits were examined at the city level and then pooled using either fixed or random effects models depending on whether heterogeneity among effect estimates was found to be statistically significant. Across cities, in an all-year analysis, the authors found that short-term O_3 exposure was associated with a positive increase (3.5% [95% CI: 0.33, 6.8%] at lag 2 for a 20 ppb increase in 24-h avg O_3 concentrations) in asthma ED visits. The authors did not present the results from seasonal analyses for asthma, but state that no associations were observed between any pollutant and respiratory ED visits in the winter season. As stated previously, in analyses of 3-h avg O_3 concentrations, the authors observed no evidence of consistent associations between any pollutant and any respiratory outcome, including

asthma. A single-city study conducted in Alberta, Canada (Villeneuve et al., 2007) from 1992-2002 among individuals two years of age and older provides additional support for the findings from Stieb et al. (2009), but also attempts to identify those lifestages (i.e., 2-4, 5-14, 15-44, 45-64, 65-74, or 75+) most susceptible to O_3-induced asthma ED visits. In a time-referent case-crossover analysis, Villeneuve et al. found an increase in asthma ED visits in an all-year analysis across all ages (12.0% [95% CI: 6.8, 17.2] for a 30 ppb increase in max 8-h avg O_3 concentrations at lag 0-2) with associations being stronger during the warmer months (19.0% [95% CI: 11.9, 28.1]). When stratifying by age, the strongest associations were observed in the warm season for individuals 5-14 (28.1% [95% CI: 11.9, 45.1]; lag 0-2) and 15-44 (19.0% [95% CI: 8.5, 31.8]; lag 0-2). These associations were not found to be confounded by the inclusion of aeroallergens in age-specific models.

Several additional single-city studies have also provided evidence of an association between asthma ED visits and ambient O_3 concentrations. Ito et al. (2007b) examined the association between short-term exposure to air pollution and asthma ED visits for all ages in New York City from 1999 to 2002. Ito et al. (2007b) used three different weather models with varying extent of smoothing to account for temporal relationships and multicollinearity among pollutants and meteorological variables (i.e., temperature and dew point) to examine the effect of model selection on the air pollutant-asthma ED visit relationship. When examining O_3, the authors reported a positive association with asthma ED visits, during the warm season across the models (ranging from 8.6 to 16.9%) and an inverse association in the cool season (ranging from -23.4 to -25.1%), at lag 0-1 for a 30 ppb increase in 8-h max O_3 concentrations. Using a simplified version of the weather model used in NMMAPS analyses (i.e., terms for same-day temperature and 1-3 day average temperature), Ito et al. (2007b) found that O_3 effects were not substantially changed in copollutant models with $PM_{2.5}$, NO_2, SO_2, and CO during the warm season (Figure 6-19; Table 6-27).



Source: Used with permission from American Thoracic Society (Strickland et al., 2010).

The reference for the rate ratio is the estimated rate at the 5th percentile of the pollutant concentration. Estimates are presented for the 5th percentile through the 95th percentile of pollutant concentrations due to instability in the dose-response estimates at the distribution tails.

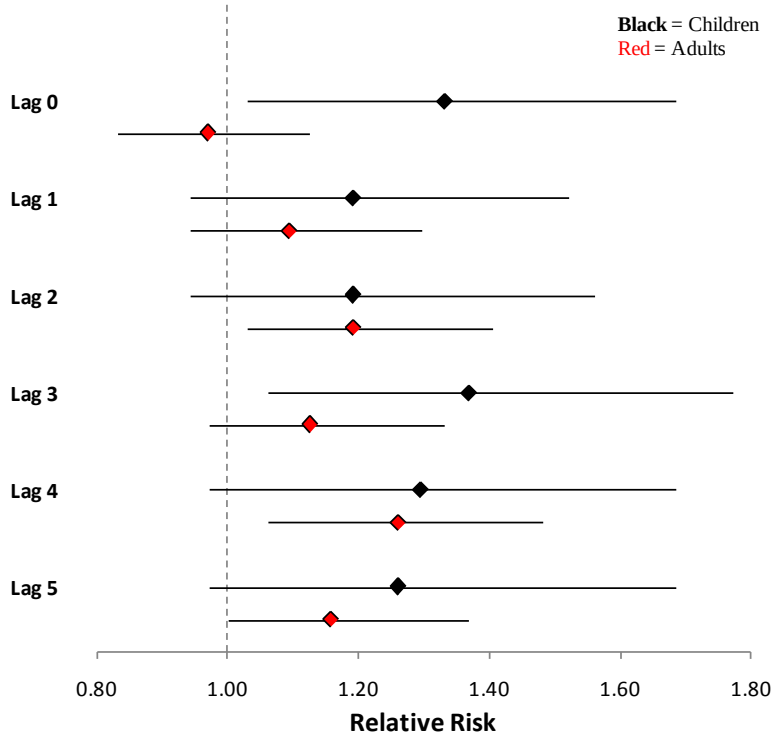
Figure 6-17 Loess dose-response estimates and twice-standard error estimates from generalized additive models for associations between 3-day avg ozone concentrations and ED visits for pediatric asthma.

Strickland et al. (2010) examined the association between O_3 exposure and pediatric asthma ED visits (ages 5-17 years) in Atlanta between 1993 and 2004 using the same air quality data as Darrow et al. (2011b) and Tolbert et al. (2007). However, unlike Darrow et al. (2011b) and Tolbert et al. (2007), which used single centrally located monitors or an average of monitors, respectively, Strickland et al. (2010) used population-weighting to combine daily pollutant concentrations across monitors. In this study, the authors developed a statistical model using hospital-specific time-series data that is essentially equivalent to a time-stratified case-crossover analysis (i.e., using interaction terms between year, month, and day-of-week to mimic the approach of selecting referent days within the same month and year as the case day). The authors observed a 6.4% (95% CI: 3.2, 9.6%) increase in ED visits for a 30 ppb increase in 8-h max O_3 concentrations at lag 0-2 in an all-year analysis. In seasonal analyses, stronger associations were observed during the warm season (i.e., May-October) (8.4% [95% CI: 4.4, 12.7%]; lag 0-2) than the cold season (4.5% [95% CI: -0.82, 10.0%]; lag 0-2). Strickland et al. (2011) confirmed these findings in an additional analysis using the same dataset, and found that the metric used to assign exposure (i.e., centrally located monitor, unweighted average

across monitors, and population-weighted average across monitors) did not influence pediatric asthma ED visit risk estimates for spatially homogeneous pollutants such as O_3.

In copollutant analyses, Strickland et al. (2010) found that O_3 effect estimates were not substantially changed when controlling for other pollutants (CO, NO_2, $PM_{2.5}$ elemental carbon, $PM_{2.5}$ sulfate) (results not presented quantitatively). The authors also examined the C-R relationship between O_3 exposure and pediatric asthma ED visits and found that both quintile and loess dose-response analyses (Figure 6-17) suggest that there are elevated associations with O_3 at concentrations as low as 30 ppb. These dose-response analyses do not provide evidence of a threshold level.

In a single-city study conducted on the West coast, Mar and Koenig (2009) examined the association between O_3 exposure and asthma ED visits (ICD-9 codes_ 493-493.9) for children (< 18) and adults (≥ 18) in Seattle, WA from 1998 to 2002. Of the total number of visits over the study duration, 64% of visits in the age group < 18 comprised boys, and 70% of visits in the ≥ 18 age group comprised females. Mar and Koenig (2009) conducted a time-series analysis using both 1-h max and max 8-h avg O_3 concentrations. Although a similar pattern of associations was observed using both metrics, only those results using the max 8-h avg O_3 metric are discussed here since they are more applicable to the current O_3 NAAQS. Mar and Koenig (2009) presented results for single day lags of 0 to 5 days, but found consistent positive associations across individual lag days which supports the findings from the studies discussed above that examined multi-day exposures. For children, consistent positive associations were observed across all lags, ranging from a 19.1-36.8% increase in asthma ED visits for a 30 ppb increase in 8-h max O_3 concentrations with the strongest associations observed at lag 0 (33.1% [95% CI: 3.0, 68.5]) and lag 3 (36.8% [95% CI: 6.1, 77.2]) (Figure x). O_3 was also found to be positively associated with asthma ED visits for adults at all lags, ranging from 9.3-26.0%, except at lag 0 (Figure 6-18). The slightly different lag times for children and adults suggest that children may be more immediately responsive to O_3 exposures than adults (Mar and Koenig, 2009).



Adapted from Mar and Koenig (2009).

Figure 6-18 Relative risk of asthma ED visits children and adults for a 30 ppb increase in max 8-h avg O3 concentrations in Seattle, WA, 1998-2002.

Respiratory Infection

Although an increasing number of studies have examined the association between O_3 exposure and cause-specific respiratory ED visits this trend has not included an extensive examination of the association between O_3 exposure and respiratory infection ED visits. Stieb et al. (2009) also examined the association between short-term O_3 exposure and respiratory infection ED visits in 7 Canadian cities. In an all-year analysis, there was no evidence of an association between O_3 exposure and respiratory infection ED visits at all lags examined (i.e., 0, 1, and 2). Across cities, respiratory infections comprised the single largest diagnostic category, approximately 32%, of all the ED visits examined, which also included myocardial infarction, heart failure, dysrhythmia, asthma, and COPD.

6.2.7.4 Outpatient and Physician Visit Studies

Several studies have examined the association between ambient O_3 concentrations and physician or outpatient (non-hospital, non-ED) visits for acute conditions in various geographic locations. Burra et al. (2009) examined asthma physician visits among patients aged 1-17 and 18-64 years in Toronto, Canada from 1992 to 2001. The authors found little or no evidence of an association between asthma physician visits and O_3; however, seasonal analyses were not conducted. It should be noted that in this study, most of the relative risks for O_3 were less than one and statistically significant, perhaps indicating an inverse correlation with another pollutant or an artifact of the strong seasonality of asthma visits. Villeneuve et al. (2006b) also focused on physician visits to examine the effect of short-term O_3 exposure on allergic rhinitis among individuals aged 65 or older in Toronto from 1995 to 2000. The authors did not observe any evidence of an association between allergic rhinitis physician visits and ambient O_3 concentrations in single-day lag models in an all-year analysis (results not presented quantitatively).

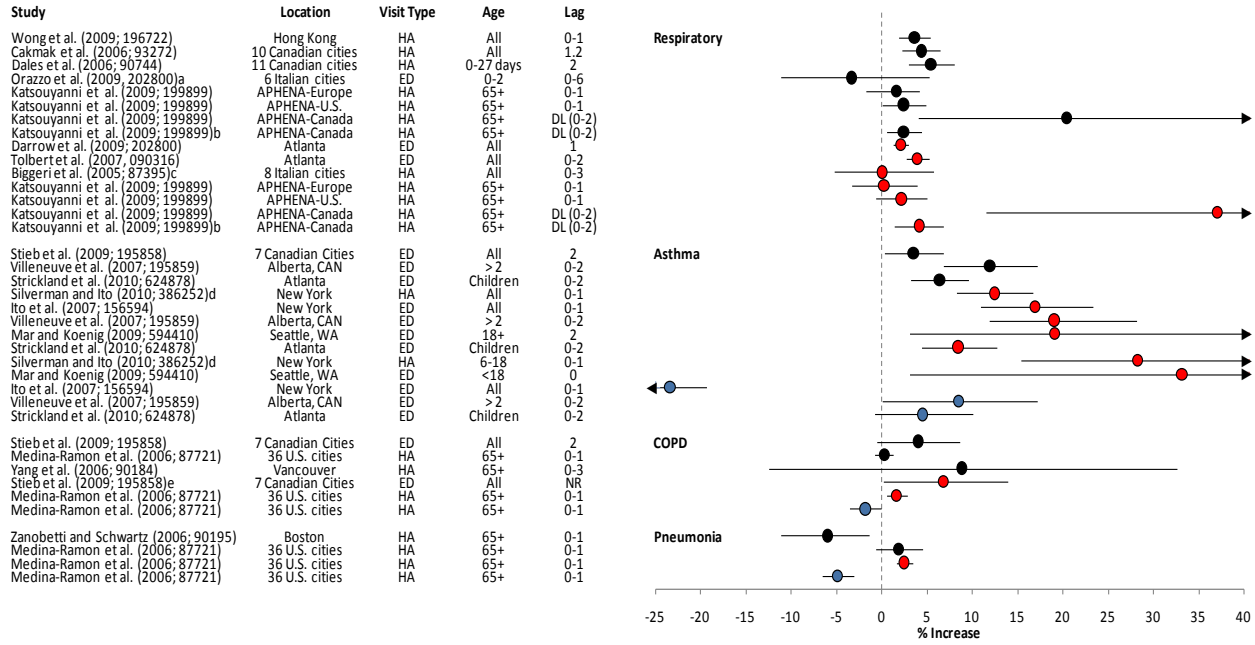
In a study conducted in Atlanta, Sinclair et al. (2010) examined the association of acute asthma and respiratory infection (e.g., upper respiratory infections and lower respiratory infections) outpatient visits from a managed care organization with ambient O_3 concentrations as well as multiple PM size fractions and species from August 1998 through December 2002. The authors separated the analysis into two time periods (the first 25 months of the study period and the second 28 months of the study period), in order to compare the air pollutant concentrations and relationships between air pollutants and acute respiratory visits for the 25-month time-period examined in Sinclair et al. (2004) to an additional 28-month time-period of available data from the Atlanta Aerosol Research Inhalation Epidemiology Study (ARIES). The authors found little evidence of an association between O_3 and asthma visits, for both children and adults, or respiratory infection visits in all-year analyses and seasonal analyses. For example, a slightly elevated relative risk (RR) for childhood asthma visits was observed during the 25-month period in the cold season (RR: 1.12 [95% CI: 0.86, 1.41]; lag 0-2 for a 30 ppb increase in 8-h max O_3), but not in the warm season (RR: 0.97 [95% CI: 0.86, 1.10]; lag 0-2). During the 28-month period at lag 0-2, a slightly larger positive effect was observed during the warm season (RR: 1.06 [95% CI: 0.97, 1.17]), compared to the cold season (RR: 1.03 [95% CI: 0.87, 1.21]). Overall, these results contradict those from Strickland et al. (2010) discussed above. Although the mean number of asthma visits and O_3 concentrations in Sinclair et al. (2010) and Strickland et al. (2010) are similar the difference in results between the two studies could be attributed to the severity of O_3-induced asthma exacerbations (i.e., more severe symptoms requiring a visit to a hospital) and behavior, such as delaying a visit to the doctor for less severe symptoms.

6.2.7.5 Summary

The results of the recent studies evaluated largely support the conclusion of the 2006 O_3 AQCD. While fewer studies were published overall since the previous review, several multicity studies (e.g., Cakmak et al., 2006b; Dales et al., 2006) and a multi-continent study (Katsouyanni et al., 2009) provide supporting evidence for an association between short-term O_3 exposure and an increase in respiratory-related hospital admissions and ED visits. Collectively, in the studies evaluated, both single-city and multicity, there is continued evidence for increases in both hospital admissions and ED visits when examining all respiratory outcomes combined. Additionally, new studies support an association between short-term O_3 exposure and asthma (Strickland et al., 2010; Stieb et al., 2009) and COPD (Stieb et al., 2009; Medina-Ramon et al., 2006) hospital admissions and ED visits, with more limited evidence for pneumonia hospital admissions and ED visits (Medina-Ramon et al., 2006; Zanobetti and Schwartz, 2006). In seasonal analyses, stronger associations were observed in the warm season or summer months compared to the cold season, particularly for asthma (Strickland et al., 2010; Ito et al., 2007b) and COPD (Medina-Ramon et al., 2006) (Figure 6-19; Table 6-27), which is consistent with the conclusions of the 2006 O_3 AQCD. There is also continued evidence that children are particularly susceptible to O_3-induced respiratory effects (Silverman and Ito, 2010; Strickland et al., 2010; Mar and Koenig, 2009; Villeneuve et al., 2007; Dales et al., 2006). Although the collective evidence indicates a consistent positive association between O_3 exposure and respiratory-related hospital admissions and ED visits, the magnitude of these associations may be underestimated due to behavioral modification in response to forecasted air quality (Neidell and Kinney, 2010; Neidell, 2009) (Section 4.6.4).

Additional studies that focused on respiratory-related outpatient or physician visits found no evidence of an association with short-term O_3 exposure, but this could be attributed to the severity of O_3-induced respiratory effects requiring more immediate treatment or behavioral factors that result in delayed visits to a physician.

The studies that examined the potential confounding effects of copollutants found that O_3 effect estimates remained relatively robust upon the inclusion of PM and gaseous pollutants in two-pollutant models (Figure 6-19; Table 6-27), including (Strickland et al., 2010; Tolbert et al., 2007; Medina-Ramon et al., 2006), which did not present results quantitatively. These findings are consistent with the studies evaluated in the 2006 O_3 AQCD (U.S. EPA, 2006b) (Figure 7-12, p. 7-80) which found O_3 respiratory hospital admissions risk estimates remained robust to the inclusion of PM in copollutant models.



[a] Wheeze used as indicator of lower respiratory disease.

[b] APHENA-Canada results standardized to approximate IQR of 5.1 ppb for 1 h max O_3 concentrations.

[c] Study included 8 cities; but of those 8, only 4 had O_3 data.

[d] non-ICU effect estimates.

[e] The study did not specify the lag day of the summer season estimate.

Effect estimates are for a 20 ppb increase in 24 hours; 30 ppb increase in 8-h max; and 40 increase in 1-h max ozone concentrations. HA=hospital admission; ED=emergency department. Black=All-year analysis; Red=Summer only analysis; Blue=Winter only analysis.

Figure 6-19 Percent increase in respiratory-related hospital admission and ED visits in studies that presented all-year and/or seasonal results.

Table 6-27 Corresponding Effect Estimates for Figure 6-19

Study	ED Visit or Hospital Admission	Location	Age	Lag	Avg Time	% Increase (95% CI)
Respiratory						
All-year						
Wong et al. (2009)	Hospital Admission	Hong Kong	All	0-1	8-h max	3.58 (1.90, 5.29)
Cakmak et al. (2006b)	Hospital Admission	10 Canadian cities	All	1.2	24-h avg	4.38 (2.19, 6.46)
Dales et al. (2006)	Hospital Admission	11 Canadian cities	0-27 days	2	24-h avg	5.41 (2.88, 7.96)
Orazzo et al. (2011b)[a]	ED Visit	6 Italian cities	0-2	0-6	8-h max	-3.34 (-11.2, 5.28)
Katsouyanni et al. (2009)	Hospital Admission	APHENA-Europe	65+	0-1	1-h max	1.58 (-1.71, 4.15)
		APHENA-U.S.	65+	0-1	1-h max	2.38 (0.00, 4.89)
		APHENA-Canada	65+	DL(0-2)	1-h max	20.4 (4.07, 40.2)
		APHENA-Canada	65+	DL(0-2)b	1-h max	2.4 (0.51, 4.40)
Warm						
Darrow et al. (2011b)	ED Visit	Atlanta	All	1	8-h max	2.08 (1.25, 2.91)
Tolbert et al. (2007)	ED Visit	Atlanta	All	0-2	8-h max	3.90 (2.70, 5.20)
Biggeri et al. (2005)[c]	Hospital Admission	8 Italian cities	All	0-3	8-h max	0.06 (-5.24, 5.66)
Katsouyanni et al. (2009)	Hospital Admission	APHENA-Europe	65+	0-1	1-h max	0.24 (-3.32, 3.91)
		APHENA-U.S.	65+	0-1	1-h max	2.14 (-0.63, 4.97)
		APHENA-Canada	65+	DL(0-2)	1-h max	37.1 (11.5, 67.5)
		APHENA-Canada	65+	DL(0-2)[b]	1-h max	4.1 (1.40, 6.80)
Asthma						
All-year						
Stieb et al. (2009)	ED Visit	7 Canadian cities	All	2	24-h avg	3.48 (0.33, 6.76)
Villeneuve et al. (2007)	ED Visit	Alberta, CAN	> 2	0-2	8-h max	11.9 (6.8, 17.2)
Strickland et al. (2010)	ED Visit	Atlanta	Children	0-2	8-h max	6.38 (3.19, 9.57)
Warm						
Silverman and Ito (2010)[d]	Hospital Admission	New York	All	0-1	8-h max	12.5 (8.27, 16.7)
Ito et al. (2007b)	ED Visit	New York	All	0-1	8-h max	16.9 (10.9, 23.4)
Villeneuve et al. (2007)	ED Visit	Alberta, CAN	> 2	0-2	8-h max	19.0 (11.9, 28.1)
Mar and Koenig (2009)	ED Visit	Seattle, WA	18+	2	8-h max	19.1 (3.00, 40.5)
Strickland et al. (2010)	ED Visit	Atlanta	Children	0-2	8-h max	8.43 (4.42, 12.7)
Silverman and Ito (2010)[d]	Hospital Admission	New York	6-18	0-1	8-h max	28.2 (15.3, 41.5)
Mar and Koenig (2009)	ED Visit	Seattle, WA	< 18	0	8-h max	33.1 (3.00, 68.5)
Cold						
Ito et al. (2007b)	ED Visit	New York	All	0-1	8-h max	-23.4 (-27.3, -19.3)
Villeneuve et al. (2007)	ED Visit	Alberta, CAN	> 2	0-2	8-h max	8.50 (0.00, 17.2)
Strickland et al. (2010)	ED Visit	Atlanta	Children	0-2	8-h max	4.52 (-0.82, 10.1)
COPD						
All-year						
Stieb et al. (2009)	ED Visit	7 Canadian cities	All	2	24-h avg	4.03 (-0.54, 8.62)
Medina-Ramon et al. (2006)	Hospital Admission	36 U.S. cities	65+	0-1	8-h max	0.24 (-0.78, 1.21)
Yang et al. (2005b)	Hospital Admission	Vancouver	65+	0-3	24-h avg	8.80 (-12.5, 32.6)
Warm						
Stieb et al. (2009)[e]	ED Visit	7 Canadian cities	All	NR	24-h avg	6.76 (0.11, 13.9)
Medina-Ramon et al. (2006)	Hospital Admission	36 U.S. cities	65+	0-1	8-h max	1.63 (0.48, 2.85)
Cold						
Medina-Ramon et al. (2006)	Hospital Admission	36 U.S. cities	65+	0-1	8-h max	-1.85 (-3.60, -0.06)

Study	ED Visit or Hospital Admission	Location	Age	Lag	Avg Time	% Increase (95% CI)
Pneumonia						
All-year						
Zanobetti and Schwartz (2006)	Hospital Admission	Boston	65+	0-1	24-h avg	-5.96 (-11.1, -1.36)
Medina-Ramon et al. (2006)	Hospital Admission	36 U.S. cities	65+	0-1	8-h max	1.81 (-0.72, 4.52)
Warm						
Medina-Ramon et al. (2006)	Hospital Admission	36 U.S. cities	65+	0-1	8-h max	2.49 (1.57, 3.47)
Cold						
Medina-Ramon et al. (2006)	Hospital Admission	36 U.S. cities	65+	0-1	8-h max	-4.88 (-6.59, -3.14)

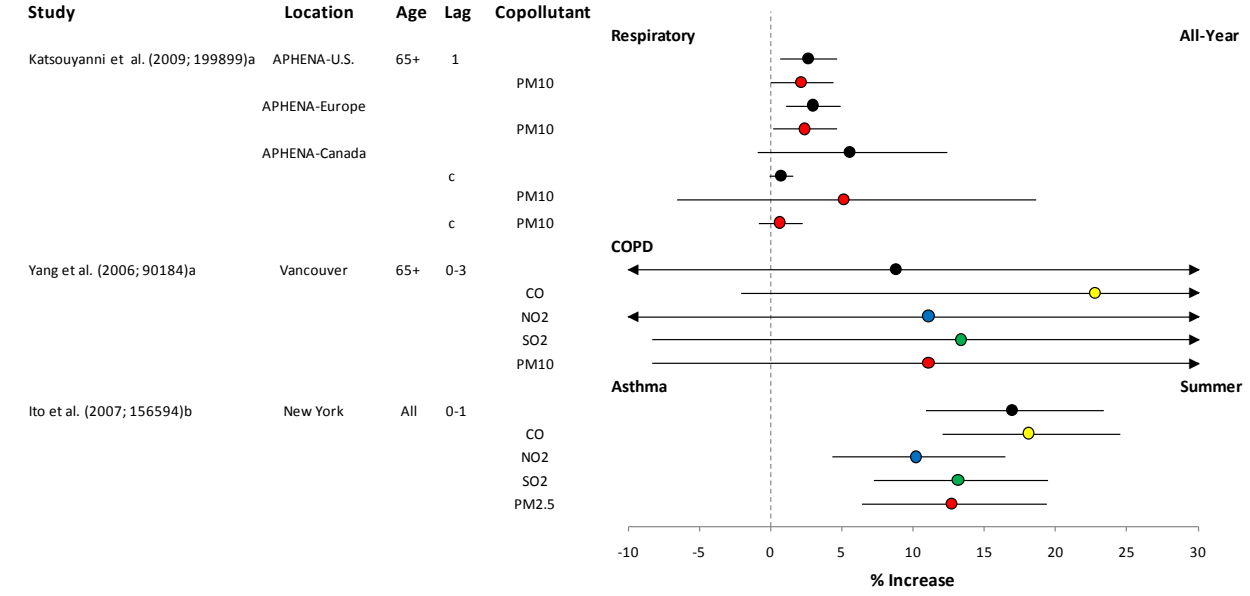
[a]Wheeze used as indicator of lower respiratory disease.

[b]APHENA-Canada results standardized to approximate IQR of 5.1 ppb for 1-h max O_3 concentrations.

[c]Study included 8 cities, but of those 8 only 4 had O_3 data.

[d]Non-ICU effect estimates.

[e]The study did not specify the lag day of the summer season estimate.



Effect estimates are for a 20 ppb increase in 24 hours; 30 ppb increase in 8-h max; and 40 ppb increase in 1-h max ozone concentrations. An "a" represents studies that examined hospital admissions, "b" represents a study that examined ED visits, and "c" represents risk estimates from APHENA -Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in ozone concentrations. Black = results from single-pollutant models; Red = results from copollutant models with PM_{10} or $PM_{2.5}$; Yellow = results from copollutant models with CO; Blue = results from copollutant models with NO_2; Green = results from copollutant models with SO_2.

Figure 6-20 Percent increase in respiratory-related hospital admissions and ED visits for studies that presented single and copollutant model results.

Table 6-28 Corresponding effect estimates for Figure 6-20

Study[a]	Location	Visit Type	Age	Lag	Copollutant	% Increase (95% CI)
All-year						
Respiratory						
Katsouyanni et al. (2009)		APHENA-U.S.	HA	65+	1	2.62 (0.63, 4.64)
					PM_{10}	2.14 (-0.08, 4.40)
		APHENA-Europe				2.94 (1.02, 4.89)
					PM_{10}	2.38 (0.08, 4.64)
		APHENA-Canada				5.54 (-0.94, 12.4)
						0.69 (-0.12, 1.50)b
					PM_{10}	5.13 (-6.62, 18.6)
					PM_{10}	0.64 (-0.87, 2.20)b
		COPD				
Yang et al. (2005b)		Vancouver	HA	65+	0-3	8.80 (-12.5, 32.6)
					CO	22.8 (-2.14, 50.7)
					NO_2	11.1 (-10.4, 37.6)
					SO_2	13.4 (-8.40, 40.2)
					PM_{10}	11.1 (-8.40, 37.6)
Summer						
Asthma						
Ito et al. (2007b)		New York	ED	All	0-1	16.9 (10.9, 23.4)
					CO	18.1 (12.1, 24.5)
					NO_2	10.2 (4.29, 16.4)
					SO_2	13.1 (7.16, 19.5)
					$PM_{2.5}$	12.7 (6.37, 19.3)

[a]Averaging times: Katsouyanni et al. (2009) = 1-h max; Yang et al. (2005b) = 24-h avg; and Ito et al. (2007b) = 8-h max.

[b]Risk estimates standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O_3 concentrations.

Additionally, a preliminary examination of the C-R relationship found no evidence of a threshold between short-term O_3 exposure and pediatric asthma ED visits (Silverman and Ito, 2010; Strickland et al., 2010). Overall, the new body of evidence supports an association between short-term O_3 exposure and respiratory-related hospital admissions and ED visits, with additional evidence for stronger associations during the warm season for specific respiratory outcomes such as asthma and COPD.

6.2.8 Respiratory Mortality

The epidemiologic, controlled human exposure, and toxicological studies discussed within this section (Section 6.2) provides evidence for multiple respiratory effects in response to short-term O_3 exposure. Additionally, the evidence from experimental studies indicates multiple potential pathways of O_3-induced respiratory effects, which support the continuum of respiratory effects that could potentially result in respiratory-related mortality. The 2006 O_3 AQCD found inconsistent evidence for an association between short-term O_3 exposure and respiratory mortality (U.S. EPA, 2006b). Although some studies reported a strong positive association between O_3 exposure and respiratory

mortality, additional studies reported a small association or no association. Recent multicity studies found consistent positive associations between short-term O_3 exposure and respiratory mortality, specifically during the summer months.

The APHENA study, described earlier in Section 6.2.7.2, (Katsouyanni et al., 2009) also examined associations between short-term O_3 exposure and mortality and found consistent positive associations for respiratory mortality in all-year analyses with stronger associations in analyses restricted to the summer season. Additional multicity studies from the U.S. (Zanobetti and Schwartz, 2008b), Europe (Samoli et al., 2009), Italy (Stafoggia et al., 2010), and Asia (Wong et al., 2010) that conducted summer season and/or all-year analyses provide additional support for an association between short-term O_3 exposure and respiratory mortality (Figure 6-37).

Of the studies evaluated, only the APHENA study (Katsouyanni et al., 2009) and the Italian multicity study (Stafoggia et al., 2010) conducted an analysis of the potential for copollutant confounding of the O_3-respiratory mortality relationship. In the APHENA study, in the European dataset, when focusing on the natural spline model with 8 df/year (as discussed in Section 6.2.7.2) and lag 1 results (as discussed in Section 6.6.2.1), respiratory mortality risk estimates were robust to the inclusion of PM_{10} in copollutant models in all-year analyses with O_3 respiratory mortality risk estimates increasing in the Canadian and U.S. datasets. In summer season analyses, respiratory O_3 mortality risk estimates were robust in the U.S. dataset and attenuated in the European dataset. Similarly, in the Italian multicity study (Stafoggia et al., 2010), which was limited to the summer season, respiratory mortality risk estimates were attenuated in copollutant models with PM_{10}. Based on the APHENA and Italian multicity results, O_3 respiratory mortality risk estimates appear to be moderately to substantially sensitive (e.g., increased or attenuated) to inclusion of PM_{10}. However, in the APHENA study, the mostly every-6th-day sampling schedule for PM_{10} in the Canadian and U.S. datasets greatly reduced their sample size and limits the interpretation of these results.

6.2.9 Summary and Causal Determination

The 2006 O_3 AQCD concluded that there was clear, consistent evidence of a causal relationship between short-term O_3 exposure and respiratory effects (U.S. EPA, 2006b). This conclusion was substantiated by evidence from controlled human exposure and toxicological studies indicating a range of respiratory effects in response to short-term O_3 exposure, including pulmonary function decrements, respiratory symptoms, lung inflammation, increased lung permeability, and airway hyperresponsiveness. Toxicological studies provided additional evidence for O_3-induced impairment of host

defenses. Combined, these findings from experimental studies provided support for epidemiologic evidence, in which short-term O_3 exposure was consistently associated with decreases in lung function in populations with increased outdoor exposures, children with asthma, and healthy children; increases in respiratory symptoms and asthma medication use in children with asthma; and increases in respiratory-related hospital admissions and asthma-related ED visits. Short-term O_3 exposure also was consistently associated with all-cause and cardiopulmonary mortality; however, the contribution of respiratory causes to these findings was uncertain.

Building on the large body of evidence presented in the 2006 O_3 AQCD, recent studies support associations between short-term O_3 exposure and respiratory effects. Controlled human exposure studies continue to provide the strongest evidence for lung function decrements in young healthy adults over a range of O_3 concentrations. Studies previously reported mean O_3-induced FEV_1 decrements of 6-8% at 80 ppb O_3 (Adams, 2006a, 2003a; McDonnell et al., 1991; Horstman et al., 1990), and new evidence additionally indicates mean FEV_1 decrements of 6% at 70 ppb O_3 (Schelegle et al., 2009) and 2-3% at 60 ppb O_3 (Kim et al., 2011; Brown et al., 2008; Adams, 2006a) (Section 6.2.1.1). In healthy young adults, O_3-induced decrements in FEV_1 do not appear to depend on gender (Hazucha et al., 2003), body surface area or height (McDonnell et al., 1997), lung size or baseline FVC (Messineo and Adams, 1990). There is limited evidence that blacks may experience greater O_3-induced decrements in FEV_1 than do age-matched whites (Que et al.; Seal et al., 1993). Healthy children experience similar spirometric responses but lesser symptoms from O_3 exposure relative to young adults (McDonnell et al., 1985b). On average, spirometric and symptom responses to O_3 exposure appear to decline with increasing age beyond about 18 years of age (McDonnell et al., 1999; Seal et al., 1996). There is also a tendency for slightly increased spirometric responses in mild asthmatics and allergic rhinitics relative to healthy young adults (Jorres et al., 1996). Spirometric responses in asthmatics appear to be affected by baseline lung function, i.e., responses increase with disease severity (Horstman et al., 1995).

Available information from controlled human exposure studies on recovery from O_3 exposure indicates that an initial phase of recovery in healthy individuals proceeds relatively rapidly, with acute spirometric and symptom responses resolving within about 2 to 4 h (Folinsbee and Hazucha, 1989). Small residual lung function effects are almost completely resolved within 24 h. Effects of O_3 on the small airways persisting a day following exposure, assessed by persistent decrement in FEF_{25-75} and altered ventilation distribution, may be due in part to inflammation (Frank et al., 2001; Foster et al., 1997). In more responsive individuals, this recovery in lung function takes longer (as much as 48 hours) to return to baseline. Some cellular responses may not return to baseline levels in humans for more than 10-20 days following O_3 exposure (Devlin et al., 1997). Airway

hyperresponsiveness and increased epithelial permeability are also observed as late as 24 h postexposure (Que et al.).

With repeated O_3 exposures over several days, spirometric and symptom responses become attenuated in both healthy individuals and asthmatics, but this tolerance is lost after about a week without exposure (Gong et al., 1997a; Folinsbee et al., 1994; Kulle et al., 1982). Airway responsiveness also appears to be somewhat attenuated with repeated O_3 exposures in healthy individuals, but becomes increased in individuals with preexisting allergic airway disease (Gong et al., 1997a; Folinsbee et al., 1994). Some indicators of pulmonary inflammation are attenuated with repeated O_3 exposures. However, other markers such as epithelial integrity and damage do not show attenuation, suggesting continued tissue damage during repeated O_3 exposure (Devlin et al., 1997).

Collectively, epidemiologic evidence supports observations from controlled human exposure studies of O_3-induced decrements in lung function (Section 6.2.1.2). A notable difference among newer studies was the relatively limited investigation of the effect of ambient O_3 exposure on lung function in populations engaged in outdoor recreation, exercise, or work, which contributed to the weight of evidence in previous AQCDs. As in previous AQCDs, recent epidemiologic investigation focused on and most consistently demonstrated associations between increases in ambient O_3 exposure and decreases in lung function in children with asthma. Across the diverse populations examined in epidemiologic studies, ambient O_3 exposure was associated with 1-8% decreases in mean lung function per standardized increment in O_3 concentration[1]. Larger decreases (3-8%) were observed in children with asthma with increased outdoor exposures, CS use, or concurrent URI and older adults with airway hyperresponsiveness, elevated BMI, or GSTP1 Val/Val genotype, indicating the existence of groups within the population with potentially increased sensitivity to O_3 exposure. Further, several epidemiologic studies found that O_3-associated decreases in lung function were associated with concomitant increases in respiratory symptoms. Biological plausibility for O_3-associated decrements in lung function in controlled human exposure, epidemiologic, and animal studies is provided by the well-documented effects of O_3 activating bronchial C-fibers (Section 5.3.2).

Across disciplines, studies have examined factors that may potentially increase an individual's susceptibility to O_3-induced decrements in lung function. In the controlled human exposure studies, there is a large degree of intersubject variability in lung function decrements, symptomatic responses, pulmonary inflammation, airway hyperresponsiveness, and altered epithelial permeability in healthy adults exposed to O_3

[1] Effect estimates were standardized to a 40-ppb increase for 1-h max O_3, a 30-ppb increase for 8-h max O_3, and a 20-ppb increase for 24-h avg O_3.

(Que et al.; Holz et al., 2005; McDonnell, 1996). The magnitude of pulmonary inflammation, airway hyperresponsiveness, and increases in epithelial permeability do not appear to be correlated, nor are these responses to O_3 correlated with changes in lung function, suggesting that different mechanisms may be responsible for these processes (Que et al.; Balmes et al., 1997; Balmes et al., 1996; Aris et al., 1995). However, these responses tend to be reproducible within a given individual over a period of several months indicating differences in the intrinsic responsiveness of individuals (Holz et al., 2005; Hazucha et al., 2003; Holz et al., 1999; McDonnell et al., 1985a). Numerous reasons for differences in the susceptibility of individuals to O_3 exposure have been reported in the literature. Dosimetric and mechanistic considerations are discussed in Section 5.4. Evidence in all three disciplines suggests a role for antioxidant defenses in modulating respiratory responses to O_3. The biological plausibility of these findings is provided by the well-characterized evidence for O_3 exposure leading to the formation of secondary oxidation products, which subsequently activate neural reflexes that mediate lung function decrements (Section 5.3.2). Secondary oxidation products also initiate pulmonary inflammation (Sections 5.3.3). Epidemiologic studies additionally have found that atopy (Khatri et al., 2009), concurrent respiratory infection (Lewis et al., 2005), AHR, and elevated BMI (Alexeeff et al., 2007) may modify respiratory responses to O_3 exposure (Section 6.2.1.2). Retrospective analyses of controlled human exposure studies of data pooled across 15 controlled human exposure studies also show larger O_3-induced FEV_1 decrements in adults with higher BMI (McDonnell et al., 2010; Bennett et al., 2007).

Additional respiratory effects induced by short-term O_3 exposures in controlled human exposure studies of healthy, young adults include increases in respiratory symptoms with O_3 concentrations <80 ppb (Schelegle et al., 2009; Adams, 2006a) (Section 6.2.1.1). Similarly, epidemiologic studies collectively demonstrate that increases in short-term ambient O_3 exposure are associated with increases in respiratory symptoms and asthma medication use among subjects with asthma (Section 6.2.4.1). Among recent epidemiologic studies, the strongest evidence of O_3-associated respiratory symptoms was found in populations with multiple potential susceptibility factors, specifically, individuals with asthma and atopy (Khatri et al., 2009; Escamilla-Nuñez et al., 2008; Feo Brito et al., 2007) and children with asthma with diminished antioxidant enzyme activity (Romieu et al., 2006).

Recent controlled human exposure studies (Section 6.2.3.1) and toxicological studies (Section 6.2.3.3) also continue to demonstrate lung injury and inflammatory responses upon O_3 exposure. Evidence from more than a hundred toxicological studies clearly indicates that O_3 induces damage and inflammation in the lung, and studies continue to

elucidate the mechanistic pathways involved (Section 5.3). Though inflammation may resolve, continued inflammation may alter theJanetrita2010

structure and function of pulmonary tissues. New controlled human studies support previous findings for pulmonary inflammation at 60 ppb O_3, the lowest concentration evaluated . Building on the extensive experimental evidence, epidemiologic studies provide new evidence for ambient O_3-associated increases in pulmonary inflammation in individuals with asthma. These associations were observed primarily for 8-h max or 8-h average O_3 exposures but for both same-day and multiday average exposures. Multiple studies examined and found increases in eNO (Berhane et al., 2011; Khatri et al., 2009; Barraza-Villarreal et al., 2008). The clinical significance of these findings was supported by observations of concomitant O_3-associated increases in respiratory symptoms (Khatri et al., 2009; Barraza-Villarreal et al., 2008). A smaller number of studies examined and found associations with cytokines such as IL-6 or IL-8 in nasal lavage samples (Barraza-Villarreal et al., 2008; Sienra-Monge et al., 2004) inflammatory cells in blood (e.g., eosinophils) (Khatri et al., 2009), decreased levels of antioxidants (Sienra-Monge et al., 2004), and increased levels of indicators of oxidative stress (Romieu et al., 2008) (Section 6.2.3.2).

Modification of innate and adaptive immunity is emerging as a mechanistic pathway underlying the effects of ozone on asthma and allergic airways disease (Section 5.3.6). While the majority of evidence comes from animal studies, results from controlled human exposure studies suggest that these pathways may be relevant to humans and may lead to the induction and exacerbation of asthma (Alexis et al., 2010; Hernandez et al., 2010; Alexis et al., 2009; Bosson et al., 2003). Further, differences between asthmatics and healthy controls in ozone-mediated innate and adaptive immune responses have been noted (Section 5.4.2.2).

The subclinical and overt respiratory effects observed across disciplines collectively provide support for epidemiologic studies that demonstrate consistently positive associations of short-term O_3 exposure with respiratory-related hospital admissions and ED visits (Section 6.2.7). Consistent with evidence presented in the 2006 O_3 AQCD, new multicity studies and a multicontinent study (i.e., APHENA) (Katsouyanni et al., 2009) found risk estimates ranging from an approximate 1.6 to 5.4% increase in all respiratory-related hospital admissions and ED visits in all-year analyses for standardized increases in ambient O_3 concentrations[1]. Positive associations persisted in analyses restricted to the summer season, but the magnitude varied depending on the study location (Figure 6-19). Compared with studies reviewed in the 2006 O_3 AQCD, a larger number of recent studies

[1] Effect estimates were standardized to a 20-ppb increase for 24-h avg O_3, a 30-ppb increase for 8-h max O_3, and a 40-ppb increase for 1-h max O_3.

examined hospital admissions and ED visits for specific respiratory outcomes. Although still limited in number, both single- and multicity studies found consistent, positive associations between short-term O_3 exposures and asthma and COPD hospital admissions and ED visits, with more limited evidence for pneumonia. Consistent with the conclusions of the 2006 O_3 AQCD, in studies that conducted seasonal analyses, risk estimates were elevated in the warm season compared to cold season or all-season analyses, specifically for asthma and COPD. Although recent studies did not include detailed age-stratified results, the increased risk of asthma hospital admissions (Silverman and Ito, 2010; Strickland et al., 2010; Dales et al., 2006) observed for children strengthens the conclusion from the 2006 O_3 AQCD that children are particularly susceptible to O_3-induced respiratory effects (U.S. EPA, 2006b). Although the concentration-response relationship has not been extensively examined, preliminary examinations found no evidence of a threshold between short-term O_3 exposure and asthma hospital admissions and pediatric asthma ED visits (Silverman and Ito, 2010; Strickland et al., 2010).

New evidence extends the potential range of well-established O_3-associated respiratory effects by demonstrating associations between short-term ambient O_3 exposure and respiratory-related mortality. In all-year analyses, a multicontinent (APHENA) and multicity (PAPA) study found consistent, positive associations with respiratory mortality for all ages but less consistent evidence in analyses restricted to ages 75+. Further, multicity studies in the U.S. and Europe that conducted seasonal analyses found stronger associations during the summer season (Section 6.2.8).

Several studies of respiratory morbidity and mortality evaluated the potential confounding effects of copollutants, in particular, PM_{10}, $PM_{2.5}$, or NO_2. In most cases, effect estimates remained robust to the inclusion of copollutants; however, in several studies, changes were observed in the magnitude of the O_3 association. In studies of lung function and respiratory symptoms, larger effects frequently were estimated for O_3 when copollutants were added to models. Ozone effect estimates for respiratory-related hospital admissions and ED visits remained relatively robust upon the inclusion of PM and gaseous pollutants in two-pollutant models (Strickland et al., 2010; Tolbert et al., 2007; Medina-Ramon et al., 2006). Although copollutant confounding was not extensively examined in mortality studies, the O_3-respiratory mortality relationship was moderately to substantially sensitive (e.g., increased or attenuated) to the inclusion of PM_{10} in copollutant models (Stafoggia et al., 2010; Katsouyanni et al., 2009). However, interpretation of these results requires caution due to the limited PM datasets used in these studies. Together, these findings across respiratory endpoints provide support for the independent effects of short-term ambient O_3 exposures.

In summary, new studies evaluated since the completion of the 2006 O_3 AQCD support and expand upon the strong body of evidence that indicated a causal relationship between short-term O_3 exposure and respiratory health effects. New controlled human exposure studies continue to demonstrate O_3-induced decreases in FEV_1 and pulmonary inflammation at concentrations as low as 60 ppb. New epidemiologic studies provide evidence for associations of ambient O_3 exposure with biological markers of pulmonary inflammation and oxidative stress. Toxicological studies have continued to support the biological plausibility for the O_3-induced respiratory effects observed in the controlled human exposure and epidemiologic studies. Additionally, recent epidemiologic studies further confirm that respiratory morbidity and mortality associations are stronger during the warm/summer months and remain relatively robust after adjustment for copollutants. However, despite the consistency of association between short-term O_3 exposure and respiratory effects, new evidence suggests that the magnitude of association may be underestimated due to behavioral modification in response to forecasted air quality (Section 4.6.4). Collectively, the new evidence integrated across toxicological, controlled human exposure, and epidemiologic studies, in conjunction with that reviewed in previous AQCDs, is sufficient to conclude that **there is a causal relationship between short-term O_3 exposure and respiratory health effects.**

6.3 Cardiovascular Effects

6.3.1 Controlled Human Exposure

O_3 reacts rapidly on contact with respiratory system tissue and is not absorbed or transported to extrapulmonary sites to any significant degree as such. Controlled human exposure studies discussed in the previous AQCDs failed to demonstrate any consistent extrapulmonary effects. Some controlled human exposure studies have attempted to identify specific markers of exposure to O_3 in blood. Foster et al. (1996) found a reduction in the serum levels of the free radical scavenger α-tocopherol after O_3 exposure. Liu et al. (1999; 1997) used a salicylate metabolite, 2,3, dehydroxybenzoic acid (DHBA), to indicate increased levels of hydroxyl radical which hydroxylates salicylate to DHBA. Increased DHBA levels after exposure to 120 and 400 ppb suggest that O_3 increases production of hydroxyl radical. The levels of DHBA were correlated with changes in spirometry.

Gong et al. (1998) observed a small, statistically significant O_3-induced increase in the alveolar-to-arterial PO_2 gradient in both healthy (n = 6) and hypertensive (n = 10) adult males (aged 41-78 years) exposed for 3 hours with exercise to 300 ppb O_3. The

mechanism for the decrease in arterial oxygen tension in the Gong et al. (1998) study could be due to an O_3-induced ventilation-perfusion mismatch. Gong et al. (1998) suggested that by impairing alveolar-arterial oxygen transfer, the O_3 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. In studies evaluating the exercise performance of healthy adults, no significant effect of O_3 on arterial O_2 saturation has been observed (Schelegle and Adams, 1986).

More recently, Fakhri et al. (2009) evaluated changes in HRV among adult volunteers (n=50; 27 ± 7 years) during 2-h exposures to $PM_{2.5}$ CAPs (127±62 μg/m^3) and O_3 (114±7 ppb), alone and in combination. High frequency HRV was increased following CAPs-only (p=0.046) and O_3-only (p=0.051) exposures, but not in combination. The standard deviation of NN intervals and the square root of the mean squared differences of successive NN intervals also showed marginally significant ($0.05<p<0.10$) effect due to O_3 but not CAPS. Diastolic blood pressure increased by 2 mmHg following the combined O_3 + CAPs exposure, but was not altered by either O_3 or CAPs alone. Ten of the subjects in this study were characterized as "mildly" asthmatic, however, asthmatic status was not found to modify these effects. For a subset of the subjects without asthma in the Fakhri et al. (2009) study, Urch et al. (2005) previously reported a 6 mmHg increase in diastolic blood pressure following a 2-h resting exposure to O_3 (120 ppb) + $PM_{2.5}$ CAPs (150 μg/m^3) in healthy adults (n=23; 32 ± 107 years), which was statistically different from the 1 mmHg increase seen following FA exposure.

6.3.2 Epidemiology

The 2006 O_3 AQCD concluded that the "generally limited body of evidence is highly suggestive that O_3 directly and/or indirectly contributes to cardiovascular-related morbidity," including physiologic effects (e.g., release of platelet activating factor [PAF]), HRV, arrhythmias, and myocardial infarctions, although the available body of evidence reviewed during the 2006 O_3 AQCD does not "fully substantiate links between ambient O_3 exposure and adverse cardiovascular outcomes" (U.S. EPA, 2006b). Since the completion of the 2006 O_3 AQCD an increasing number of studies have examined the relationship between short-term O_3 exposure and cardiovascular morbidity and mortality. These new studies, as well as evidence from the previous AQCDs, are presented within this section.

6.3.2.1 Arrhythmia

In the 2006 O_3 AQCD, conflicting results were observed when examining the effect of O_3 on arrhythmias (Dockery et al., 2005; Rich et al., 2005). A study by Dockery et al. (2005) reported no association between O_3 levels and ventricular arrhythmias among patients with implantable cardioverter defibrillators (ICD) living in Boston, MA, although when O_3 was categorized into quintiles, there was weak evidence of an association with increasing O_3 concentration (median O_3 concentration: 22.9 ppb). Rich et al. (2005) performed a re-analysis of this cohort using a case-crossover design and detected a positive association between O_3 exposure and ventricular arrhythmias. Recent studies were conducted in various locations and each used a different cardiac episode to define an arrhythmic event and a different time period of exposure, which may help explain observed differences across studies. Ozone levels for each new study are reported in Table 6-29.

Table 6-29 Characterization of ozone concentrations (in ppb) from studies of arrhythmias

`Reference	Location	Averaging Time	Mean Concentration (Standard Deviation)	Upper Range of Concentration
Anderson et al. (2010)	London, England	8-h max	8.08	75th: 11.5
Metzger et al. (2007)	Atlanta, GA	8-h max Summer only	53.9 (23)	Max: 148
Rich et al. (2006a)	St. Louis, MO	24-h	21*	75th: 31
Rich et al. (2006b)	Boston, MA	1-h	22.2*	75th: 33 Max: 119.5
		24-h	22.6*	75th: 30.9 Max: 77.5
Sarnat et al. (2006a)	Steubenville, OH	24-h Summer and Fall only	21.8 (12.6)	75th: 28.5 Max: 74.8
		5 days	22.2 (9.1)	75th: 29.1 Max: 44

*Median presented (information on mean not given).

Multiple studies examined O_3-related effects on individuals with ICDs. One study of 518 ICD patients who had at least 1 tachyarrythmia within a 10-year period (totaling 6287 tachyarrhythmic event-days; 1993-2002) was conducted in Atlanta, Georgia (Metzger et al., 2007). Tachyarrhythmic events were defined as any ventricular tachyarrhythmic event, any ventricular tachyarrhythmic event that resulted in electrical therapy, and any ventricular tachyarrhythmic event that resulted in defibrillation. In the primary analysis, no evidence of an association was observed for a 30 ppb increase in 8-h max O_3 concentrations and tachyarrhythmic events (OR: 1.00 [95% CI: 0.92, 1.08]; lag 0). Season-specific as well as several sensitivity analyses (including the use of an

unconstrained distributed lag model [lags 0-6]) were conducted resulting in similar null associations. A strength of this study is that it incorporated a large sample size over a long time period.

In a case-crossover analysis, a population of ICD patients in Boston, previously examined by (Rich et al., 2005) was used to assess the association between air pollution and paroxysmal atrial fibrillation (PAF) episodes (Rich et al., 2006b). In addition to ventricular arrhythmias, ICD devices may also detect supraventricular arrhythmias, of which atrial fibrillation is the most common. Although atrial fibrillation is generally not considered lethal, it has been associated with increased premature mortality as well as hospitalization and stroke. Ninety-one electrophysiologist-confirmed episodes of PAF were ascertained among 29 patients. An association (OR: 3.86 [95% CI: 1.44, 10.28] per 40 ppb increase in 1-h max O_3 concentrations) was observed between increases in O_3 during the concurrent hour and PAF episodes (lag 0-h). The estimated OR for the 24-h moving average concentration was elevated (OR: 1.81 [95% CI: 0.86, 3.83] per 20 ppb), but weaker than the estimate for the shorter exposure window. The association between PAF and O_3 in the concurrent hour during the cold months was comparable to that during the warm months. In addition, no evidence of a deviation from linearity between O_3 concentration and the log odds of PAF was observed. Authors report that the difference between O_3 exposure and observed effect between this study (PAF and 1-h O_3) and their previous study (ventricular arrhythmias and 24-h moving average O_3) (Rich et al., 2005) suggest a more rapid response to air pollution for PAF (Rich et al., 2006b).

In an additional study, Rich et al. (2006a) employed a case-crossover design to examine the association between air pollution and 139 confirmed ventricular arrhythmias among 56 ICD patients in St Louis, Missouri. The authors observed a positive association with O_3 (OR: 1.17 [95% CI: 0.58, 2.38] per 20 ppb increase in 24-h moving avg O_3 concentrations [lags 0-23 hours]). Although the authors concluded these results were similar to their results from Boston (Rich et al., 2005), they postulated that the pollutants responsible for the increased risk in ventricular arrhythmias are different (O_3 and $PM_{2.5}$ in Boston and sulfur dioxide in St Louis).

Anderson et al. (2010) used a case-crossover framework to assess air pollution and activation of ICDs among patients from all 9 ICD clinics in the London National Health Service hospitals. “Activation” was defined as tachycardias for which the defibrillator delivered treatment. Investigators modeled associations using unconstrained distributed lags from 0 to 5 days. The sample consisted of 705 patients with 5,462 activation days (O_3 information was for 543 patients and 4,092 activation days). Estimates for O_3 were consistently positive, although weak (OR: 1.09 [95% CI: 0.76, 1.55] per 30 ppb for 0-

1 day lag; OR: 1.04 [95% CI: 0.60, 1.81] per 30 ppb for 0-5 day lag) (Anderson et al., 2010).

In contrast to arrhythmia studies conducted among ICD patients, Sarnat et al. (2006a) recruited non-smoking adults (age range: 54-90 years) to participate in a study of air pollution and arrhythmias conducted over two 12-week periods during summer and fall of 2000 in a region characterized by industrial pollution (Steubenville, Ohio). Continuous ECG data acquired on a weekly basis over a 30-minute sampling period were used to assess ectopy, defined as extra cardiac depolarizations within the atria (supraventricular ectopy, SVE) or the ventricles (ventricular ectopy, VE). Increases in the 5-day moving average (days 1-5) of O_3 were associated with an increased odds of SVE (OR: 2.17 [95% CI: 0.93, 5.07] per 20 ppb increase in 24-h avg O_3 concentrations). A weaker association was observed for VE (OR: 1.62 [95% CI: 0.54, 4.90] per 20 ppb increase in 24-h avg O_3 concentrations). The results of the effect of 5-day O_3 on SVE were robust to the inclusion of SO_4^{2-} in the model [OR: 1.62 (95% CI: 0.54, 4.90)]. The authors indicate that the strong associations observed at the 5-day moving averages, as compared to shorter time periods, suggests a relatively long-acting mechanistic pathways, such as inflammation, may have promoted the ectopic beats in this population (Sarnat et al., 2006a).

Although many studies report positive associations, collectively, studies of arrhythmias report inconsistent results. This may be due to variation in study populations, length and season of averaging time, and outcome under study. Future studies are expected to provide additional evidence for the various outcomes and exposure periods.

6.3.2.2 Heart Rate/Heart Rate Variability

In the 2006 O_3 AQCD, two large population-based studies of air pollution and HRV were summarized (Park et al., 2005b; Liao et al., 2004a). In addition, the biological mechanisms and potential importance of HRV were discussed. Briefly, the study of acute adverse effects of air pollution on cardiac autonomic control is based on the hypothesis that increased air pollution levels may stimulate the autonomic nervous system and lead to an imbalance of cardiac autonomic control characterized by sympathetic activation unopposed by parasympathetic control (U.S. EPA, 2006b). Examples of HRV indices include the standard deviation of normal-to-normal intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (r-MSSD), high-frequency power (HF), low-frequency power (LF), and the LF/HF ratio. Liao et al. (2004a) examined the association between air pollution and cardiac autonomic control in the fourth cohort examination (1996-1998) of the U.S.-based Atherosclerosis Risk in Communities Study. A decrease in log-transformed HF was associated with an

increase in O_3 concentration among white study participants. Park et al. (2005b) examined the effects of air pollution on indices of HRV in a population-based study among men from the Normative Aging Study in Boston, Massachusetts. Several associations were observed with O_3 and HRV outcomes; a reduction in LF was associated with increased O_3 concentration, which was robust to inclusion of $PM_{2.5}$. The associations with all HRV indices and O_3 were stronger among those with ischemic heart disease and hypertension. In addition to these population-based studies included in the 2006 O_3 AQCD was a study by Schwartz et al. (2005), who conducted a panel study to assess the relationship between exposure to summertime air pollution and HRV. A weak association of O_3 during the hour immediately preceding the health measures was observed with r-MSSD among a study population that consisted of mostly older female participants. In summary, these studies suggest that short-term exposures to O_3 are predictors of decreased HRV and that the relationship may be stronger among certain subgroups. The generally consistent (although weak) associations between pollutants and reduced cardiac autonomic control were observed at relatively low pollution concentrations typically experienced by the U.S. general population on a daily basis (U.S. EPA, 2006b). More recent studies of O_3 and HRV and are described below. The O_3 concentrations for these studies are presented in Table 6-30.

Table 6-30 Characterization of ozone concentrations (in ppb) from studies of heart rate variability

Reference	Location	Averaging Time	Mean Concentration (Standard Deviation)	Upper Range of Concentration
Baja et al. (2010)	Boston, MA	0 lag	23 (16)	
		10-h lag	21 (15)	
Chan et al. (2005a)	Taipei, Taiwan	1-h	21.9 (15.4)	Max: 114.9
Chuang et al. (2007a)	Taipei, Taiwan	24-h	28.4 (12.1)	Max: 49.3
		48-h	33.3 (8.9)	Max: 47.8
		72-h	33.8 (7.1)	Max: 48.3
Chuang et al. (2007b)	Taipei, Taiwan	1-h	35.1	Max: 192.0
Park et al. (2007)	Boston, MA	24-h	Range of 17.0-29.1	
Park et al. (2008)	Boston, MA	24-h	23.4 (13)	
Ruidavets et al. (2005a)	Toulouse, France	8-h	38.3 (14.8)	75th: 46.9
				Max: 80.3
Wheeler et al. (2006)	Atlanta, GA	4-h	18.5	75th: 22.5
		24-h	29.4	
Wu et al. (2010)	Taipei, Taiwan	Working period	24.9 (14.0)	Max: 59.2
Zanobetti et al. (2010)	Boston, MA	0.5-h	20.7*	75th: 30.33
		2-h	20.5*	75th: 30.08
		3-D	21.9*	75th: 28.33
		5-D	22.8*	75th: 29.28

*Median presented (information on mean not given).

Several follow-up examinations of HRV were conducted among the participants of the Normative Aging Study in Boston. A trajectory cluster analysis was used to assess whether pollution originating from different locations had varying relationships with HRV (Park et al., 2007). Subjects who were examined on days when air parcels originated in the west had the strongest associations with O_3; however, the O_3 concentration in this cluster was low (24-h avg, 17.0 ppb) compared to the other clusters (24-h avg of 21.3-29.1 ppb). LF and SDNN decreased with increases in the 4-h moving average of O_3 from the west (LF decreased by 51.2% [95% CI: 1.6, 75.9%] and SDNN decreased by 28.2% [95% CI: -0.5, 48.7%] per 30 ppb increase in 4-h avg O_3 concentrations) (Park et al., 2007). The Boston air mass originating in the west traveled over Illinois, Indiana, and Ohio; states typically characterized by coal-burning power plants. Due to the low O_3 concentrations observed in the west cluster, the authors hypothesize that O_3 on those days could be capturing the effects of other, secondary and/or transported pollutants from the coal belt or that the relationship between ambient O_3 and personal exposure to O_3 is stronger during that period (supported by a comparatively low apparent temperature which could indicate a likelihood to keep windows open and reduced air conditioning use) (Park et al., 2007). An additional follow-up evaluation using the Normative Aging Study examined the potential for effect modification by chronic lead exposure on the relationship between air pollution and HRV (Park et al., 2008). Authors observed graded reductions in HF and LF of HRV in relation to O_3 (and sulfate) across increasing quartiles of tibia and patella lead (HF: %change 32.3 [95% CI: -32.5, 159.3] for the first quartile of tibia Pb and -59.1 [95% CI: -77.3, -26.1] for the fourth quartile of tibia Pb per 30 ppb increase in 4-h avg O_3 concentrations; LF: %change 8.0 [95% CI: -36.9, 84.9] for the first quartile of tibia Pb and -59.3 [95% CI: -74.6, -34.8] for the fourth quartile of tibia Pb per 30 ppb increase in 4-h avg O_3 concentrations). In addition, O_3 associations were similar when education and cumulative traffic-adjusted bone lead levels were used in analyses. Authors indicate the possibility that O_3 (which has low indoor concentrations) was acting as a proxy for sulfate (correlation coefficient for O_3 and sulfate = 0.57). Investigators of a more recent follow-up to the Normative Aging Study hypothesized that the relationships between short-term air pollution exposures and ventricular repolarization, as measured by changes in the heart-rate corrected QT interval (QTc), would be modified by participant characteristics (e.g., obesity, diabetes, smoking history) and genetic susceptibility to oxidative stress (Baja et al., 2010). No evidence of an association between O_3 (using a quadratic constrained distributed lag model and hourly exposure lag models over a 10-h time window preceding the visit) and QTc was reported (change in mean QTc -0.74 [95% CI: -3.73, 2.25]); therefore, potential effect modification of personal and genetic characteristics with O_3 was not assessed (Baja et al., 2010). Collectively, the results from studies that examined the Normative Aging Study cohort found an association between

increases in short-term exposures to O_3 and decreases in HRV (Park et al., 2008; Park et al., 2007; Park et al., 2005b) although not consistently in all of the studies (Baja et al., 2010). Further, observed relationships appear to be stronger among those with ischemic heart disease, hypertension, and elevated bone lead levels, as well as when air masses arrive from the west (the coal belt). However, it is not clear if O_3 is acting as a proxy for other, secondary particle pollutants (such as sulfate) (2008; 2007; Park et al., 2005b). In addition, since the Normative Aging Study participants were older, predominately white men, results may not be generalizable to women, younger individuals, or those of different racial/ethnic groups (Baja et al., 2010).

Additional studies of populations not limited to the Normative Aging Study have also examined associations between O_3 exposure and HRV. A panel study among 18 individuals with COPD and 12 individuals with recent myocardial infarction (MI) was conducted in Atlanta, Georgia (Wheeler et al., 2006). HRV was assessed for each participant on 7 days in fall 1999 and/or spring 2000. The mean 4-h O_3 concentration (time period immediately preceding the HRV measures) was 18.5 ppb; however, O_3 concentrations differed substantially within study sites (8.0 – 33.8 ppb). Ozone concentrations were not associated with HRV (SDNN) among all subjects (percent change of 2.36% [95% CI: -10.8%, 17.5%] per 30 ppb 4-h O_3 increase) or when stratified by disease type (COPD, recent MI, and baseline FEV_1) (Wheeler et al., 2006).

HRV and air pollution was assessed in a panel study among 46 predominately white male patients (study population: 80.4% male, 93.5% white) aged 43-75 years in Boston, Massachusetts, with coronary artery disease (Zanobetti et al., 2010). Up to four home visits were made to assess HRV over the year following the index event. Pollution lags used in analyses ranged between 30 minutes to a few hours and up to 5 days prior to the HRV assessments. Decreases in r-MSSD were reported for all averaging times of O_3 (percent change of -5.18% [95% CI: -7.89, -2.30] per 20 ppb of 5-day moving average of O_3 concentration), but no evidence of an association between O_3 and HF was observed (quantitative results not provided). In two-pollutant models with O_3 and either $PM_{2.5}$ or BC, O_3 associations remained robust.

A few studies were conducted outside of the U.S. to assess the relationship between air pollution concentrations and heart rate and HRV (Wu et al., 2010; Chuang et al., 2007b; Chuang et al., 2007a; Chan et al., 2005a; Ruidavets et al., 2005a). No associations were reported between O_3 and HRV among CHD patients and patients with one or more major CHD risk factors residing in Taipei, Taiwan (Chan et al., 2005a). Another study in Taipei, Taiwan examined mail carriers and reported O_3 levels measured using personal monitors. No association was observed between O_3 and the measures of HRV (percent change for SDNN: 0.57 [95% CI: -21.27, 28.46], r-MSSD: -7.10 [95% CI: -24.24, 13.92],

HF: -1.92 [95% CI: -23.68, 26.02], LF: -4.82 [95% CI: -25.34, 21.35] per 40 ppb O_3) (Wu et al., 2010). In addition, no consistent relationships were identified between O_3 and resting heart rate among middle-aged (35-64 years) participants residing in Toulouse, France (Ruidavets et al., 2005a). A negative trend was reported for the 3-day cumulative (lag days 1-3) concentration of O_3 with heart rate (p for trend = 0.02); however, the individual odds ratios comparing quintiles of exposure showed no association (OR for O_3 of 0.93 [95% CI: 0.86, 1.01] for the highest quintile of resting heart rate compared to the lowest). When stratified by current smoking status, non-smokers had a decreased trend with increased 3-day cumulative O_3 concentrations but none of the quintiles for heart rate were statistically significant. A panel study was conducted in Taiwan to assess the relationship between air pollutants and inflammation, oxidative stress, blood coagulation, and autonomic dysfunction (Chuang et al., 2007b; Chuang et al., 2007a). Participants were apparently healthy college students (aged 18-25 year) who were living in a university dormitory in metropolitan Taipei. Health endpoints were measured three times from April to June in 2004 or 2005. Ozone was assessed in statistical models using the average of the 24, 48, and 72 hours before the hour of each blood sampling. Decreases in HRV (measured as SDNN, r-MSSD, LF, and HF) were associated with increases in O_3 concentrations in single-pollutant models (percent change for SDNN: -13.45 [95% CI: -16.26, -10.60], r-MSSD -13.76 [95% CI: -21.62, -5.44], LF -9.16 [95% CI: -13.29, -4.95], HF -10.76 [95% CI: -18.88, -2.32] per 20 ppb 3-day avg O_3 concentrations) and remained associated with 3-day O_3 concentrations in two-pollutant models with sulfate. Another study in Taiwan recruited individuals with coronary heart disease or at risk for cardiovascular disease from outpatient clinics (Chuang et al., 2007b). Mean O_3 concentrations were 35.1 ppb (SD 27.5 ppb) during the study period (two weeks in February). No association was observed between O_3 concentration and HRV measures (SDNN, r-MSSD, LF, HF) (numerical results not provided in publication).

Overall, studies of O_3 concentration and HRV report inconsistent results. Multiple studies in Boston observed positive associations but the authors of many of these studies postulated that O_3 was possibly acting as a proxy for other pollutants. The majority of other studies, both in the U.S. and internationally, report null findings. The inconsistencies observed are further complicated by the different HRV measures and averaging times used by the studies.

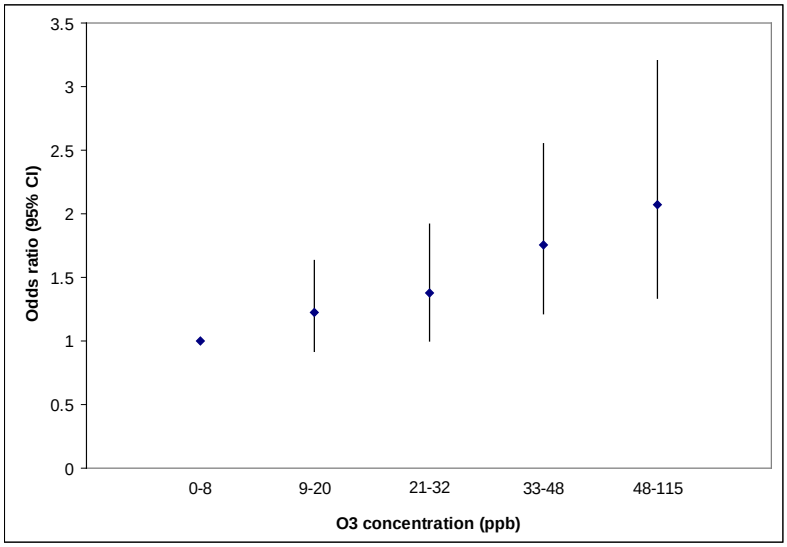
6.3.2.3 Stroke

The 2006 O_3 AQCD did not identify any studies that examined the association between short-term O_3 exposure and stroke. However, recent studies have attempted to examine this relationship. Lisabeth et al. (2008) used a time-series approach to assess the

relationship between daily counts of ischemic stroke and transient ischemic attack (TIA) with O_3 concentrations in a southeast Texas community among residents 45 years and older (2001-2005; median age of cases, 72 years). The median O_3 (hourly average per 24-h time-period) concentration was 25.6 ppb (IQR 18.1-33.8). The associations between same-day (RR: 1.03 [95% CI: 0.96, 1.10] per 20 ppb increase in 24-h avg O_3 concentrations) and previous-day (RR: 1.05 [95% CI: 0.99, 1.12] per 20 ppb increase in 24-h avg O_3 concentrations) O_3 concentrations and stroke/TIA risk were positive. Associations were robust to adjustment for $PM_{2.5}$. The effect of season on the relationship was not assessed.

A case-crossover design was used in a study conducted in Dijon, France between March 1994 and December 2004, among those 40 years of age and older who presented with first-ever stroke (Henrotin et al., 2007). The mean O_3 concentration, calculated over 8-h daytime periods, was 14.95 ppb (IQR: 6-22 ppb). No association was observed between O_3 concentration at 0, 1, 2, or 3 days lag and hemorrhagic stroke. However, an association between ischemic stroke occurrence and O_3 concentrations with a 1-day lag was observed (OR: 1.54 [95% CI: 1.14, 2.09] per 30 ppb increase in 8-h max O_3 concentrations). The effect of O_3 persisted in two-pollutant models with PM_{10}, SO_2, NO_2, or CO. This association was stronger among men (OR: 2.12 [95% CI: 1.36, 3.30] per 30 ppb increase in 8-h max O_3 concentrations) than among women (OR: 1.17 [95%CI: 0.77, 1.78] per 30 ppb increase in 8-h max O_3 concentrations) in single pollutant models. When stroke was examined by subtype among men, an association was observed for ischemic strokes of large arteries and for transient ischemic attacks but not for cardioembolic or lacunar ischemic strokes. The subtype analysis was not performed for women. Additionally, for men a linear exposure-response was observed when O_3 was assessed based on quintiles (p for trend = 0.01) (Figure 6-21). A potential limitation of this study is that 67.4% of the participating men were smokers compared to 9.3% of the women.

Another study, performed in Dijon, France, examined the association between O_3 concentration and incidence of fatal and non-fatal ischemic cerebrovascular events (ICVE) (Henrotin et al., 2010). Mean 8-h O_3 concentration was 19.1 ppb (SD 12.2 ppb). A positive association was observed between recurrent ICVE and O_3 concentration with a 3-day lag (OR: 1.92 [95% CI 1.17, 3.12]), but not for other lags (0, 1, 2, 4) or cumulative days (0-1, 0-2, 1-2, 1-3). Although some ORs for incident ICVEs were elevated, none were statistically significant. Results for associations using the maximum daily 1-h O_3 concentrations were similar to the 8-h results but slightly attenuated. ORs were similar in two pollutant models (data not given). In stratified analyses, the association between 1-day lagged O_3 concentration and incident and recurrent ICVE was greater among those with multiple other preexisting vascular conditions. Increased associations with ICVE were also observed for individuals with diabetes or hypertension.



Source: Henrotin et al. (2007).

Figure 6-21 Odds ratio (95% confidence interval) for stroke by quintiles of ozone.

6.3.2.4 Biomarkers

An increasing number of studies have examined the relationship between air pollution and biomarkers in an attempt to elucidate the biological mechanisms linking air pollution and cardiovascular disease. A wide range of markers assessed as well as different types of study designs and locations chosen make comparisons across studies difficult. Table 6-31 provides an overview of the O_3 concentrations reported in each of the studies evaluated.

Table 6-31 Characterization of ozone concentrations (in ppb) from studies of biomarkers

Reference	Location	Averaging Time	Mean Concentration (Standard Deviation)	Upper Range of Concentration
Baccarelli et al. (2007)	Lombardia, Italy	1-h	18.3*	75th: 35.1 Max: 202.3
Chen et al. (2007)	Los Angeles and San Francisco, CA	8-h/2 wk	30.8*	Max: 47.9
		8-h/1 mo	28.3*	Max: 43.1
Chuang et al. (2010)	Taiwan		26.83 (9.7)	Max: 62.1
Chuang et al. (2007a)	Taipei, Taiwan	24-h	28.4 (12.1)	Max: 49.3
		48-h	33.3 (8.9)	Max: 47.8
		72-h	33.8 (7.1)	Max: 48.3
Goldberg et al. (2008)	Montreal, Quebec	24-h	NS	
Liao et al. (2005)	3 U.S. counties	8-h	40 (20)	
Rudez et al. (2009)	Rotterdam, the Netherlands	24-h	22*	75th: 31.5 Max: 90
Steinvil et al. (2008)	Tel-Aviv, Israel	0.5-h	29.2 (9.7)	75th: 36
Thompson et al. (2010)	Toronto, Ontario	1-h/1 yr	21.94 (15.78)	
Wellenius et al. (2007)	Boston, MA	1-h/24-h	25.1 (12.9)	

*Median presented (information on mean not given).

Hemostasis and coagulation markers

Multiple studies used various markers to examine if associations were present between O_3 concentrations and hemostatis and coagulation. Some of the markers included in these studies were as follows: fibrinogen, von Willebrand factor (vWF), plasminogen activator fibrinogen inhibitor-1 (PAI-1), tissue-type plasminogen activator (tPA), platelet aggregation, and thrombin generation.

A population-based study in the United States was conducted to assess the relationship between short-term exposure to air pollution and markers of blood coagulation using the Atherosclerosis Risk in Communities (ARIC) study cohort (Liao et al., 2005). Significant curvilinear associations were observed for O_3 (1 day prior to blood draw) and fibrinogen and vWF (quantitative results not provided for regression models although adjusted means [SE] of vWF were given as 118% [0.79%] for O_3 concentrations <40 ppb, 117% [0.86%] for O_3 concentrations 40-70 ppb, and 124% [1.97%] for O_3 concentrations of 70 ppb). The association between O_3 and fibrinogen was more pronounced among those with a history of cardiovascular disease (CVD) and was statistically significant among only this subgroup of the population. The curvilinear relationship between exposure and outcome suggested stronger relationships at higher concentrations of O_3 which could indicate threshold effects. The authors note that the most pronounced associations occurred when the pollutants were 2-3 standard deviations above the mean. The results

from this relatively large-scale cross-sectional study suggest weak associations with O_3 and fibrinogen (among those with a history of CVD) and vWF.

A retrospective repeated measures analysis was performed in Toronto, Canada among adults aged 18-40 years (n=45) between the years of 1999 and 2006 (Thompson et al., 2010). Single pollutant models were used with moving averages up to 7 days. No evidence of an association was observed for O_3 and fibrinogen.

A repeated measures study was conducted in 40 healthy individuals living or working in the city center of Rotterdam, the Netherlands to assess the relationship between air pollution and markers of hemostatis and coagulation (platelet aggregation, thrombin generation, and fibrinogen) (Rudez et al., 2009). Each participant provided between 11 and 13 blood samples throughout a 1-year period (498 samples on 197 days). Examined lags ranged from 6 hours to 3 days prior to blood sampling. No consistent evidence of an association was observed between O_3 and any of the biomarkers (percent change of max platelet aggregation: -6.87 [95% CI: -21.46, 7.70] per 20 ppb 4-day average $O_{3;}$ percent change of endogenous thrombin potential: 0.95 [95% CI: -3.05, 4.95] per 20 ppb 4-day avg $O_{3;}$ percent change of fibrinogen: -0.57 [95% CI: -3.05, 2.00] per 20 ppb lag 1-day $O_{3;}$). Some associations with O_3 were in the opposite direction to that hypothesized which may be explained by the negative correlation between O_3 and the other pollutants (correlation coefficients ranged from -0.4 to -0.6). The statistically significant inverse effects observed with O_3 in single-pollutant models were no longer apparent when PM_{10} was included in the models (Rudez et al., 2009).

A panel study in Taiwan measured health endpoints using blood samples from healthy individuals (n=76) at three times from April to June in 2004 or 2005 (Chuang et al., 2007a). Increases in fibrinogen and PAI-1 were associated with increases in O_3 concentrations in single-pollutant models (percent change in fibrinogen: 11.76 [95% CI: 4.03, 19.71] per 20 ppb 3-day avg O_3; percent change in PAI-1: 6.08 [95% CI: 38.91, 84.27] per 20 ppb 3-day avg O_3). These associations were also observed at 1 and 2 day averaging times. Associations between PAI-1 and 3-day O_3 concentrations remained robust in two-pollutant models with sulfate. No association was seen between O_3 and tPA, a fibrinolytic factor (percent change 16.15 [95% CI: -4.62, 38.34] per 20 ppb 3-day avg O_3).

A study in Israel examined the association between pollutant concentrations and fibrinogen among 3659 apparently healthy individuals (Steinvil et al., 2008). In single pollutant models, O_3 was associated with an increase in fibrinogen at a 4-day lag among men and a same-day O_3 concentration among women but results for other lags (0 through 7 days) were mixed (some positive, some negative; none statistically significant).

Inflammatory markers

Air pollution and inflammatory markers (C-reactive protein [CRP], white blood cell [WBC] count, albumin, and Interleukin-6 [IL-6]) were also examined in several studies.

The ARIC study cohort, which included men and women aged 45-64 years old at the start of the study, was utilized to assess the association between O_3 concentrations and makers of inflammation (Liao et al., 2005). No association was observed between O_3 concentrations and albumin or WBC count.

Thompson et al. (2010) assessed ambient air pollution exposures and IL-6. This retrospective repeated measures analysis was conducted among 45 adults (18-40 years of age) in Toronto, Canada between the years of 1999 and 2006. Single pollutant models were used to analyze the repeated-measures data using moving averages up to 7 days. A positive association was observed between IL-6 and O_3 with the strongest effects observed for the 4-day moving average of O_3 (quantitative results not provided). No association was seen for shorter averaging times (<1 day). When examined by season using 2-day moving averages, the association between O_3 and IL-6 was positive during only the spring and summer.

In Rotterdam, the Netherlands, a repeated measures study of healthy individuals living or working in the city center reported no association between O_3 concentration and CRP (Rudez et al., 2009). Each of the 40 participants provided between 11 and 13 blood samples throughout a 1-year period (498 samples on 197 days). No consistent evidence of an association was observed between O_3 and CRP (percent change: -0.48 [95% CI: -14.05, 13.10] per 20 ppb lag 1-day O_3). Additionally, no association was observed with 2 or 3 day lags.

The relationship between pollutant concentrations and one-time measures of inflammatory biomarkers was assessed in sex-stratified analyses among 3659 apparently healthy individuals in Tel Aviv, Israel (Steinvil et al., 2008). No evidence of an association was observed between O_3 and CRP or WBC for men and women.

A panel study of healthy individuals (n=76) was conducted in Taiwan to assess the relationship between air pollutants and inflammation (Chuang et al., 2007a). Health endpoints were measured three times from April to June in 2004 or 2005. Ozone effects were assessed in statistical models using the average of the 24 hours (1 day), 48 hours (2 days), and 72 hours (3 days) before the hour of each blood sampling. Increases in CRP were associated with increases in O_3 concentrations in single-pollutant models (percent change in CRP: 244.38 [95% CI: 4.54, 585.15] per 20 ppb 3-day avg O_3). The association was also observed using a 2-day averaging time, but no association was present with a 1-day averaging time.

Oxidative stress markers

A few studies have reported on the relationships between O_3 concentration and oxidative stress markers. The association between O_3 exposure and markers of lipid peroxidation and antioxidant capacity was examined among 120 nonsmoking healthy college students, aged 18-22 years, from the University of California, Berkeley (February-June 2002) (Chen et al., 2007). By design, students were chosen that had experienced different geographic concentrations of O_3 over their lifetimes and during recent summer vacation in either greater Los Angeles (LA) or the San Francisco Bay Area (SF). Long-term (based on lifetime residential history) and shorter-term (based on the moving averages of 8-h max concentrations 1-30 days prior to the day of blood collection) O_3 exposures were estimated (lifetime exposure results presented in the chronic exposure section). A marker of lipid peroxidation, 8-isoprostane (8-iso-PGF), was assessed. This marker is formed continuously under normal physiological conditions but has been found at elevated concentrations in response to environmental exposures. A marker of overall antioxidant capacity, ferric reducing ability of plasma (FRAP), was also measured. Substantial overlap in the more recent O_3 exposure estimates (8-h moving averages) was observed between the two geographic areas sampled. Levels of 8-iso-PGF were associated with 2-week ($\beta = 0.035$ [pg/mL]/8-h ppb O_3, $p = 0.007$) and 1-month ($\beta = 0.031$ [pg/mL]/8-h ppb O_3, $p = 0.006$) estimated O_3 exposure levels. No evidence of association was observed between O_3 and FRAP. A chamber study performed among a subset of study participants supported the primary study results. The concentrations of 8-iso-PGF increased immediately after the 4-h controlled O_3 exposure ended ($p = 0.10$). However, levels returned to near baseline by 18 hours without further exposure. The authors note that O_3 was highly correlated with $PM_{10-2.5}$ and NO_2 in this study population; however, inclusion of these pollutants in the O_3 models did not substantially change the magnitude of the associations with O_3.

Using blood samples collected between April and June of 2004 or 2005 in Taiwan, the association between O_3 concentrations and a marker of oxidative stress was studied among healthy individuals (n=76) (Chuang et al., 2007a). Increases in 8-hydroxy-2'-deoxyguanosine (8-OHdG) were associated with increases in O_3 concentrations in single-pollutant models (percent change in 8-OHdG: 2.46 [95% CI: 1.01, 3.92] per 20 ppb 1-day avg O_3). The association did not persist with 2- or 3-day averaging times.

Markers of overall cardiovascular health

Multiple studies used markers that assess overall cardiovascular well-being. Wellenius et al. (2007) examined B-type natriuretic peptide (BNP), a marker of heart failure, in a repeated-measures study conducted in Boston among 28 patients with congestive heart

failure and impaired systolic function. The authors found no evidence of an association between BNP and short-term O_3 exposures at lags 0-3 days (quantitative results not provided). BNP was chosen because it is directly associated with cardiac hemodynamics and symptom severity among those with heart failure and is, therefore, considered a marker of functional status. However, the authors conclude that the use of BNP may not be useful in studies of the health effects of ambient air pollutants due to the large amount of within-person variability in BNP levels observed in this population.

The relationship between air pollution and oxygen saturation and pulse rate, markers of physiological well-being, was examined in a 2-month panel study among 31 congestive heart failure patients (aged 50-85 years) in Montreal, Canada from July 2002 to October 2003 (Goldberg et al., 2008). All participants had limited physical functioning (New York Heart Association Classification ≥ II) and an ejection fraction (the fraction of blood pumped out of the heart per beat) less than or equal to 35% (normal is above 55%). Daily mean O_3 concentrations were calculated based on hourly measures at 10 monitoring stations. There was an inverse association between O_3 (lag-0) and oxygen saturation when adjustment was made for temporal trends. In the models incorporating personal covariates and weather factors, the association remained but was not statistically significant. The associations of O_3 with a lag of 1 day or a 3-day mean were not statistically significant. No evidence of association was observed between O_3 exposure and pulse rate.

Total homocysteine (tHcy) is an independent risk factor for vascular disease and measurement of this marker after oral methionine load is used to identify individuals with mild impairment of homocysteine metabolism. The effects of air pollution on fasting and postmethionine-load tHcy levels were assessed among 1,213 apparently healthy individuals from Lombardia, Italy from January 1995 to September 2005 (Baccarelli et al., 2007). An increase in the 24-h O_3 concentrations was associated with an increase in fasting tHcy (percent change 6.25 [95% CI: 0.84, 11.91] per 20 ppb O_3) but no association was observed with postmethionine-load tHcy (percent change 3.36 [95% CI: -1.30, 8.39] per 20 ppb O_3). In addition, no evidence of association was observed between 7-day O_3 concentrations and tHcy (percent change for fasting tHcy 4.16 [95% CI: -1.76, 10.42] and percent change for postmethionine-load tHcy -0.65 [95% CI: -5.66, 4.71] per 20 ppb O_3). No evidence of effect modification by smoking was observed.

Blood lipids and glucose metabolism markers

Chuang et al. (2010) conducted a population-based cross-sectional analysis of data collected on 7,778 participants during the Taiwanese Survey on Prevalence of Hyperglycemia, Hyperlipidemia, and Hypertension in 2001. Apolipoprotein B (ApoB),

the primary apolipoprotein among low-density lipoproteins, was associated with 3-day avg O_3 at the $p < 0.10$ level. The 5-day mean O_3 concentration was associated with an increase in triglycerides at $p < 0.10$. In addition, the 1-, 3-, and 5-day mean O_3 concentrations were associated with increased HbA1c levels (a marker used to monitor the degree of control of glucose metabolism) at the $p < 0.05$ level. The 5-day mean O_3 was associated with increased fasting glucose levels ($p < 0.10$). No association was observed between O_3 concentration and ApoA1. Copollutant models were not assessed.

6.3.2.5 Myocardial Infarction (MI)

The 2006 O_3 AQCD did not report consistent results indicating an association between short-term O_3 exposure and MI. One study reported a positive association between current day O_3 concentration and acute MI, especially among the oldest age group (55- to 64-year olds) (Ruidavets et al., 2005b). No association was observed in a case-crossover study of O_3 during the hours surrounding the event and MI (Peters et al., 2001). Since the 2006 O_3 AQCD, a few new epidemiologic studies have examined the association between O_3 exposure and MI (Henrotin et al., 2010; Rich et al., 2010), as well as one study published on arterial stiffness (Wu et al., 2010) and one study published on ST-segment depression (Delfino et al., 2011).

One of the studies conducted in the U.S. examined hospital admissions for first MI and reported no association with O_3 concentrations (Rich et al., 2010). More details on this study are reported in the section on hospital admissions. Another study, performed in Dijon, France, examined the association between O_3 concentration and incident and recurrent MI (Henrotin et al., 2010). The mean 8-h O_3 concentration was 19.1 ppb (SD 12.2 ppb). Odds ratios for the association between cumulative O_3 concentrations and recurrent MIs were elevated but none of the results were statistically significant (OR: 1.71 [95% CI: 0.91, 3.20] per 20 ppb for cumulative 1-3 day O_3 exposure). No association was observed for incident MIs. In analyses stratified by vascular risk factors, positive associations were observed between 1-day lagged O_3 concentrations and MIs (incident and recurrent combined) among those who reported having hypercholesterolaemia (OR: 1.52 [95% CI: 1.08, 2.15] per 20 ppb O_3) and a slight inverse association was observed among those who reported not having hypercholesterolaemia (OR: 0.69 [95% CI: 0.50, 0.94] per 20 ppb O_3). In other stratified analyses combining different vascular factors, only those containing individuals with hypercholesterolaemia demonstrated a positive association; none were inverse associations.

Wu et al. (2010) examined mail carriers aged 25-46 years and measured exposure to O_3 through personal monitors [mean O_3 24.9 (SD 14.0) ppb]. Ozone exposure was positively

associated with arterial stiffness (percent change 11.24% [95% CI: 3.67, 19.62] per 40 ppb O_3) and was robust to adjustment for ultrafine PM.

A study performed in the Los Angeles basin reported on the association between O_3 exposure and ST-segment depression, a measure representing cardiac ischemia (Delfino et al., 2011). Study participants were nonsmokers, at least 65 years old, had a history of coronary artery disease, and were living in a retirement community. Study periods included five consecutive days in both July to mid-October and mid-October to February. Mean 24-h O_3 concentrations were 27.1 ppb (SD 11.5 ppb). No association was observed between O_3 concentrations and ST-segment depression of at least 1.0 mm during any of the exposure periods (i.e., 1-h, 8-h, 1-day, 2-day avg, 3-day avg, 4-day avg).

6.3.2.6 Blood Pressure

In the 2006 O_3 AQCD, no epidemiologic studies examined O_3-related effects on blood pressure (BP). Recent studies have been conducted to evaluate this relationship and overall the findings are inconsistent. The O_3 concentrations for these studies are listed in Table 6-32.

Table 6-32 Characterization of ozone concentrations (in ppb) from studies of blood pressure

Reference	Location	Averaging Time	Mean Concentration (Standard Deviation)	Upper Range of Concentration
Choi et al. (2007)	Incheon, South Korea	8-h (warm season)	26.6 (11.8)	75th: 34.8 Max: 62.4
		8-h (cold season)	17.5 (7.3)	75th: 22.9 Max: 33.9
Delfino et al. (2010b)	Los Angeles, California	24-h	27.1 (11.5)	Max: 60.7
Zanobetti et al. (2004)	Boston, Massachusetts	1-h	20	
		5-days	24	
Chuang et al. (2010)	Taiwan		26.83 (9.7)	Max: 62.1

Zanobetti et al. (2004) examined the relationship between air pollutants and BP from May 1999 to January 2001 for 631 repeat visits among 62 Boston residents with CVD. In single-pollutant models, higher resting diastolic blood pressure (DBP) was associated with the 5-day (0-4 days) averages of O_3 (RR: 1.03 [95% CI: 1.00, 1.05] per 20 ppb increase in 24-h O_3 concentrations). However, this effect was no longer apparent when $PM_{2.5}$ was included in the model (data were not presented) (Zanobetti et al., 2004). Delfino et al. (2010b) examined 64 subjects 65 years and older with coronary artery

disease, no tobacco smoke exposure, and living in retirement communities in the Los Angeles air basin with hourly (up to 14-h/day) ambulatory BP monitoring for 5 days during a warm period (July-mid-October) and 5 days during a cool period (mid-October-February). Investigators assessed lags of 1, 4, and 8 hours, 1 day, and up to 9 days before each BP measure; no evidence of association was observed for O_3 exposures (change in BP associated with a 20 ppb change in 24-h O_3 was 0.67 [95% CI: -1.16, 2.51 for systolic BP [SBP] and -0.25 [95% CI: -1.25, 0.75] for DBP) (Delfino et al., 2010b). Choi et al. (2007) conducted a cross-sectional study to investigate the relationship between air pollutants and BP among 10,459 participants of the Inha University Hospital health examination from 2001 to 2003. These individuals had no medical history of cardiovascular disease or hypertension. O_3 exposure was associated with an increase in SBP for 1-day lag in the warm season and similar effect estimates were observed during the cold season but were not statistically significant (quantitative results not provided). Associations between O_3 and DBP were present in the cold season but not the warm season (quantitative results not provided). The interaction term between O_3 and season was statistically significant. Chuang et al. (2010) conducted a similar type of study among 7,578 participants of the Taiwanese Survey on Prevalence of Hyperglycemia, Hyperlipidemia, and Hypertension in 2001. Investigators examined 1-, 3-, and 5-day avg O_3 concentrations. An increase in DBP was associated with the 3-day mean O_3 concentration (change in BP for a 20 ppb increase in O_3 was 0.61 [95% CI: 0.07, 1.14]) (Chuang et al., 2010). Associations were not observed for other days or with SBP.

6.3.2.7 Hospital Admissions and Emergency Department Visits

Upon evaluating the collective evidence for O_3-related cardiovascular hospital admissions (HAs) and emergency department (ED) visits, the 2006 O_3 AQCD concluded that "a few studies observed positive O_3 associations, largely in the warm season. Overall, however, the currently available evidence is inconclusive regarding any association between ambient O_3 exposure on cardiovascular hospitalizations" (U.S. EPA, 2006b). Table 6-33 below provides information on the O_3 concentrations reported in each of the recent HA and ED visit studies evaluated.

Multiple recent studies of O_3 exposure and cardiovascular HAs and ED visits have been conducted in the U.S. and Canada. Peel et al. (2007) used a case-crossover framework (using a time-stratified approach matching on day of the week in the calendar month of the event) to assess the relationship between air pollutants and cardiovascular disease ED visits among those with and without secondary comorbid conditions (hypertension, diabetes, chronic obstructive pulmonary disease [COPD], congestive heart failure [CHF],

Table 6-33 Characterization of ozone concentrations (in ppb) from studies of HAs and ED visits

Study	Location	Averaging Time	Mean Concentration (Standard Deviation)	Upper Range of Concentration
Azevedo et al. (2011)	Portugal	1-h	NR	
Ballester et al. (2006)	Multicity, Spain	8-h warm season	24.2 - 44.3	
Bell et al. (2008)	Taipei, Taiwan	24-h	21.4	Max: 53.4
Buadong et al. (2009)	Bangkok, Thailand	1-h	14.4 (3.2)	Max: 41.9
Cakmak et al. (2006a)	Multicity, Canada	1-h max	17.4	
Chan et al. (2006)	Taipei, Taiwan	1-h max	50.9 (26.4)	Max: 150.3
Halonen et al. (2009)	Helsinki, Finland	8-h max warm season	35.7*	75th: 42.1 Max: 79.6
Hosseinpoor et al. (2005)	Tehran, Iran	8-h max	4.9 (4.8)	75th: 7.2 Max: 99.0
Lanki et al. (2006)	Multicity, Europe	8-h max warm season	31.7 - 57.2*	
Larrieu et al. (2007)	Multicity France	8-h max warm season	34.2 - 53.1	
Lee et al. (2003b)	Seoul, Korea	1-h max	36.0 (18.6)	75th: 44.9
Lee et al. (2007)	Kaohsiung, Taiwan	24-h	26.5	75th: 35.5 Max: 83.0
Middleton et al. (2008)	Nicosia, Cyprus	8-h max	28.7 - 54.9	
Peel et al. (2007)	Atlanta, GA	8-h max warm season	55.6 (23.8)	
Rich et al. (2010)	New Jersey	24-h	NR	
Stieb et al. (2009)	Multicity, Canada	24-h	18.4	
Symons et al. (2006)	Baltimore, MD	8-h warm season	31.0 (20.0)	Max: 120.0
Tolbert et al. (2007)	Atlanta, GA	8-h max warm season	53.0	75th: 67.0 Max: 147.5
Villeneuve et al. (2006a)	Edmonton, Canada	24-h	17 (9.1)	75th: 23.5
		24-h warm season	21.8 (8)	75th: 27.0
		24-h cold season	12.2 (7.4)	75th: 17.0
Von Klot et al. (2005)	Multicity, Europe	8 h max warm season	16.4 - 28.0	
Wellenius et al. (2005)	Allegheny County, PA	24-h	24.3 (12.2)	75th: 32.0
Yang (2008)	Taipei, Taiwan	24-h	21.0	75th: 26.3 Max: 62.8
Zanobetti and Schwartz (2006)	Boston, MA	24-h	22.4*	75th: 31.0

*Median presented (information on mean not given). NR: Not reported

and dysrhythmia). Data on over 4 million ED visits from 31 hospitals were collected from January 1993 to August 2000. Ozone was monitored from March to October. This study was a re-analysis of a time series study conducted to assess the main effects of air pollutants on cardiovascular ED visits in Atlanta (Tolbert et al., 2007; Metzger et al., 2004). In the initial study, no evidence of associations was observed between O_3 and all CVD visits or visits for CVD subgroups, such as dysrhythmia, CHF, ischemic heart disease (IHD), and peripheral vascular and cerebrovascular disease. The relative risk for all CVD visits was 1.01 (95% CI: 0.99, 1.02) for a 20 ppb increase in the 3-day moving avg (lags 0-2 days) of 8-h O_3 (Metzger et al., 2004). Similar to the initial investigation using a time-series analysis, no evidence of an association was observed for the O_3 3-day moving average and CVD visits among the entire population using the case-crossover design (Peel et al., 2007). However, the relationship between O_3 and peripheral and cerebrovascular disease visits was stronger among patients with comorbid COPD (OR: 1.19 [95% CI: 1.03-1.36] per 20 ppb, lag 0-2 days) as compared to patients without COPD (OR: 1.01 [95% CI: 0.97-1.04] per 20 ppb, lag 0-2 days). The same research group expanded upon the number of Atlanta hospitals providing ED visit data (41 hospitals) as well as the length of the study period (1993-2004) (Tolbert et al., 2007). Again, models assessing the health effects of O_3 utilized data collected from March through October. Similar to the results presented by Metzger et al. (2004) and Peel et al. (2007) among the entire study population, no evidence of associations was observed for O_3 and CVD visits (Tolbert et al., 2007).

A study of HAs for MI was performed using a statewide registry from New Jersey between January 2004 and December 2006 (Rich et al., 2010). Using a case-crossover design, the association between the previous 24 hr O_3 concentration and transmural infarction (n=1,003) was examined. No association was observed (OR: 0.94 [95% CI: 0.79, 1.13] per 20 ppb) and this did not change with the inclusion of $PM_{2.5}$ in the model.

Cakmak et al, (2006b) investigated the relationship between gaseous air pollutants and cardiac hospitalizations in 10 large Canadian cities using a time-series approach. A total of 316,234 hospital discharge records for primary diagnosis of congestive heart failure, ischemic heart disease, or dysrhythmia were obtained from April 1993 through March 2000. Correlations between pollutants varied substantially across cities, which could partially explain discrepancies in effect estimates observed across the cities. In addition, pollutant lags differed across cities; the average lag for O_3 was 2.9 days. The pooled effect estimate for a 20 ppb increase in the daily 1-h max O_3 concentration and the percent change in hospitalizations among all 10 cities was 2.3 (95% CI: 0.11, 4.50) in an all-year analysis. The authors reported no evidence of effect modification by gender, neighborhood-level education, or neighborhood-level income. A similar multicity time-series study was conducted using nearly 400,000 ED visits to 14 hospitals in seven

Canadian cities from 1992 to 2003 (Stieb et al., 2009). Primary analyses considered daily O_3 single day lags of 0-2 days; in addition, sub-daily lags of 3-h avg concentrations up to 12 hours before presentation to the ED were considered. Seasonal variation was assessed by stratifying analyses by warm and cold seasons. No evidence of effect of O_3 on CVD ED visits was observed. One negative, statistically significant association was reported between a 1-day lag of O_3 and visits for angina/myocardial infarction. Ozone was negatively correlated with many of the other pollutants, particularly during the cold season.

The effect of air pollution on daily ED visits for ischemic stroke (n=10,881 visits) in Edmonton, Canada was assessed from April 1992 through March 2002 (Szyszkowicz, 2008). A 26.4% (95% CI: 3.16-54.5) increase in stroke ED visits was associated with a 20 ppb increase in O_3 at lag 1 among men aged 20-64 years in the warm season. No associations were present among women or among men age 65 and older. In addition, no associations were observed for the cold season or for other lags (lag 0 or lag 2). A similar investigation over the same time period in Edmonton, Canada, assessed the relationship between air pollutants and ED visits for stroke (ischemic stroke, hemorrhagic stroke, and transient ischemic attack) among those 65 years of age and older using a case-crossover framework (Villeneuve et al., 2006a). Two-pollutant models were assessed. No evidence of association was reported for O_3 and stroke hospitalization (Villeneuve et al., 2006a).

Additional studies reported no evidence of an association between O_3 concentrations and ED visits, hospitalizations, or symptoms leading to hospitalization (Symons et al., 2006; Zanobetti and Schwartz, 2006; Wellenius et al., 2005). Symons et al. (2006) used a case-crossover framework to assess the relationship between air pollutants and the onset of symptoms (dyspnea) severe enough to lead to hospitalization (through the ED) for congestive heart failure. The study was conducted from April to December of 2002 in Baltimore, Maryland. Exposures were assigned using 3 index times: 8-h and 24-h periods prior to symptom onset and date of hospital admission. No evidence of association was reported for O_3 concentrations. Although seasonal variation was not assessed, the time frame for the study did not involve an entire year (April to December). Wellenius et al. (2005) investigated the association between air pollutants and congestive heart failure hospitalization among Medicare beneficiaries in Pittsburgh, Pennsylvania from 1987 to 1999 utilizing a case-crossover framework. A total of 55,019 admissions from the emergency room with a primary discharge diagnosis of CHF were collected. No evidence of an association was reported for O_3 and CHF hospitalization (Wellenius et al., 2005). Finally, Zanobetti and Schwartz (2006) assessed the relationship between air pollutants and hospital admissions through the ED for myocardial infarction and pneumonia among patients aged 65 and older residing in the greater Boston area (1995-1999) using a case-crossover framework with control days in the same month matched on temperature.

Pollution exposures were assigned for the same day and for the mean of the exposure the day of and the day before the admission. Ozone was not associated with MI admissions in all-year and seasonal analyses.

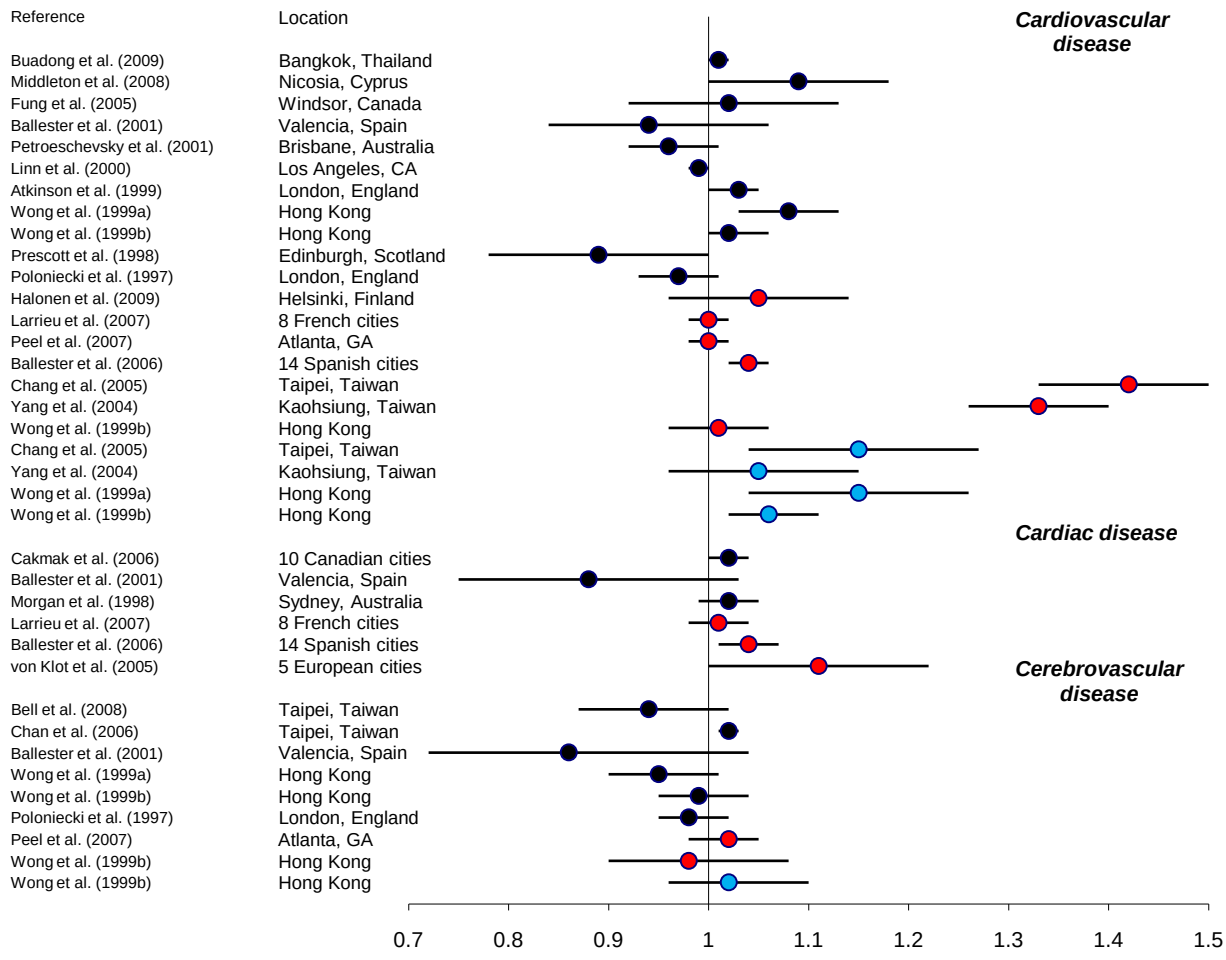
Several recent studies have examined the relationship between air pollution and CVD hospital admissions and/or emergency department visits in Asia. Of note, some areas of Asia have a more tropical climate than the U.S. and do not experience similar seasonal changes. In Taiwan, fairly consistent positive associations have been reported for O_3 and congestive heart failure hospital admissions (for single- and copollutant models) in Taipei on warm days (Yang, 2008) and in Kaohsiung (Lee et al., 2007); cerebrovascular disease ED visits (for lag 0 single- and two-pollutant models but not other lags or 3-pollutant models) in Taipei (Chan et al., 2006); and arrhythmia ED visits in Taipei among those without comorbid conditions (Chiu et al., 2009; Lee et al., 2008a) and in Taipei on warm days among those with and without comorbid conditions (Lee et al., 2008a; Jansson et al., 2001). However, one study in Taiwan did not shown an association. Bell et al. (2008) reported no evidence of an O_3 association with hospital admissions for ischemic heart disease or cerebrovascular disease. Three studies based in Asia but outside Taiwan were performed. First, a Hong Kong-based investigation (Wong et al., 2009) reported no consistent evidence of a modifying effect of influenza on the relationship between O_3 and CVD admissions. Second, among elderly populations in Thailand, O_3 was associated with CVD visits, but this association was not detected among younger age groups (15-64) (Buadong et al., 2009). Third, a study performed in Seoul, Korea reported a positive association between O_3 levels and HAs for ischemic heart disease; the association was slightly greater among those over 64 years of age (Lee et al., 2003b).

Positive effects of O_3 on CVD hospital admissions and/or ED visits have been reported in other areas of the world as well (Azevedo et al., 2011; Linares and Diaz, 2010; Middleton et al., 2008; Turner et al., 2007; Yallop et al., 2007; Ballester et al., 2006; De Pablo et al., 2006; Von Klot et al., 2005), although not consistently as some studies reported no association (Oudin et al., 2010; Halonen et al., 2009; Larrieu et al., 2007; Barnett et al., 2006; Hinwood et al., 2006; Lanki et al., 2006; Hosseinpoor et al., 2005; Simpson et al., 2005).

A couple of studies (U.S. and Australia) have examined cardiac arrests where emergency services attempted treatment/resuscitation. No evidence of an association between O_3 and out-of-hospital cardiac arrest was observed (Dennekamp et al., 2010; Silverman et al., 2010).

An increasing number of air pollution studies have investigated the relationship between O_3 concentrations and CVD hospital admissions and/or ED visits. As summarized in the 2006 O_3 AQCD, some, especially those reporting results stratified by season (or

temperature) or comorbid conditions have reported positive associations. However, even studies performing these stratified analyses are not consistent and the overall evidence remains inconclusive regarding the effects of O_3 on CVD HAs and ED visits. These HA and ED visit studies are summarized in Figures 6-22 through 6-26, which depict the associations for studies in which numerical associations were presented for an overall study population. Tables 6-34 through 6-38 provide the numerical results displayed in the figures.



Note: Increase in O_3 standardized to 20 ppb for 24-h avg period, 30 ppb for 8-h avg period, and 40 ppb for 1-h avg period. Ozone concentrations in ppb. Seasons depicted by colors – black: all year; red: warm season; light blue: cold season. Age groups of study populations were not specified or were adults with the exception of Fung et al. (2005), Wong et al. (1999b), and Prescott et al. (1998), which included only individuals aged 65+.

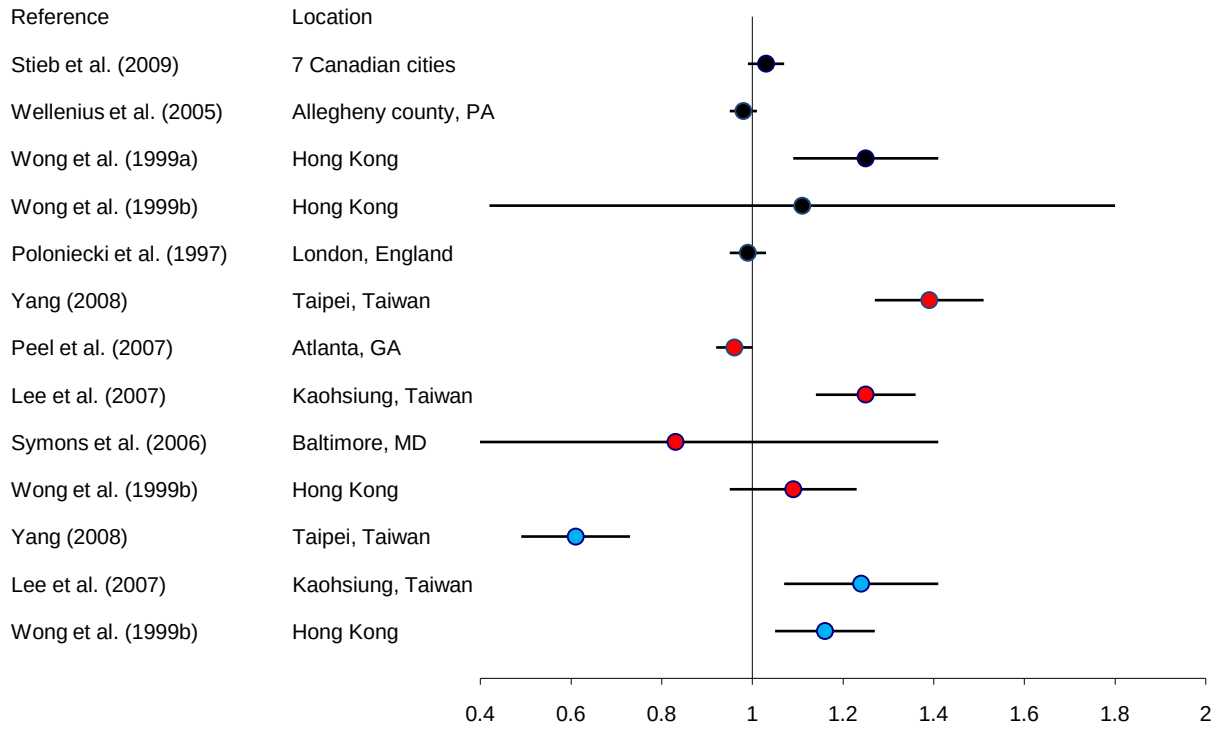
Figure 6-22 Odds ratio (95% CI) per increment ppb increase in ozone for over all cardiovascular ED visits or HAs.

Table 6-34 Odds ratio (95% CI) per increment ppb increase in ozone for overall cardiovascular ED visits or HAs in studies presented in Figure 6-22

Study	Location	Outcome	Averaging Time	Standardized Estimate (95% CI)
Atkinson et al. (2006a)	London, England	Cardiovascular disease	8-h	1.03 (1.00, 1.05)
Ballester et al. (2006)	Multicity, Spain	Cardiovascular disease	8-h warm season	1.04 (1.02 , 1.06)
		Cardiac disease	8-h warm season	1.04 (1.01, 1.07)
Ballester et al. (2006)	Valencia, Spain	Cardiovascular disease	8-h	0.94 (0.84, 1.06)
		Cardiac disease	8-h	0.88 (0.75, 1.03)
		Cerebrovascular disease	8-h	0.86 (0.72, 1.04)
Bell et al. (2008)	Taipei, Taiwan	Cerebrovascular disease	24-h	0.94 (0.87, 1.02)
Buadong et al. (2009)	Bangkok, Thailand	Cardiovascular disease	1-h	1.01 (1.00, 1.02)
Cakmak et al. (2006a)	Multicity, Canada	Cardiac disease	1-h max	1.02 (1.00, 1.04)
Chan et al. (2006)	Taipei, Taiwan	Cerebrovascular disease	1-h max	1.02 (1.01, 1.03)
Chang et al. (2005)	Taipei, Taiwan	Cardiovascular disease	24-h warm season	1.42 (1.33 , 1.50)
			24-h cold season	1.15 (1.04, 1.27)
Fung et al. (2006a)	Windsor, Canada	Cardiovascular disease	1-h	1.02 (0.92, 1.13)
Halonen et al. (2009)	Helsinki, Finland	Cardiovascular disease	8-h max warm season	1.05 (0.96, 1.14)
Larrieu et al. (2007)	Multicity France	Cardiac disease	8-h max warm season	1.01 (0.98, 1.04)
Linn et al. (2006a)	Los Angeles, California	Cardiovascular disease	24-h	0.99 (0.98, 1.00)
Middleton et al. (2008)	Nicosia, Cyprus	Cardiovascular disease	8-h max	1.09 (1.00, 1.18)
Morgan et al. (2008)	Sydney, Australia	Cardiac disease	1-h max	1.02 (0.99, 1.05)
Peel et al. (2007)	Atlanta, GA	Cardiovascular disease	8-h warm season	1.00 (0.98, 1.02)
		Cerebrovascular disease	8-h warm season	1.02 (0.98, 1.05)
Petroeschevsky et al. (2001)	Brisbane, Australia	Cardiovascular disease	8-h	0.96 (0.92, 1.01)
Poloniecki et al. (2006a)	London, England	Cardiovascular disease	8-h	0.97 (0.93, 1.01)
		Cerebrovascular disease	8-h	0.98 (0.95, 1.02)
Prescott et al. (1998)	Edinburgh, Scotland	Cardiovascular disease	24-h	0.89 (0.78, 1.00)
Von Klot et al. (2005)	Multicity, Europe	Cardiac disease	8-h max warm season	1.11 (1.00, 1.22)
Wong et al. (1999b)	Hong Kong	Cardiovascular disease	24-h	1.08 (1.03 , 1.13)
			24-h cold season	1.15 (1.04, 1.26)
		Cerebrovascular disease	24-h	0.95 (0.90, 1.01)
Wong et al. (1999a)	Hong Kong	Cardiovascular disease	24-h	1.02 (1.03 , 1.06)
			24-h warm season	1.01 (0.96, 1.06)
			24-h cold season	1.06 (1.02, 1.11)
		Cerebrovascular disease	24-h	0.99 (0.95, 1.04)
			24-h warm season	0.98 (0.90, 1.08)
			24-h cold season	1.02 (0.96, 1.10)
Yang et al. (2005)	Kaohsiung, Taiwan	Cardiovascular disease	24-h warm season	1.33 (1.26 , 1.40)
			24-h cold season	1.05 (0.96, 1.15)

Note: Increase in O_3 standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb. Age groups of study populations were not specified or were adults with the exception of Fung et al. (2006a), Wong et al. (1999a), and Prescott et al. (1998), which included only individuals aged 65+.

Warm season defined as: March-October (Peel et al., 2007), May-October (Ballester et al., 2005; Wong et al., 1999a), May-September (Halonen et al., 2009), April-September (Larrieu et al., 2007; Von Klot et al., 2005), ≥ 20°C (Chang et al., 2005) and ≥ 25°C (Yang et al., 2004). Cold season defined as: November-April (Wong et al., 1999a), <20°C (Chang et al., 2005) and <25°C (Yang et al., 2004), December-March (Wong et al., 1999b)



Note: Increase in O_3 standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb. Seasons depicted by colors: black: all year; red: warm season; light blue: cold season. Outcomes were all congestive heart failure, with the exception of Symons et al. (2006), which examined onset of congestive heart failure symptoms leading to a heart attack. Age groups of study populations were not specified or were adults with the exception of Wellenius et al. (2005) and Wong et al. (1999a), which included only individuals aged 65+.

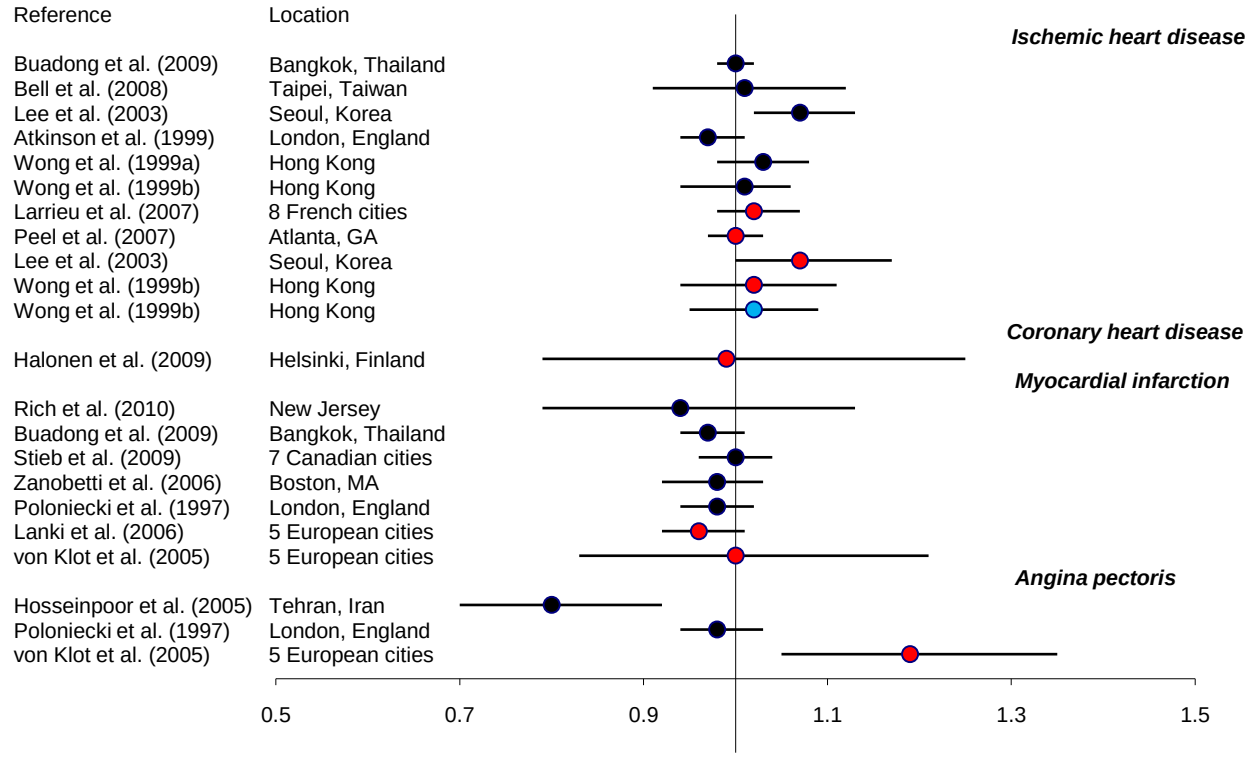
Figure 6-23 Odds Ratio (95% CI) per increment ppb increase in ozone for congestive heart failure ED visits or HAs.

Table 6-35 Odds Ratio (95% CI) per increment ppb increase in ozone for congestive heart failure ED visits or HAs for studies in Figure 6-23

Study	Location	Outcome	Averaging Time	Standardized Estimate (95% CI)
Lee et al. (2007)	Kaohsiung, Taiwan	congestive heart failure	24-h warm season	1.25 (1.15, 1.36)
		congestive heart failure	24-h cold season	1.24 (1.09, 1.41)
Peel et al. (2007)	Atlanta, GA	congestive heart failure	8-h warm season	0.96 (0.93, 1.00)
Poloniecki et al. (1997)	London, England	congestive heart failure	8-h	0.99 (0.95, 1.03)
Stieb et al. (2009)	Multicity, Canada	congestive heart failure	24-h	1.03 (0.98, 1.07)
Symons et al. (2006)	Baltimore, MD	onset of congestive heart failure symptoms leading to heart attack	8-h warm season	0.83 (0.49, 1.41)
Wellenius et al. (2005)	Allegheny county, PA	congestive heart failure	24-h	0.98 (0.96, 1.01)
Wong et al. (1999a)	Hong Kong	congestive heart failure	24-h	1.11 (1.04, 1.80)
			24-h warm season	1.09 (0.96, 1.23)
			24-hcold season	1.16 (1.06, 1.27)
Yang (2008)	Taipei, Taiwan	congestive heart failure	24-h warm season	1.39 (1.27, 1.51)
		congestive heart failure	24-h cold season	0.61 (0.52, 0.73)
Wong et al. (1999b)	Hong Kong	congestive heart failure	24-h	1.25 (1.11, 1.41)

Note: Increase in O_3 standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb. Outcomes were all congestive heart failure, with the exception of Symons et al. (2006), which examined onset of congestive heart failure symptoms leading to a heart attack. Age groups of study populations were not specified or were adults with the exception of Wellenius et al. (2005) and Wong et al. (1999a), which included only individuals aged 65+.

Warm season defined as: March-October (Peel et al., 2007), April-November (Symons et al., 2006), May-October (Wong et al., 1999a) ≥ 20°C (Yang, 2008), and >25°C (Lee et al., 2007). Cold season defined as: November-April (Wong et al., 1999a), <20°C (Yang, 2008), and <25°C (Lee et al., 2007).



Note: Increase in O_3 standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb. Seasons depicted by colors: black: all year; red: warm season; light blue: cold season. Age groups of study populations were not specified or were adults with the exception of Wong et al. (1999a) and Atkinson et al. (2006a), which included only individuals aged 65+.

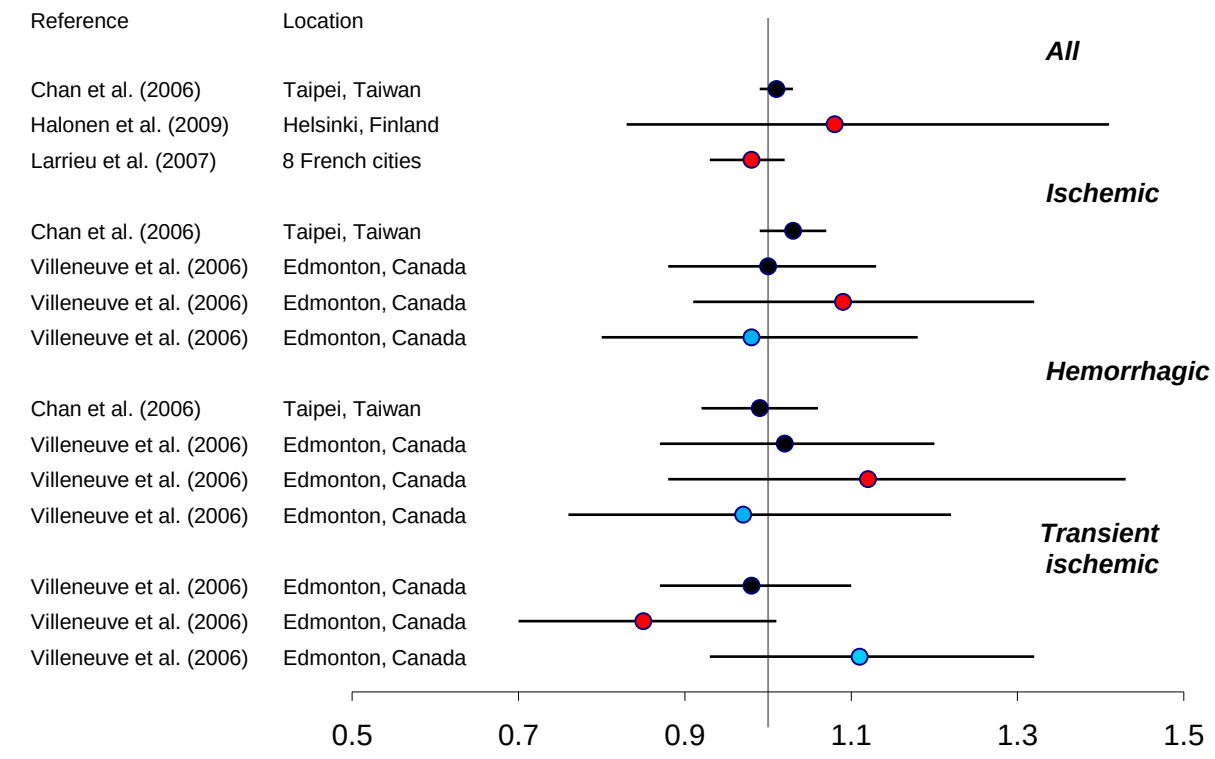
Figure 6-24 Odds Ratio (95% confidence interval) per increment ppb increase in ozone for ischemic heart disease, coronary heart disease, myocardial infarction, and angina pectoris ED visits or HAs.

Table 6-36 Odds Ratio (95% CI) per increment ppb increase in ozone for ischemic heart disease, coronary heart disease, myocardial infarction, and angina pectoris ED visits or HAs for studies presented in Figure 6-24

Study	Location	Outcome	Averaging Time	Standardized Estimate (95% CI)
Atkinson et al. (1999)	London, England	Ischemic heart disease	8-h	0.97 (0.94, 1.01)
Bell et al. (2008)	Taipei, Taiwan	Ischemic heart disease	24-h	1.01 (0.91, 1.12)
Buadong et al. (2009)	Bangkok, Thailand	Ischemic heart disease	1-h	1.00 (0.98, 1.02)
		Myocardial infarction	1-h	0.97 (0.94, 1.01)
Halonen et al. (2009)	Helsinki, Finland	Coronary heart disease	8-h max warm season	0.99 (0.79, 1.25)
Hosseinpoor et al. (2005)	Tehran, Iran	Angina	8-h max	0.80 (0.70, 0.92)
Lanki et al. (2006)	Multicity, Europe	Myocardial infarction	8-h max warm season	0.96 (0.92, 1.01)
Larrieu et al. (2007)	Multicity France	Ischemic heart disease	8-h max warm season	1.02 (0.98, 1.07)
Lee et al. (2003b)	Seoul, Korea	Ischemic heart disease	1-h max	1.07 (1.02, 1.13)
		Ischemic heart disease	1-h max warm season	1.07 (1.00, 1.17)
Peel et al. (2007)	Atlanta, GA	Ischemic heart disease	8-h warm season	1.00 (0.97, 1.03)
Poloniecki et al. (1997)	London, England	Myocardial infarction	8-h	0.98 (0.94, 1.02)
		Angina	8-h	0.98 (0.94, 1.03)
Rich et al. (Rich et al., 2010)	New Jersey	Myocardial infarction	24-h	0.94 (0.79, 1.13)
Stieb et al. (2009)	Multicity, Canada	Myocardial infarction	2-h	1.00 (0.96, 1.04)
Von Klot et al. (2005)	Multicity, Europe	Myocardial infarction	8-h max warm season	1.00 (0.83, 1.21)
		Angina	8-h max warm season	1.19 (1.05, 1.35)
Wong et al. (2009)	Hong Kong	Ischemic heart disease	24-h	1.01 (0.94, 1.06)
			24-h warm season	1.02 (0.94, 1.11)
			24-h cold season	1.02 (0.95, 1.09)
Wong et al. (2008)	Hong Kong	Ischemic heart disease	24-h	1.03 (0.98, 1.08)
Zanobetti and Schwartz (2006)	Boston, MA	Myocardial infarction	24-h	0.98 (0.92, 1.03)

Note: Increase in O_3 standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb. Age groups of study populations were not specified or were adults with the exception of Wong et al. (1999a) and Atkinson et al. (2006a), which included only individuals aged 65+.

Warm season defined as: March-October (Peel et al., 2007), June-August (Lee et al., 2003b), May-September (Halonen et al., 2009), May-October (Buadong et al., 2009), and April-September (Larrieu et al., 2007; Lanki et al., 2006; Von Klot et al., 2005). Cold season defined as: November-April (Buadong et al., 2009)



Note: Increase in O_3 standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb. Seasons depicted by colors: black: all year; red: warm season; light blue: cold season. Age groups of study populations were not specified or were adults with the exception of Villeneuve et al. (2006a), which included only individuals aged 65+, and Chan et al. (2006), which included only individuals aged 50+.

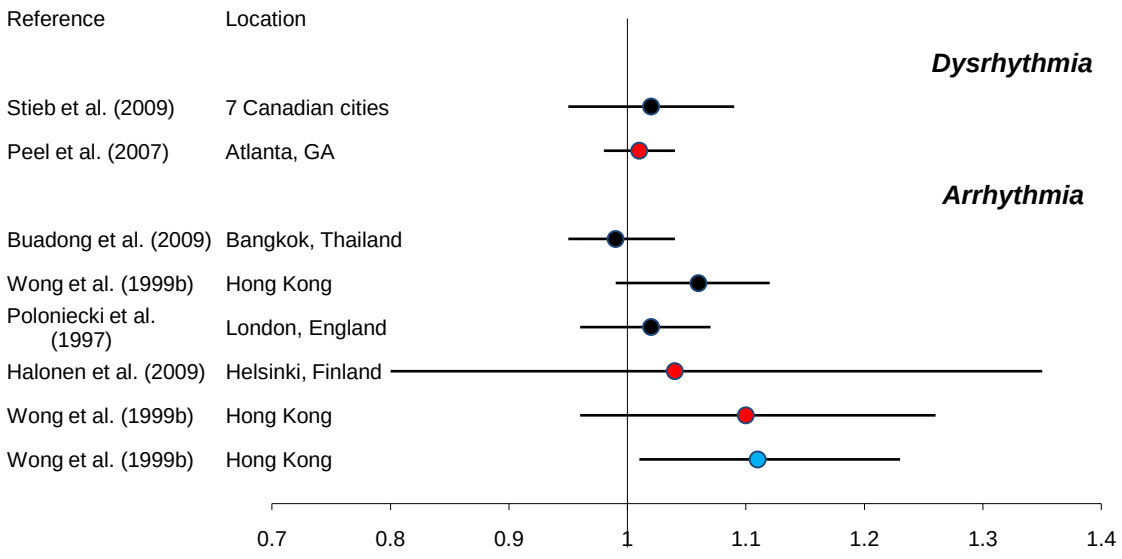
Figure 6-25 Odds Ratio (95% confidence interval) per increment ppb increase in ozone for stroke ED visits or HAs.

Table 6-37 Odds Ratio (95% CI) per increment ppb increase in ozone for stroke ED visits or HAs for studies presented in Figure 6-25

Study	Location	Outcome	Averaging Time	Standardized Estimate (95% CI)
Chan et al. (2006)	Taipei, Taiwan	All/non-specified stoke	1-h max	1.01 (0.99 ,1.03)
		Ischemic stroke	1-h max	1.03 (0.99, 1.07)
		Hemorrhagic stroke	1-h max	0.99 (0.92, 1.06)
Halonen et al. (2009)	Helsinki, Finland	All/non-specified stoke	8-h max warm season	1.08 (0.83, 1.41)
Larrieu et al. (2007)	Multicity, France	All/non-specified stoke	8-h max warm season	0.98 (0.93 , 1.02)
Villeneuve et al. (2006a)	Edmonton, Canada	Ischemic stroke	24-h	1.00 (0.88, 1.13)
		Ischemic stroke	24-h warm season	1.09 (0.91, 1.32)
		Ischemic stroke	24-h cold season	0.98 (0.80, 1.18)
		Hemorrhagic stroke	24-h	1.02 (0.87, 1.20)
		Hemorrhagic stroke	24-h warm season	1.12 (0.88, 1.43)
		Hemorrhagic stroke	24-h cold season	0.97 (0.76, 1.22)
		Transient ischemic stroke	24-h	0.98 (0.87, 1.10)
		Transient ischemic stroke	24-h warm season	0.85 (0.70, 1.01)
		Transient ischemic stroke	24-h cold season	1.11 (0.93, 1.32)

Note: Increase in O_3 standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb. Age groups of study populations were not specified or were adults with the exception of Villeneuve et al. (2006a), which included only individuals aged 65+, and Chan et al. (2006), which included only individuals aged 50+.

Warm season defined as: May-September (Halonen et al., 2009), and April-September (Larrieu et al., 2007; Villeneuve et al., 2006a). Cold season defined as: October-March (Villeneuve et al., 2006a).



Note: Increase in O_3 standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb. Seasons depicted by colors: black: all year; red: warm season; light blue: cold season. Age groups of study populations were not specified or were adults with the exception of Wong et al. (1999a), which included only individuals aged 65+.

Figure 6-26 Odds Ratio (95% confidence interval) per increment ppb* increase in ozone for arrhythmia and dysrhythmia ED visits or HAs.

Table 6-38 Odds Ratio (95% CI) per increment ppb* increase in ozone for arrhythmia and dysrhythmia ED visits or HAs for studies presented in Figure 6-26

Study	Location	Outcome	Averaging Time	Standardized Estimate (95% CI)
Buadong et al. (2009)	Bangkok, Thailand	Arrhythmia	1-h	0.99 (0.95, 1.04)
Halonen et al. (2009)	Helsinki, Finland	Arrhythmia	8-h max warm season	1.04 (0.80, 1.35)
Peel et al. (2007)	Atlanta, GA	Dysrhythmia	8-h warm season	1.01 (0.98, 1.04)
Poloniecki et al. (2009)	London, England	Arrhythmia	8-h	1.02 (0.96, 1.07)
Stieb et al. (2009)	Multicity, Canada	Dysrhythmia	24-h	1.02 (0.95, 1.09)
Wong et al. (2009)	Hong Kong	Arrhythmia	24-h	1.06 (0.99, 1.12)
			24-h warm season	1.10 (0.96, 1.26)
			24-h cold season	1.11 (1.01, 1.23)

Note: Increase in O_3 standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb. Age groups of study populations were not specified or were adults with the exception of (Wong et al., 1999a), which included only individuals aged 65+. Warm season defined as: March-October (Peel et al., 2007), May-October (Wong et al., 1999a) and May-September (Halonen et al., 2009). Cold season defined as: November-April (Wong et al., 1999a).

6.3.2.8 Cardiovascular Mortality

As discussed within this section (Section 6.3), epidemiologic studies provide inconsistent evidence of an association between short-term O_3 exposure and cardiovascular effects. However, toxicological studies have demonstrated O_3-induced cardiovascular effects, specifically enhanced atherosclerosis and ischemia, which could lead to death. The 2006 O_3 AQCD

provided evidence, primarily from single-city studies, of consistent positive associations between short-term O_3 exposure and cardiovascular mortality. Recent multicity studies conducted in the U.S., Canada, and Europe further confirm the association between short-term O_3 exposure and cardiovascular mortality.

As discussed in Section 6.2.7.2, the APHENA study (Katsouyanni et al., 2009) also examined associations between short-term O_3 exposure and mortality and found consistent positive associations for cardiovascular mortality in all-year analyses with associations persisting in analyses restricted to the summer season. Additional multicity studies from the U.S. (Zanobetti and Schwartz, 2008b), Europe (Samoli et al., 2009), Italy (Stafoggia et al., 2010), and Asia (Wong et al., 2010) that conducted summer season and/or all-year analyses provide additional support for an association between short-term O_3 exposure and cardiovascular mortality (Figure 6-37).

Of the studies evaluated, only the APHENA study (Katsouyanni et al., 2009) and the Italian multicity study (Stafoggia et al., 2010) conducted an analysis of the potential for copollutant confounding of the O_3-cardiovascular mortality relationship. In the European

dataset, when focusing on the natural spline model with 8 df/year (Section 6.2.7.2) and lag 1 results in order to compare results across study locations (Section 6.6.2.1), cardiovascular mortality risk estimates were robust to the inclusion of PM_{10} in copollutant models in all-year analyses with more variability in the Canadian and U.S. datasets (i.e., cardiovascular O_3 mortality risk estimates were reduced or increased in copollutant models). In summer season analyses, cardiovascular O_3 mortality risk estimates were robust in the European dataset and attenuated but remained positive in the U.S. dataset. Similarly, in the Italian multicity study (Stafoggia et al., 2010), which was limited to the summer season, cardiovascular mortality risk estimates were robust to the inclusion of PM_{10} in copollutant models. Based on the APHENA and Italian multicity results, O_3 cardiovascular mortality risk estimates appear to be robust to inclusion of PM_{10} in copollutant models. However, in the U.S. and Canadian datasets there was evidence that O_3 cardiovascular mortality risk estimates are moderately to substantially sensitive (e.g., increased or attenuated) to PM_{10}. The mostly every-6th-day sampling schedule for PM_{10} in the Canadian and U.S. datasets greatly reduced their sample size and limits the interpretation of these results.

6.3.2.9 Summary of Epidemiologic Studies

Overall, the available body of evidence examining the relationship between short-term exposures to O_3 and cardiovascular morbidity is inconsistent. Differences in exposure metrics and windows of exposure, a wide variety of biomarkers considered, and a lack of consistency among definitions used for specific cardiovascular disease endpoints (e.g. arrhythmias, HRV) make comparisons across studies difficult. In addition, several investigators reporting associations between O_3 and cardiovascular morbidity postulate that O_3 may be acting as a proxy for sulfate; differences reported across multicity studies and across studies conducted in specific cities/regions point to the importance of considering multipollutant relationships that vary across geographic regions. Additionally mortality studies indicate a consistent positive association between O_3 and cardiovascular mortality.

6.3.3 Toxicology

6.3.3.1 Summary of Findings from Previous Ozone AQCDs

In the previous O_3 AQCDs (U.S. EPA, 2006b, 1996a) experimental animal studies have reported relatively few cardiovascular system alterations after exposure to O_3 and other

photochemical oxidants. The limited amount of research directed at examining O_3-induced cardiovascular effects has primarily found alterations in heart rate (HR) and BP after O_3 exposure. A group of studies (Arito et al., 1992; Arito et al., 1990; Uchiyama and Yokoyama, 1989; Yokoyama et al., 1989; Uchiyama et al., 1986) report O_3 (0.1-1.0 ppm) exposure in rats decreased core temperature (T_{CO}), HR, and mean arterial pressure (MAP). However, these cardiovascular responses to O_3 could be attenuated by increased ambient temperatures, exhibited adaptation, and were the result of the rodent hypothermic response (Watkinson et al., 2003; Watkinson et al., 1993). This hypothermic response could be an attempt to minimize the irritant effects of O_3 inhalation, serving as a physiological and behavioral defense mechanism (Iwasaki et al., 1998; Arito et al., 1997). As humans do not appear to exhibit decreased HR, MAP, and T_{CO} with routine environmental exposures to O_3, caution must be used in extrapolating the results of these animal studies to humans (Section 6.3.1).

Other studies have shown that O_3 can increase BP in animal models. Rats exposed to 0.6 ppm O_3 for 33 days had increased systolic pressure and HR (Revis et al., 1981). Increased BP triggers the release of atrial natriuretic factor (ANF), which has been found in increased levels in the heart, lungs, and circulation of O_3 exposed (0.5 ppm) rats (Vesely et al., 1994a, b, c). High concentration O_3 exposure (1.0 ppm) has also been found to lead to heart and lung edema (Friedman et al., 1983), which could be the result of increased ANF levels. Thus, O_3 may increase blood pressure and HR, leading to increased ANF and tissue edema.

The toxicological studies that have examined the effect of O_3 on the cardiovascular system demonstrate O_3-induced responses, but it remains unclear if the mechanism is through a reflex response or due to O_3 reaction products, which have been sparsely studied. Oxysterols derived from cholesterol ozonation, such as β-epoxide and 5β,6β-epoxycholesterol (and its metabolite cholestan-6-oxo-3,5-diol), have been implicated in inflammation associated with cardiovascular disease (Pulfer et al., 2005; Pulfer and Murphy, 2004). Two other cholesterol ozonolysis products, atheronal-A and -B (e.g. cholesterol secoaldehyde), have been found in human atherosclerotic plaques and shown *in vitro* to induce foam cell formation and induce cardiomyocyte apoptosis and necrosis (Sathishkumar et al., 2005; Wentworth et al., 2003); however, these products have not been found in the lung compartment or systemically after O_3 exposure. The ability to form these cholesterol ozonation products in the circulation in the absence of O_3 exposure complicates their implication in O_3 induced cardiovascular disease.

Although it has been proposed that O_3 reaction products released after the interaction of O_3 with ELF constituents (See Section 5.1.2 on O_3 interaction with ELF) are responsible for systemic effects, it is not known whether they gain access to the vascular space.

Alternatively, extrapulmonary release of diffusible mediators, such as cytokines or endothelins, may initiate or propagate inflammatory responses in the vascular or systemic compartments (Cole and Freeman, 2009) (Section 5.1.9.1). Ozone reacts within the lung to amplify ROS production, induce pulmonary inflammation, and activate inflammatory cells, resulting in a cascading proinflammatory state and extrapulmonary release of diffusible mediators that could lead to cardiovascular injury.

6.3.3.2 Recent Cardiovascular Toxicology Studies

According to recent short-term O_3 exposure animal toxicology studies, O_3 plays a role in inducing vascular oxidative stress and proinflammatory mediators, altering HR and HRV, and regulating the pulmonary endothelin system (study details are provided in Table 6-39). A number of these effects were variable between strains examined, suggesting a genetic component to development of O_3 induced cardiovascular effects. Further, new studies provide evidence that extended O_3 exposure enhances susceptibility to ischemia-reperfusion (I/R) injury and atherosclerotic lesion development. Still, few studies have investigated the role of O_3 reaction products in these processes, but more evidence is provided for elevated inflammatory and reduction-oxidation (redox) cascades known to initiate these cardiovascular pathologies.

A recent study in young mice and rhesus monkeys examined the effects of short-term O_3 exposure on a number of cardiovascular endpoints (Chuang et al., 2009). Mice exposed to O_3 for 5 days had increased HR as well as mean and diastolic blood pressure. Increased blood pressure could be explained by the inhibition in endothelial-dependent (acetylcholine) vasorelaxation from decreased bioavailability of aortic nitric oxide (·NO). Ozone caused a decrease in aortic NO_X (nitrite and nitrate levels) and a decrease in total, but not phosphorylated, endothelial nitric oxide synthase (eNOS). Ozone also increased vascular oxidative stress in the form of increased aortic and lung lipid peroxidation (F2-isoprostane), increased aortic protein nitration (3-nitrotyrosine), decreased aortic superoxide dismutase (SOD2) protein and activity, and decreased aortic aconitase activity, indicating specific inactivation by O_2^- and $ONOO^-$. Mitochondrial DNA (mtDNA) damage was also used as a measure of oxidative and nitrative stress in mice and infant rhesus monkeys exposed to O_3. Chuang et al. (2009) observed that MtDNA damage accumulated in the lung and aorta of mice after 1 and 5 days of O_3 exposure and in the proximal and distal aorta of O_3 treated nonhuman primates. Additionally, genetically hyperlipidemic mice exposed to O_3 for 8 weeks had increased aortic atherosclerotic lesion area (Section 7.3.1), which may be associated with the short-term exposure changes discussed. Overall, this study suggests that O_3 initiates an oxidative environment by increasing O_2^- production, which leads to mtDNA damage and ·NO

consumption, known to perturb endothelial function (Chuang et al., 2009). Endothelial dysfunction is characteristic of early and advanced atherosclerosis and coincides with impaired vasodilation and blood pressure regulation.

Vascular occlusion resulting from atherosclerosis can block blood flow causing ischemia. The restoration of blood flow in the vessel or reperfusion can cause injury to the tissue from subsequent inflammation and oxidative damage. Perepu et al. (2010) observed that O_3 exposure enhanced the sensitivity to myocardial I/R injury in rats while increasing oxidative stress levels and pro-inflammatory mediators and decreasing production of anti-inflammatory proteins. Ozone was also found to decrease the left ventricular developed pressure, rate of change of pressure development, and rate of change of pressure decay while increasing left ventricular end diastolic pressure in isolated perfused hearts. In this ex vivo heart model, O_3 induced oxidative stress by decreasing SOD enzyme activity and increasing malondialdehyde levels. Ozone also elicited a proinflammatory state which was evident by an increase in TNF-α and a decrease in the anti-inflammatory cytokine IL-10. Perepu et al. (2010) concluded that O_3 exposure may result in a greater I/R injury.

Heart Rate and Heart Rate Variability

Strain differences in HR and HRV have been observed in response to a 2-h O_3 pretreatment followed by exposure to carbon black (CB) in mice (C3H/HeJ [HeJ], C57BL/6J [B6], and C3H/HeOuJ [OuJ]) (Hamade and Tankersley, 2009; Hamade et al., 2008). These mice strains were chosen from prior studies on lung inflammatory and hyperpermeability responses to be susceptible (B6 and OuJ) and resistant (HeJ) to O_3-induced health effects (Kleeberger et al., 2000). HR decreased during O_3 pre-exposure for all strains, but recovered during the CB exposure (Hamade et al., 2008). This is contrary to the tachycardia that was reported in 6-week-old B6 mice treated on 1 or 5 days with O_3, as described above (Chuang et al., 2009). Percent change in HRV parameters, SDNN (indicating total HRV) and rMSSD (indicating beat-to-beat HRV), were increased in both C3H mice strains, but not B6 mice, during O_3 pre-exposure and recovered during CB exposure when compared to the filtered air group. The two C3H strains differ by a mutation in the Toll-like receptor 4 (TLR4) gene, but these effects did not seem to be related to this mutation since similar responses were observed. Hamade et al. (2008) speculate that the B6 and C3H strains differ in mechanisms of HR response after O_3 exposure between withdrawal of sympathetic tone and increase of parasympathetic tone; however, no direct evidence for this conclusion was reported. The strain differences observed in HR and HRV suggest that genetic variability affects cardiac responses after acute air pollutant exposures.

Hamade and Tankersley (2009) continued this investigation of gene-environment interactions on cardiopulmonary adaptation of O_3 and CB induced changes in HR and HRV using the previously described (Hamade et al., 2008) daily exposure scheme for 3 consecutive days. By comparing day-1 interim values it is possible to observe that O_3 exposure increased SDNN and rMSSD, but decreased HR in all strains. Measures of HR and HRV in B6 and HeJ mice recovered to levels consistent with filtered air treated mice by day 3; however, these responses in OuJ mice remained suppressed. B6 mice had no change in respiratory rate (RR) after O_3 treatment, whereas HeJ mice on days 1 and 2 had increased RR and OuJ mice on days 2 and 3 exhibited increased RR. V_T did not change with treatment among the strains. Overall, B6 mice were mildly responsive with rapid adaptation, whereas C3 mice were highly responsive with adaptation only in HeJ mice with regards to changes in cardiac and respiratory responses. HR and HRV parameters were not equally correlated with V_T and RR between the three mice strains, which suggest that strains vary in the integration of the cardiac and respiratory systems. These complex interactions could help explain variability in interindividual susceptibility to adverse health effects of air pollution.

Hamade et al. (2010) expanded their investigation to explore the variation of these strain dependent cardiopulmonary responses with age. As was observed previously, all experimental mouse strains (B6, HeJ, and OuJ) exhibited decreased HR and increased HRV after O_3 exposure. Younger O_3-exposed mice had a significantly lower HR compared to older exposed mice, indicating an attenuation of the bradycardic effect of O_3 with age. Younger mice also had a greater increase in rMSSD in HeJ and OuJ strains and SDNN in HeJ mice. Conversely, B6 mice had a slightly greater increase in SDNN in aged mice compared to the young mice. No change was observed in the magnitude of the O_3 induced increase of SDNN in OuJ mice or rMSSD in B6 mice. The B6 and HeJ mice genetically vary in respect to the nuclear factor erythroid 2-related factor 2 (Nrf-2). The authors propose that the genetic differences between the mice strains could be altering the formation of ROS, which tends to increase with age, thus modulating the changes in cardiopulmonary physiology after O_3 exposure.

Strain and age differences in HR and heart function were further investigated in B6 and 129S1/SvlmJ (129) mice in response to a sequential O_3 and filtered air or CB exposure (Tankersley et al., 2010). Young 129 mice showed a decrease in HR after O_3 or O_3 and CB exposure. This bradycardia was not observed in B6 or older animals in this study, suggesting a possible alteration or adaptation of the autonomic nervous system activity with age. However, these authors did previously report bradycardia in similarly aged young B6 mice (Hamade et al., 2010; Hamade and Tankersley, 2009; Hamade et al., 2008). Ozone exposure in 129 mice also resulted in an increase in left ventricular chamber dimensions at end diastole (LVEDD) in young and old mice and a decrease in

left ventricular posterior wall thickness at end systole (PWTES) in older mice. The increase in LVEDD caused a decrease in fractional shortening, which can be used as a rough indicator of left ventricular function. Regression analysis revealed a significant interaction between age and strain on HR and PWTES, which implies that aging affects the HR and function in response to O_3 differently between mouse strains.

Effects on Cardiovascular-Related Proteins

Increased BP, changes in HRV, and increased atherosclerosis may be related to increases in the vasoconstrictor peptide, endothelin-1 (amino acids 1-21, ET-$1_{[1-21]}$). Regulation of the pulmonary endothelin system can be affected in rats by inhalation of PM (0, 5, 50 mg/m^3, EHC-93) and O_3 (Thomson et al., 2006; Thomson et al., 2005). Exposure to either O_3 (0.8 ppm) or PM increased plasma ET-$1_{[1-21]}$, ET-$3_{[1-21]}$, and the ET-1 precursor peptide, bigET-1. Increases in circulating ET-$1_{[1-21]}$ could be a result of a transient increase in the gene expression of lung preproET-1 and endothelin converting enzyme-1 (ECE-1) immediately following inhalation of O_3 or PM. These latter gene expression changes (e.g. preproET-1 and ECE-1) were additive with co-exposure to O_3 and PM. Conversely, preproET-3 decreased immediately after O_3 exposure, suggesting the increase in ET-$3_{[1-21]}$ was not through de novo production. A recent study also found increased ET-1 gene expression in the aorta of O_3 exposed rats (Kodavanti et al., 2011). These rats also exhibited an increase in ET_BR after O_3 exposure; however, they did not demonstrate increased biomarkers for vascular inflammation, thrombosis, or oxidation.

O_3 can oxidize protein functional groups and disturb the affected protein. For example, the soluble plasma protein fibrinogen is oxidized by O_3 (0.01-0.03 ppm) *in vitro*, creating fibrinogen and fibrin aggregates, characteristically similar to defective fibrinogen (Rosenfeld et al., 2009; Rozenfeld et al., 2008). In these studies, oxidized fibrinogen retained the ability to form fibrin gels that are involved in coagulation, however the aggregation time increased and the gels were rougher than normal with thicker fibers. Oxidized fibrinogen also developed the ability to self assemble creating fibrinogen aggregates that may play a role in thrombosis. Since O_3 does not readily translocate past the ELF and pulmonary epithelium and fibrinogen is primarily a plasma protein, it is uncertain if O_3 would have the opportunity to react with plasma fibrinogen. However, fibrinogen can be released from the basolateral face of pulmonary epithelial cells during inflammation, where the deposition of fibrinogen could lead to lung injury (Lawrence and Simpson-Haidaris, 2004).

Studies on Ozone Reaction Products

Although recent toxicological studies have demonstrated O_3-induced effects on the cardiovascular system, as concluded in previous O_3 AQCDs, it remains unclear if the mechanism is through a reflex response or the result of effects from O_3 reaction products (U.S. EPA, 2006b, 1996a). A new study that examined O_3 reaction byproducts has shown that cholesterol secoaldehyde (e.g., atheronal A) induces apoptosis *in vitro* in mouse macrophages (Gao et al., 2009b) and cardiomyocytes (Sathishkumar et al., 2009). Additionally, atheronal-A and -B has been found to induce *in vitro* macrophage and endothelial cell proinflammatory events involved in the initiation of atherosclerosis (Takeuchi et al., 2006). These O_3 reaction products when complexed with low density lipoprotein upregulate scavenger receptor class A and induce dose-dependent macrophage chemotaxis. Atheronal-A increases expression of the adhesion molecule, E-selectin, in endothelial cells, while atheronal-B induces monocyte differentiation. These events contribute to both monocyte recruitment and foam cell formation in atherosclerotic vessels. It is unknown whether these O_3 reaction products gain access to the vascular space from the lungs. Alternative explanations include the extrapulmonary release of diffusible mediators that may initiate or propagate inflammatory responses in the vascular or systemic compartments.

Table 6-39 Characterization of study details for Section 6.3.3.2[a]

Study	Model	O_3 (ppm)	Exposure Duration	Effects
Chuang et al. (2009)	Mice; C57Bl/6; M; 6 weeks	0.5	1 or 5 days, 8-h/day	Increased HR and blood pressure. Initiated an oxidative environment by increasing vascular O_2^- production, which lead to mtDNA damage and ·NO consumption, known to perturb endothelial function.
	Monkey; rhesus *Macaca mulatta*; M; Infant (180 days old)	0.5	5 days, 8-h/day	
Perepu et al. (2010)	Rat; Sprague-Dawley; 50-75 g	0.8	28 days, 8-h/day	Enhanced the sensitivity to myocardial I/R injury while increasing oxidative stress and pro-inflammatory mediators and decreasing production of anti-inflammatory proteins.
Hamade et al. (2008)	Mice; C57Bl/6J, C3H/HeJ, and C3H/HeOuJ; M; 18-20 weeks	0.6 (subsequent CB exposure, 536 µg/m^3)	2-h followed by 3 h of CB	Decreased HR. Strain differences observed in HRV suggest that genetic variability affects cardiac responses.
Hamade and Tankersley (2009)	Mice; C57Bl/6J, C3H/HeJ, and C3H/HeOuJ; M; 18-20 weeks	0.6 (subsequent CB exposure, 536 µg/m^3)	3 days, 2-h/day followed by 3-h of CB	Strains varied in integration of the cardiac and respiratory systems, implications in interindividual variability. B6 mice were mildly responsive with rapid adaptation, whereas C3 mice were highly responsive with adaptation only in HeJ mice with regards to changes in cardiac and respiratory responses.
Hamade et al. (2010)	Mice; C57Bl/6J, C3H/HeJ, and C3H/HeOuJ; M; 5 or 12 mo old	0.6 (subsequent CB exposure, 536 µg/m^3)	2-h followed by 3-h of CB	Aged mice exhibited attenuated changes in cardiopulmonary physiology after O_3 exposure. Genetic differences between mice strains could be altering formation of ROS, which tends to increase with age, thus modulating O_3 induced effects.
Tankersley et al. (2010)	Mice; C57Bl/6J, 129S1/SvlmJ; M/F; 5 or 18 mo old	0.6 (subsequent CB exposure, 556 µg/m^3)	2-h followed by 3-h of CB	Significant interaction between age and strain on HR and PWTES, which implies that aging affects the HR and function in response to O_3 differently between mouse strains.
Thomson et al. (2005)	Rat; Fischer-344; M; 200-250 g	0.4 or 0.8	4-h	Activation of the vasoconstricting ET system. Increased plasma ET-1 through higher production and slower clearance.
Thomson et al. (2006)	Rat; Fischer-344; M; 200-250 g	0.8	4-h	Increased plasma ET-3 not due to de novo synthesis, unlike ET-1.
Kodavanti et al. (2011)	Rat; Wistar; M; 10-12 weeks	0.5 or 1.0	2 days, 5-h/day	No changes to aortic genes of thrombosis, inflammation or proteolysis, except ET-1 and ETBR (1.0 ppm).

[a] Results from previous studies are presented in Table AX5-14 of the 2006 O_3 AQCD and Table 6-23 of the 1996 O_3 AQCD.

Summary of Toxicological Studies

Overall, animal studies suggest that O_3 exposure may disrupt both the ·NO and endothelin systems, which can result in an increase in HR, HRV, and ANF, as is observed after O_3 exposure. Conversely, studies in rodents also exhibit O_3 induced bradycardia, but it is uncertain if this decrease in HR is also observed in humans. Additionally, O_3 may increase oxidative stress and vascular inflammation promoting the progression of atherosclerosis and leading to increased susceptibility to I/R injury. As O_3 reacts quickly with the ELF and does not translocate to the heart and large vessels, studies suggest that the cardiovascular effects exhibited could be caused by reaction

byproducts of O_3 exposure. However, direct evidence of translocation of O_3 reaction products to the cardiovascular system has not been demonstrated *in vivo*. Alternatively, extrapulmonary release of diffusible mediators, such as cytokines or endothelins, may initiate or propagate inflammatory responses in the vascular or systemic compartments leading to the reported cardiovascular pathologies. Further discussion of the modes of action that may lead to cardiovascular effects can be found in Section 5.3.8.

6.3.4 Summary and Causal Determination

In past O_3 AQCDs the effects of O_3 to the cardiovascular system did not receive much attention due to the paucity of information available. However, in recent years, investigation of O_3-induced cardiovascular events has advanced. In general, compared with the epidemiologic evidence, the toxicological evidence is more supportive of O_3-induced cardiovascular effects. Epidemiologic evidence does not consistently demonstrate a positive relationship between short-term O_3 exposure and cardiovascular-related morbidity. However, most epidemiologic studies have not extensively investigated the cardiovascular effects of O_3 exposure in susceptible populations, which may further support the toxicological findings. Although the epidemiologic evidence of cardiovascular morbidity is limited, single-city studies reviewed in the 2006 O_3 AQCD, recent multicity studies, and the multicontinent APHENA study provide evidence of consistently positive associations between short-term O_3 exposure and cardiovascular mortality. However, in contrast with respiratory effects, there is weak coherence between associations for cardiovascular morbidity and mortality. Further, there is no apparent biological mechanism to explain the association observed for short-term O_3 exposure with cardiovascular mortality.

Animal toxicological studies provide evidence for O_3-induced cardiovascular effects, specifically enhanced I/R injury, disrupted NO-induced vascular reactivity, decreased cardiac function, and increased HRV. The observed increase in HRV is supported by a recent controlled human exposure study that also finds increased high frequency HRV, but not altered blood pressure, following O_3 exposure. Toxicological studies investigating the role of O_3 in heart rate regulation are mixed with both bradycardic and tachycardic responses observed. These changes in cardiac function provide evidence for O_3-induced alterations in the autonomic nervous system leading to cardiovascular complications. Epidemiologic studies showing positive association between O_3 and arrhythmias confirm the development of autonomic dysfunction following O_3 exposure. It is still uncertain how O_3 inhalation may cause systemic toxicity; however the cardiovascular effects of O_3 found in animals correspond to the development and maintenance of an extrapulmonary oxidative, proinflammatory environment.

In conclusion, animal toxicological studies provide stronger evidence for O_3 exposure leading to cardiovascular morbidity than do epidemiologic studies, among which there is a lack of coherence among endpoints. Based on the relatively strong body of toxicological evidence, and the consistent evidence of an association between O_3 and cardiovascular mortality, but weak coherence and biological plausibility for O_3-induced cardiovascular morbidity, the generally limited body of evidence **is suggestive of a causal relationship between relevant short-term exposures to O_3 and cardiovascular effects.**

6.4 Central Nervous System Effects

The 2006 O_3 AQCD included toxicological evidence that acute exposures to O_3 are associated with alterations in neurotransmitters, motor activity, short and long term memory, and sleep patterns. Additionally, histological signs of neurodegeneration have been observed. Reports of headache, dizziness, and irritation of the nose with O_3 exposure are common complaints in humans, and some behavioral changes in animals may be related to these symptoms rather than indicative of neurotoxicity. Peterson and Andrews (1963) and Tepper et al. (1983) showed that mice would alter their behavior to avoid O_3 exposure. Murphy et al. (1964) and Tepper et al. (1982) showed that running-wheel behavior was suppressed, and Tepper et al. (1985) subsequently demonstrated the effects of a 6-h exposure to O_3 on the suppression of running-wheel behavior in rats and mice, with the lowest effective concentration being about 0.12 ppm O_3 in the rat and about 0.2 ppm in the mouse. The suppression of active behavior by 6 h of exposure to 0.12 ppm O_3 has recently been confirmed by Martrette et al. (2011) in juvenile female rats, and the suppression of three different active behavior parameters was found to become more pronounced after 15 days of exposure. A table of studies examining the effects of O_3 on behavior can be found on p 6-128 of the 1996 O_3 AQCD. Generally speaking, transient changes in behavior in rodent models appear to be dependent on a complex interaction of factors such as (1) the type of behavior being measured, with some behaviors increased and others suppressed; (2) the factors motivating that behavior (differences in reinforcement); and (3) the sensitivity of the particular behavior (e.g., active behaviors are more affected than more sedentary behaviors). Many behavioral changes are likely to result from avoidance of irritation, but more recent studies indicate that O_3 also directly affects the CNS.

Research in the area of O_3-induced neurotoxicity has notably increased over the past few years, with the majority of the evidence coming from toxicological studies that examined the association between O_3 exposure, neuropathology, and neurobehavioral effects, and more limited evidence from epidemiologic studies. In an epidemiologic study conducted

by Chen and Schwartz (2009), data from the NHANES III cohort was utilized to study the relationship between long-term O_3 exposure (mean annual O_3 concentration of 26.5 ppb) and neurobehavioral effects among adults aged 20-59 years. The authors observed an association between annual exposure to O_3 and tests measuring coding ability and attention/short-term memory. Each 10-ppb increase in annual O_3 levels corresponded to an aging-related cognitive performance decline of 3.5 years for coding ability and 5.3 years for attention/short-term memory. These associations persisted in both crude and adjusted models. There was no association between annual O_3 concentrations and reaction time tests. The authors conclude that overall there is a positive association between O_3 exposure and reduced performance on neurobehavioral tests. Although Chen and Schwartz (2009) is a long-term exposure study, it is included in this section because it is the first epidemiologic study to demonstrate that exposure to ambient O_3 is associated with decrements in neurocognitive tests related to memory and attention in humans. This epidemiologic evidence of an effect on the CNS due to exposure to ambient concentrations of O_3 is coherent with animal studies demonstrating that exposure to O_3 can produce a variety of CNS effects including behavioral deficits, morphological changes, and oxidative stress in the brains of rodents. In these rodent studies, interestingly, CNS effects were reported at O_3 concentrations that were generally lower than those concentrations commonly observed to produce pulmonary or cardiac effects in rats.

A number of new studies demonstrate various perturbations in neurologic function or histology, including changes similar to those observed with Parkinson's and Alzheimer's disease pathologies occurring in similar regions of the brain (Table 6-40). Many of these include exposure durations ranging from short-term to long-term, and as such are discussed here and in Chapter 7 with emphasis on the effects resulting from exposure durations relevant to the respective chapter. Several studies assess short- and long-term memory acquisition via passive avoidance behavioral testing and find decrements in test performance after O_3 exposure, consistent with the aforementioned observation made in humans by Chen and Schwartz (2009). Impairment of long-term memory has been previously described in rats exposed to 0.2 ppm O_3 for 4 h (Rivas-Arancibia et al., 1998) and in other studies of 4-hour exposures at concentrations of 0.7 to 1 ppm (Dorado-Martinez et al., 2001; Rivas-Arancibia et al., 2000; Avila-Costa et al., 1999). More recently, statistically significant decreases in both short and long-term memory were observed in rats after 15 days of exposure to 0.25 ppm O_3 (Rivas-Arancibia et al., 2010).

The central nervous system is very sensitive to oxidative stress, due in part to its high content of polyunsaturated fatty acids, high rate of oxygen consumption, and low antioxidant enzyme capacity. Oxidative stress has been identified as one of the pathophysiological mechanisms underlying neurodegenerative disorders such as

Parkinson's and Alzheimer's disease, among others (Simonian and Coyle, 1996). It is also believed to play a role in altering hippocampal function, which causes cognitive deficits with aging (Vanguilder and Freeman, 2011). A particularly common finding in studies of O_3-exposed rats is lipid peroxidation in the brain, especially in the hippocampus, which is important for higher cognitive function including contextual memory acquisition. Performance in passive avoidance learning tests is impaired when the hippocampus is injured, and the observed behavioral effects are well correlated with histological and biochemical changes in the hippocampus, including reduction in spine density in the pyramidal neurons (Avila-Costa et al., 1999), lipoperoxidation (Rivas-Arancibia et al., 2010; Dorado-Martinez et al., 2001), progressive neurodegeneration, and activated and phagocytic microglia (Rivas-Arancibia et al., 2010). The hippocampus is also one of the main regions affected by age-related neurodegenerative diseases, including Alzheimer's disease, and it may be more sensitive to oxidative damage in aged rats. In a study of young (47 days) and aged (900 days) rats exposed to 1 ppm O_3 for 4 h, O_3-induced lipid peroxidation occurred to a greater extent in the striatum of young rats, whereas it was highest in the hippocampus in aged rats (Rivas-Arancibia et al., 2000). Martínez-Canabal et al. (2008) showed exposure of rats to 0.25 ppm, 4h/day, for 7, 15, or 30 days increased lipoperoxides in the hippocampus. This effect was observed at day 7 and continued to increase with time, indicating cumulative oxidative damage. O_3-induced changes in lipid peroxidation, neuronal death, and COX-2 positive cells in the hippocampus could be significantly inhibited by daily treatment with growth hormone (GH), which declines with age in most species. The protective effect of GH on -induced oxidative stress was greatest at 15 days of exposure and was non-significant at day 30. Consistent with these findings, lipid peroxidation in the hippocampus of rats was observed to increase significantly after a 30-day exposure to 0.25 ppm , but not after a single 4-h exposure to the same concentration (Mokoena et al., 2010). However, 4 hours of exposure was sufficient to cause significant increases in lipid peroxidation when the concentration was increased to 0.7 ppm, and another study observed lipid peroxidation after a 4-h exposure to 0.4 ppm (Dorado-Martinez et al., 2001).

Other commonly affected areas of the brain include the striatum, substantia nigra, cerebellum, olfactory bulb, and frontal/prefrontal cortex. The striatum and substantia nigra are particularly sensitive to oxidative stress because the metabolism of dopamine, central to their function, is an oxidative process perturbed by redox imbalance. Oxidative stress has been implicated in the premature death of substantia nigra dopamine neurons in Parkinson's disease. Angoa-Pérez et al. (2006) have shown progressive lipoperoxidation in the substantia nigra and a decrease in nigral dopamine neurons in ovariectomized female rats exposed to 0.25 ppm O_3, 4h/day, for 7, 15, or 30 days. Estradiol, an antioxidant, attenuated O_3-induced oxidative stress and nigral neuronal death, and the authors note that in humans, estrogen therapy can ameliorate symptoms of Parkinson's

disease, which is more prevalent in men. Progressive oxidative stress has also been observed in the striatum and substantia nigra of rats after 15 and 30 days of exposure to 0.25 ppm O_3 for 4 h/day, along with a loss of dopaminergic neurons from the substantia nigra (Pereyra-Muñoz et al., 2006). Decreases in motor activity were also observed at 15 and 30 days of exposure, consistent with other reports (Martrette et al., 2011; Dorado-Martinez et al., 2001). Using a similar O_3 exposure protocol, Santiago-López and colleagues (2010) also observed a progressive loss of dopaminergic neurons within the substantia nigra, accompanied by alterations in the morphology of remaining cells and an increase in p53 levels and nuclear translocation.

The olfactory bulb also undergoes oxidative damage in O_3 exposed animals, in some cases altering olfactory-dependent behavior. Lipid peroxidation was observed in the olfactory bulbs of ovariectomized female rats exposed to 0.25 ppm O_3 (4 h/day) for 30 or 60 days (Guevara-Guzmán et al., 2009). O_3 also induced decrements in a selective olfactory recognition memory test, and the authors note that early deficits in odor perception and memory are components of human neurodegenerative diseases. The decrements in olfactory memory were not due to damaged olfactory perception based on other tests. However, deficits in olfactory perception emerged with longer exposures (discussed in Chapter 7). As with the study by Angoa-Pérez et al. (2006) described above, a protective effect for estradiol was demonstrated for both lipid peroxidation and olfactory memory defects. The role of oxidative stress in memory deficits and associated morphological changes has also been demonstrated via attenuation by other antioxidants as well, such as α-tocopherol (Guerrero et al., 1999) and taurine (Rivas-Arancibia et al., 2000).

It is unclear how persistent these effects might be. One study of acute exposure, using 1 ppm O_3 for 4 hours, observed morphological changes in the olfactory bulb of rats at 2 hours, and 1 and 10 days, but not 15 days, after exposure (Colín-Barenque et al., 2005). Other acute studies also report changes in the CNS. Lipid peroxidation was observed in multiple regions of the brain after a 1- to 9-h exposure to 1 ppm O_3 (Escalante-Membrillo et al., 2005). Ozone has also been shown to alter gene expression of endothelin-1 (pituitary) and inducible nitric oxide synthase (cerebral hemisphere) after a single 4-h exposure to 0.8 ppm O_3, indicating potential cerebrovascular effects. This concentration-dependent effect was not observed at 0.4 ppm O_3 (Thomson et al., 2007). Vascular endothelial growth factor was upregulated in astroglial cells in the central respiratory areas of the brain of rats exposed to 0.5 ppm O_3 for 3 hours (Araneda et al., 2008). The persistence of CNS changes after a single exposure was also examined and the increase in vascular endothelial growth factor was present after a short (3 hours) recovery period. Thus, there is evidence that O_3-induced CNS effects are both concentration- and time-dependent.

Because O_3 can produce a disruption of the sleep-wake cycle (U.S. EPA, 2006b), Alfaro-Rodriguez et al. (2005) examined whether acetylcholine in a region of the brain involved in sleep regulation was altered by O_3. After a 24-h exposure to 0.5 ppm O_3, the acetylcholine concentration in the medial preoptic area was decreased by 58% and strongly correlated with a disruption in paradoxical sleep. Such behavioral-biochemical effects of O_3 are confirmed by a number of studies which have demonstrated morphological and biochemical changes in rats.

CNS effects have also been demonstrated in newborn and adult rats whose only exposure to O_3 occurred in utero. Several neurotransmitters were assessed in male offspring of dams exposed to 1 ppm O_3 during the entire pregnancy (Gonzalez-Pina et al., 2008). The data showed that catecholamine neurotransmitters were affected to a greater degree than indole-amine neurotransmitters in the cerebellum. CNS changes, including behavioral, cellular, and biochemical effects, have also been observed after in utero exposure to 0.5 ppm O_3 for 12 h/day from gestational days 5-20 (Boussouar et al., 2009). Tyrosine hydroxylase labeling in the nucleus tractus solatarius was increased after in utero exposure to O_3 whereas Fos protein labeling did not change. When these offspring were challenged by immobilization stress, neuroplasticity pathways, which were activated in air-exposed offspring, were inhibited in O_3-exposed offspring. Although an O_3 exposure concentration-response was not studied in these two in utero studies, it has been examined in one study. Santucci et al. (2006) investigated behavioral effects and gene expression after in utero exposure of mice to as little as 0.3 ppm O_3. Increased defensive/submissive behavior and reduced social investigation were observed in both the 0.3 and 0.6 ppm O_3 groups. Changes in gene expression of brain-derived neurotrophic factor (BDNF, increased in striatum) and nerve growth factor (NGF, decreased in hippocampus) accompanied these behavioral changes. Thus, these three studies demonstrate that CNS effects can occur as a result of in utero exposure to O_3, and although the mode of action of these effects is not known, it has been suggested that circulating lipid peroxidation products may play a role (Boussouar et al., 2009). Importantly, these CNS effects occurred in rodent models after in utero only exposure to relevant concentrations of O_3.

Table 6-40 Central Nervous System and Behavioral Effects of Short-term O_3 Exposure in Rats

Study	Model	O_3 (ppm)	Exposure Duration	Effects
Martrette et al. (2011)	Rat; Wistar; F; Weight: 152g; 7 weeks old	0.12	1-15 days, 6 h/day	Significant decrease in rearing, locomotor activity, and jumping activity at day 1, with a further decrease in these activities by day 15.
Angoa-Pérez et al. (2006)	Rat; Wistar; F; Weight: 300g; ovariectomized	0.25	7 to 60 days, 4-h/day, 5 days/wk	Progressive lipid peroxidation and loss of tyrosine hydrolase-immunopositive neurons in the substantia nigra starting at 7 days.
Guevara-Guzmán et al. (2009)	Rat; Wistar; F; 264g; ovariectomized	0.25	30 and 60 days, 4h/day	Estradiol treatment protected against lipid peroxidation and decreases in estrogen receptors and dopamine β-hydroxylase in olfactory bulbs along with deficits in olfactory recognition memory.
Martínez-Canabal et al. (2008)	Rat; Wistar; M; Weight: 300g	0.25	7 to 30 days, 4-h/day	Growth hormone inhibited O_3-induced increases in lipoperoxidation and COX-2 positive cells in the hippocampus.
Pereyra-Muñoz et al. (2006)	Rat; Wistar; M; 250-300g	0.25	15 and 30 days, 4-h/day	Decreased motor activity, increased lipid peroxidation, altered morphology, and loss of dopamine neurons in substantia nigra and striatum, increased expression of DARPP-32, iNOS, and SOD.
Rivas-Arancibia et al. (2010)	Rat; Wistar; M; 250-300g	0.25	15 to 90 days, 4-h/day	Ozone produced significant increases in lipid peroxidation in the hippocampus, and altered the number of p53 positive immunoreactive cells, activated and phagocytic microglia cells, GFAP immunoreactive cells, and doublecortine cells, and short- and long-term memory-retention latency.
Santiago-López et al. (2010)	Rat; Wistar; M; 250-300g	0.25	15, 30, and 60 days, 4-h/day	Progressive loss of dopamine reactivity in the substantia nigra, along with morphological changes. Increased p53 levels and nuclear translocation.
Thomson et al. (2007)	Rat; Fischer-344; M; 200-250g	0.4; 0.8	4-h; assays at 0 and 24 h post exposure	At 0.8 ppm, O_3 produced rapid perturbations in the ET-NO pathway gene expression in the brain. Ozone induced a small but significant time- and concentration-dependent increase in prepro-endothelin-1 mRNA levels in the cerebral hemisphere and pituitary, whereas TNFa and iNOS mRNA levels were decreased at 0 hrs and unchanged or increased, respectively, at 24 h.
Alfaro-Rodríguez and González-Pina (2005)	Rat; Wistar; M; 292g	0.5	24-h	During the light phase, O_3 caused a significant decrease in paradoxical sleep accompanied by a significant decrease in Ach levels in the hypothalamic medial preoptic area. The same effects occurred during the dark phase exposure to O_3 in addition to a significant increase in slow-wave sleep and decrease in wakefulness.
Araneda et al. (2008)	Rats; Sprague-Dawley; M; 280-320g	0.5	3-h (measurements taken at 0 h and 3 h after exposure)	Ozone upregulated VEGF in astroglial cells located in the respiratory center of the brain. VEGF co-located with IL-6 and TNF in cells near blood vessel walls, and blood vessel area was markedly increased.
Boussouar et al. (2009)	Rat; Sprague-Dawley; M; adult offspring of prenatally exposed dams; 403-414g	0.5	From embryonic day E5 to E20 for 12-h/day; immobilization stress	Prenatal O_3 exposure had a long term impact on the nucleus tractus solitarius of adult rats, as revealed during immobilization stress.
Soulage et al. (2004)	Rat; Sprague-Dawley; M; Approx. 7 weeks old	0.7	5-h	Ozone produced differential effects on peripheral and central components of the sympatho-adrenal system. While catecholamine biosynthesis was increased in portions of the brain, the catecholamine turnover rate was significantly increased in the heart and cerebral cortex and inhibited in the lung and striatum.

Study	Model	O_3 (ppm)	Exposure Duration	Effects
Guzmán et al. (2006; 2005)	Rat; Wistar; M; 21 days old; well-nourished and malnourished groups	0.75	15 successive days for 4-h/day	A significant decrease in body weight was observed in both well nourished (WN) and malnourished (MN) rats after O_3 exposure. Localized ATPase, TBARS, and GSH levels changed in response to ozone in certain brain areas and the ozone-induced changes were dependent on nutritional condition.
Colín-Barenque et al. (2005)	Rats; Wistar; M; 250-300g	1.0	4-h; assays at 2-h, 24-h, 10 days, and 15 days after exposure	A significant loss of dendritic spines in granule cells of the olfactory bulb occurred at 2 hrs to 10 days after exposure. Cytological and ultrastructural changes returned towards normal morphology by 15 days.
Escalante-Membrillo et al. (2005)	Rats; Wistar; M; 280-320g	1.0	1-, 3-, 6-, or 9-h	Significant increases in TBARS occurred in hypothalamus, cortex, striatum, midbrain, thalamus, and pons. Partial but significant recovery was observed by 3 h after the 9 h exposure.
Gonzalez-Pina et al. (2008)	Rat; Wistar; M;	1	12-h/day, 21 days of gestation; assays at 0, 5, & 10 days postnatal	Prenatal O_3 exposure produced significant decreases in cerebellar monoamine but not indolamine. content at 0 and 5 days after birth with a partial recovery by 10 d. 5-hydroxy-indole-acetic acid levels were significantly increased at 10 days.

6.4.1 Neuroendocrine Effects

According to the 2006 O_3 AQCD, early studies suggested an interaction of O_3 with the pituitary-thyroid-adrenal axis, because thyroidectomy, hypophysectomy, and adrenalectomy protected against the lethal effects of O_3. Concentrations of 0.7-1.0 ppm O_3 for a 1-day exposure in male rats caused changes in the parathyroid, thymic atrophy, decreased serum levels of thyroid hormones and protein binding, and increased prolactin. Increased toxicity to O_3 was reported in hyperthyroid rats and T3 supplementation was shown to increase metabolic rate and pulmonary injury in the lungs of O_3-treated animals. The mechanisms by which O_3 affects neuroendocrine function are not well understood, but previous work suggests that high ambient levels of O_3 can produce marked neural disturbances in structures involved in the integration of chemosensory inputs, arousal, and motor control, effects that may be responsible for some of the behavioral effects seen with O_3 exposure. A more recent study exposing immature female rats to 0.12 ppm O_3 demonstrated significantly increased serum levels of the thyroid hormone free T_3 after 15 days of exposure, whereas free T_4 was unchanged (Martrette et al., 2011). These results are in contrast to those previously presented whereby 1 ppm O_3 for 1 day significantly decreased T_3 and T_4 (Clemons and Garcia, 1980), although comparisons are made difficult by highly disparate exposure regimens along with sex differences. Martrette et al.(2011) also demonstrated significantly increased corticosterone levels after 15 days of exposure, suggesting a stress related response.

6.4.2 Summary and Causal Determination

In rodents, O_3 exposure has been shown to cause physicochemical changes in the brain indicative of oxidative stress and inflammation. Newer toxicological studies add to earlier evidence that acute exposures to O_3 can produce a range of effects on the central nervous system and behavior. Previously observed effects, including neurodegeneration, alterations in neurotransmitters, short and long term memory, and sleep patterns, have been further supported by recent studies. In instances where pathology and behavior are both examined, animals exhibit decrements in behaviors tied to the brain regions or chemicals found to be affected or damaged. For example, damage in the hippocampus, which is important for memory acquisition, was correlated with impaired performance in tests designed to assess memory. Thus the brain is functionally affected by O_3 exposure. The single epidemiologic study conducted showed an association between O_3 exposure and memory deficits in humans as well, albeit on a long-term exposure basis. Notably, exposure to O_3 levels as low as 0.25 ppm for 7 days has resulted in progressive neurodegeneration and deficits in both short and long-term memory in rodents. Examination of changes in the brain at lower exposure concentrations or at 0.25 ppm for shorter durations has not been reported, but 0.12 ppm O_3 has been shown to alter behavior. It is possible that some behavioral changes may reflect avoidance of irritation as opposed to functional changes in brain morphology or chemistry, but in many cases functional changes are related to oxidative stress and damage. In some instances, changes were dependent on the nutritional status of the rats (high versus low protein diet). For example, O_3 produced an increase in glutathione in the brains of rats fed the high protein diet but decreases in glutathione in rats fed low protein chow (Calderon Guzman et al., 2006). The hippocampus, one of the main regions affected by age-related neurodegenerative diseases, appears to be more sensitive to oxidative damage in aged rats (Rivas-Arancibia et al., 2000), and growth hormone, which declines with age in most species, may be protective (Martínez-Canabal and Angora-Perez, 2008). Developing animals may also be sensitive, as changes in the CNS, including biochemical, cellular, and behavioral effects, have been observed in juvenile and adult animals whose sole exposure occurred *in utero*, at levels as a low as 0.3 ppm. A number of studies demonstrate ozone-induced changes that are also observed in human neurodegenerative disorders such as Alzheimer's and Parkinson's disease, including signs of oxidative stress, loss of neurons/neuronal death, reductions in dopamine levels, increased COX-2 expression, and increases in activated microglia in important regions of the brain (hippocampus, substantia nigra).

Although evidence from epidemiologic and controlled human exposure studies is lacking, the toxicological evidence for ozone's impact on the brain and behavior is strong, and at

least **is suggestive of a causal relationship between O_3 exposure and effects on the central nervous system**.

6.5 Effects on Other Organ Systems

6.5.1 Effects on the Liver and Xenobiotic Metabolism

Early investigations of the effects of O_3 on the liver centered on xenobiotic metabolism, and the prolongation of drug-induced sleeping time, which was observed at 0.1 ppm O_3 (Graham et al., 1981). In some species, only adults and especially females were affected. In rats, high (1.0-2.0 ppm for 3 hours) acute O_3 exposures caused increased production of NO by hepatocytes and enhanced protein synthesis (Laskin et al., 1996; Laskin et al., 1994). Except for the earlier work on xenobiotic metabolism, the responses occurred only after very high acute O_3 exposures. One study, conducted at 1 ppm O_3 exposure, has been identified (Last et al., 2005) in which alterations in gene expression underlying O_3-induced cachexia and downregulation of xenobiotic metabolism were examined. A number of the down-regulated genes are known to be interferon (IFN) dependent, suggesting a role for circulating IFN. A more recent study by Aibo et al. (2010) demonstrates exacerbation of acetaminophen-induced liver injury in mice after a single 6-h exposure to 0.25 or 0.5 ppm O_3. Data indicate that O_3 may worsen drug-induced liver injury by inhibiting hepatic repair. The O_3-associated effects shown in the liver are thought to be mediated by inflammatory cytokines or other cytotoxic mediators released by activated macrophages or other cells in the lungs (Laskin and Laskin, 2001; Laskin et al., 1998; Vincent et al., 1996b). Recently, increased peroxidated lipids were detected in the plasma of O_3 exposed animals (Santiago-López et al., 2010).

In summary, mediators generated by O_3 exposure may cause effects on the liver in laboratory rodents. Ozone exposures as low as 0.1 ppm have been shown to affect drug-induced sleeping time, and exposure to 0.25 ppm can exacerbate liver injury induced by a common analgesic. However, very few studies at relevant concentrations have been conducted, and no data from controlled human exposure or epidemiologic studies are currently available. Therefore the collective evidence **is inadequate to determine if a causal relationship exists between short-term O_3 exposure and effects on the liver and metabolism.**

6.5.2 Effects on Cutaneous and Ocular Tissues

In addition to the lungs, the skin is highly exposed to O_3 and contains O_3 reactive targets (polyunsaturated fatty acids) that can produce lipid peroxides. The 2006 O_3 AQCD reported that although there is evidence of oxidative stress at near ambient O_3 concentrations, skin and eyes are only affected at high concentrations (greater than 1-5 ppm). Ozone exposure (0.8 ppm for 7 days) induces oxidative stress in the skin of hairless mice, along with proinflammatory cytokines (Valacchi et al., 2009). A recent study demonstrated that 0.25 ppm O_3 differentially alters expression of metalloproteinases in the skin of young and aged mice, indicating age-related susceptibility to oxidative stress (Fortino et al., 2007). In young mice, healing of skin wounds is not significantly affected by O_3 exposure (Lim et al., 2006). However, exposure to 0.5 ppm O_3 for 6 h/day significantly delays wound closure in aged mice. As with effects on the liver described above, the effects of O_3 on the skin and eyes have not been widely studied, and information from controlled human exposure or epidemiologic studies is not currently available. Therefore **the collective evidence is inadequate to determine if a causal relationship exists between short-term O_3 exposure and effects on cutaneous and ocular tissues.**

6.6 Mortality

6.6.1 Summary of Findings from 2006 Ozone AQCD

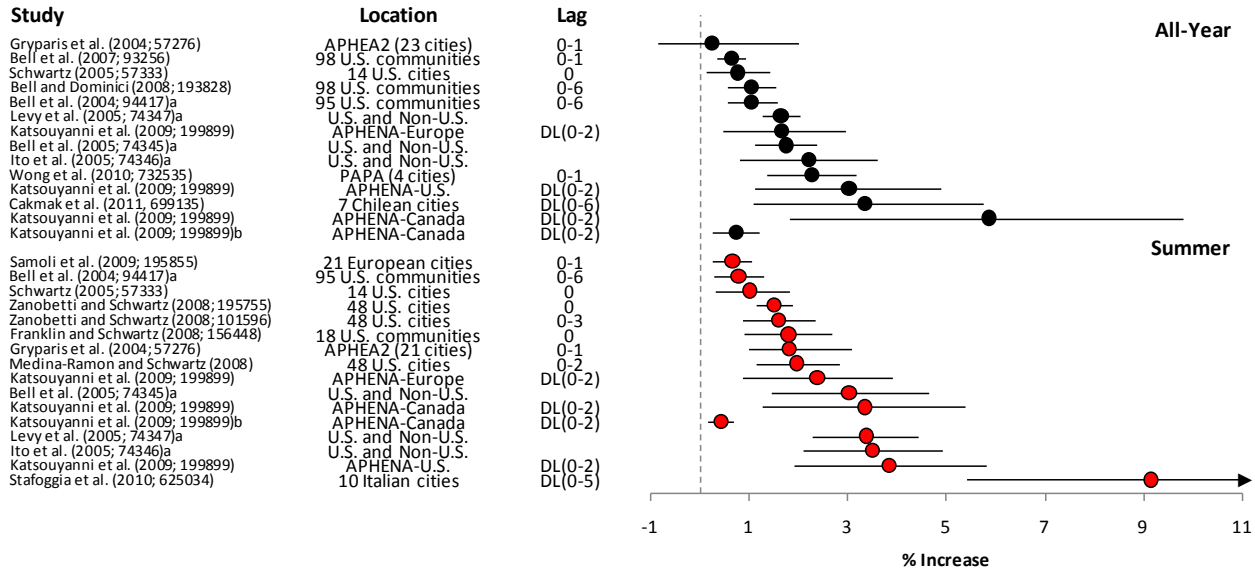
The 2006 O_3 AQCD reviewed a large number of time-series studies consisting of single- and multicity studies, and meta-analyses. In the large U.S. multicity studies that examined all-year data, summary effect estimates corresponding to single-day lags ranged from a 0.5-1% increase in all-cause (nonaccidental) mortality per the standardized unit increase[1] in O_3. The association between short-term O_3 exposure and mortality was substantiated by a collection of meta-analyses and international multicity studies. The studies evaluated found some evidence for heterogeneity in O_3 mortality risk estimates across cities and studies. Studies that conducted seasonal analyses, although more limited in number, reported larger O_3 mortality risk estimates during the warm or summer season. Overall, the 2006 O_3 AQCD identified robust associations between various measures of daily ambient O_3 concentrations and all-cause mortality, with additional evidence for associations with cardiovascular mortality, which could not be readily explained by confounding due to time, weather, or copollutants. However, it was noted

[1] In the 2006 O_3 AQCD and throughout this document to compare across studies that used the same exposure metric, effect estimates were standardized to 40 ppb for 1-h maximum, 30 ppb for 8-h maximum, and 20 ppb for 24-h average O_3 concentrations.

that multiple uncertainties remain regarding the O_3-mortality relationship including: the extent of residual confounding by copollutants; factors that modify the O_3-mortality association; the appropriate lag structure for identifying O_3-mortality effects (e.g., single-day lags versus distributed lag model); the shape of the O_3-mortality C-R function and whether a threshold exists; and the identification of susceptible populations. Collectively, the 2006 O_3 AQCD concluded that "the overall body of evidence is highly suggestive that O_3 directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality."

6.6.2 Associations of Mortality and Short-Term Ozone Exposure

The recent literature that examined the association between short-term O_3 exposure and mortality further confirmed the associations reported in the 2006 O_3 AQCD. New multicontinent and multicity studies reported consistent positive associations between short-term O_3 exposure and all-cause mortality in all-year analyses, with additional evidence for larger mortality risk estimates during the warm or summer months (Figure 6-27; Table 6-41). These associations were reported across a range of ambient O_3 concentrations that were in some cases quite low (Table 6-42).



Effect estimates are for a 40 ppb increase in 1-h max, 30 ppb increase in 8-h max, and 20 ppb increase in 24-h avg ozone concentrations. An "a" represent multicity studies and meta-analyses from the 2006 ozone AQCD. Bell et al. (2005), Ito et al. (2005), and Levy et al. (2005) used a range of lag days in the meta-analysis: Lag 0, 1, 2, or average 0-1 or 1-2; single-day lags from 0 to 3; and lag 0 and 1-2; respectively. A "b" represents risk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in ozone concentrations (see explanation in Section 6.2.7.2).

Figure 6-27 Summary of mortality risk estimates for short-term ozone exposure and all-cause (nonaccidental) mortality from all-year and summer season analyses.

Table 6-41 Corresponding effect estimates for Figure 6-27

Study	Location	Lag	Avg Time	% Increase (95% CI)
All-year				
Gryparis et al. (2004)	APHEA2 (23 cities)	0-1	1-h max	0.24 (-0.86, 1.98)
Bell et al. (2007)	98 U.S. communities	0-1	24-h avg	0.64 (0.34, 0.92)
Schwartz (2005a)	14 U.S. cities	0	1-h max	0.76 (0.13, 1.40)
Bell and Dominici (2008)	98 U.S. communities	0-6	24-h avg	1.04 (0.56, 1.55)
Bell et al. (2004)[a]	95 U.S. communities	0-6	24-h avg	1.04 (0.54, 1.55)
Levy et al. (2005)[a]	U.S. and Non-U.S.	---	24-h avg	1.64 (1.25, 2.03)
Katsouyanni et al. (2009)	APHENA-Europe	DL(0-2)	1-h max	1.66 (0.47, 2.94)
Bell et al. (2005)[a]	U.S. and Non-U.S.	---	24-h avg	1.75 (1.10, 2.37)
Ito et al. (2005)[a]	U.S. and Non-U.S.	---	24-h avg	2.20 (0.80, 3.60)
Wong et al. (2010)	PAPA (4 cities)	0-1	8-h avg	2.26 (1.36, 3.16)
Katsouyanni et al. (2009)	APHENA-U.S.	DL(0-2)	1-h max	3.02 (1.10, 4.89)
Cakmak et al. (2011)	7 Chilean cities	DL(0-6)	8-h max	3.35 (1.07, 5.75)
Katsouyanni et al. (2009)	APHENA-Canada	DL(0-2)	1-h max	5.87 (1.82, 9.81)
Katsouyanni et al. (2009)[b]	APHENA-Canada	DL(0-2)	1-h max	0.73 (0.23, 1.20)
Summer				
Samoli et al. (2009)	21 European cities	0-1	8-h max	0.66 (0.24, 1.05)
Bell et al. (2004)[a]	95 U.S. communities	0-6	24-h avg	0.78 (0.26, 1.30)
Schwartz (2005a)	14 U.S. cities	0	1-h max	1.00 (0.30, 1.80)
Zanobetti and Schwartz (2008a)	48 U.S. cities	0	8-h max	1.51 (1.14, 1.87)
Zanobetti and Schwartz (2008b)	48 U.S. cities	0-3	8-h max	1.60 (0.84, 2.33)
Franklin and Schwartz (2008)	18 U.S. communities	0	24-h avg	1.79 (0.90, 2.68)
Gryparis et al. (2004)	APHEA2 (21 cities)	0-1	8-h max	1.80 (0.99, 3.06)
Medina-Ramon and Schwartz (2008)	48 U.S. cities	0-2	8-h max	1.96 (1.14, 2.82)
Katsouyanni et al. (2009)	APHENA-Europe	DL(0-2)	1-h max	2.38 (0.87, 3.91)
Bell et al. (2005)[a]	U.S. and Non-U.S.	---	24-h avg	3.02 (1.45, 4.63)
Katsouyanni et al. (2009)	APHENA-Canada	DL(0-2)	1-h max	3.34 (1.26, 5.38)
Katsouyanni et al. (2009)	APHENA-Canada	DL(0-2)	1-h max	0.42 (0.16, 0.67)
Levy et al. (2005)[a]	U.S. and Non-U.S.	---	24-h avg	3.38 (2.27, 4.42)
Ito et al. (2005)[a]	U.S. and Non-U.S.	---	24-h avg	3.50 (2.10, 4.90)
Katsouyanni et al. (2009)	APHENA-U.S.	DL(0-2)	1-h max	3.83 (1.90, 5.79)
Stafoggia et al. (2010)	10 Italian cities	DL(0-5)	8-h max	9.15 (5.41, 13.0)

[a]Multicity studies and meta-analyses from the 2006 O_3 AQCD. Bell et al. (2005)[a], Ito et al. (2005)[a], and Levy et al. (2005)[a] used a range of lag days in the meta-analysis: Lag 0, 1, 2, or average 0-1 or 1-2; Single-day lags from 0-3; and Lag 0 and 1-2; respectively.

[b]Risk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O_3 concentrations (see explanation in Section 6.2.7.2).

Table 6-42 Range of mean and upper percentile ozone concentrations in previous and recent multicity studies

Study	Location	Years	Averaging Time	Mean Concentration (ppb)[a]	Upper Percentile Concentrations (ppb)[a]
Gryparis et al. (2004)[b]	23 European cities (APHEA2)	1990-1997	1-h max 8-h max	Summer: 1-h max: 44-117 8-h max: 30-99 Winter: 1-h max: 11-57 8-h max: 8-49	Summer: 1-h max: 62-173 8-h max: 57-154 Winter: 1-h max: 40-88 8-h max: 25-78
Schwartz (2005a)[b]	14 U.S. cities	1986-1993	1-h max	35.1-60	25th: 26.5-52 75th: 46.3-69
Bell et al. (2004)	95 U.S. communities (NMMAPS)	1987-2000	24-h avg	26.0	NR
Bell et al. (2007)	98 U.S. communities (NMMAPS)	1987-2000	24-h avg	26.0[d]	NR
Bell and Dominici (2008)	98 U.S. communities (NMMAPS)	1987-2000 (All year and May-September)	24-h avg	All year: 26.8 May-September: 30.0	Maximum: All year: 37.3 May-September: 47.2
Franklin and Schwartz (2008)	18 U.S. communities	2000-2005 (May-September)	24-h avg	21.4-48.7	NR
Katsouyanni et al. (2009)[b,e]	NMMAPS 12 Canadian cities (APHEA2)	1987-1996 (Canada and U.S.) varied by city for Europe	1-h max	U.S.: 13.3-38.4 Canada: 6.7-8.4 Europe:18.3-41.9	75th: U.S.: 21.0-52.0 Canada: 8.7-12.5 Europe: 24.0-65.8
Medina-Ramón and Schwartz (2008)[b]	48 U.S. cities	1989-2000 (May-September)	8-h max	16.1-58.8	NR
Samoli et al. (2009)[b]	21 European cities (APHEA2)	1990-1997 (June-August)	8-h max	20.0-62.8	75th: 27.2-74.8
Stafoggia et al. (2010)	10 Italian cities	2001-2005 (April-September)	8-h max	41.2-58.9	75th: 47.0-71.6
Cakmak et al. (2011)	7 Chilean cities	1997-2007	8-h max	59.0-87.6	NR
Wong et al. (2010)	PAPA (4 cities)	1999-2003 (Bangkok) 1996-2002 (Hong Kong) 2001-2004 (Shanghai) 2001-2004 (Wuhan)	8-h avg	18.7-43.7	75th: 38.4 - 60.4 Max: 92.1 - 131.8
Zanobetti and Schwartz (2008b)	48 U.S. cities	1989-2000 (June-August)	8-h max	15.1-62.8	Max: 34.3-146.2 75th: 19.8-75.9
Zanobetti and Schwartz (2008a)	48 U.S. cities[c]	1989-2000 (Winter: December-February) (Spring: March-May) (Summer: June-August) (Autumn: September-November)	8-h max	Winter: 16.5 Spring: 41.6 Summer: 47.8 Autumn: 33.5	Max: Winter: 40.6 Spring: 91.4 Summer: 103.0 Autumn: 91.2

[a]O_3 concentrations were converted to ppb if the study presented them as µg/m3 by using the conversion factor of 0.51 assuming standard temperature (25° C) and pressure (1 atm).

[b]Study only reported median O_3 concentrations.

[c]Cities with less than 75% observations in a season excluded. As a result, 29 cities examined in winter, 32 in spring, 33 in autumn, and all 48 in the summer.

[d]Bell et al. (2007)did not report mean O_3 concentrations, however, it used a similar dataset as Bell et al. (2004) which consisted of 95 U.S. communities for 1987-2000. For comparison purposes the 24-h avg O_3 concentrations for the 95 communities from Bell et al. (2004) are reported here.

[e]Study did not present air quality data for the summer months.

CV=coefficient of variation

In addition to examining the relationship between short-term O_3 exposure and all-cause mortality, recent studies attempted to address the uncertainties that remained upon the completion of the 2006 O_3 AQCD. As a result, given the robust associations between

short-term O_3 exposure and mortality presented across studies in the 2006 O_3 AQCD and supported in the new multicity studies, the following sections primarily focus on the examination of previously identified uncertainties in the O_3-mortality relationship, specifically: O_3 associations with cause-specific mortality, confounding, lag structure (e.g., multiday effects and mortality displacement), effect modification (i.e., sources of heterogeneity in risk estimates across cities); and the O_3-mortality C-R relationship. Focusing specifically on these uncertainties allows for a more detailed characterization of the relationship between short-term O_3 exposure and mortality.

6.6.2.1 Confounding

Recent epidemiologic studies examined potential confounders of the O_3-mortality relationship. These studies specifically focused on whether PM and its constituents or seasonal trends confounded the association between short-term O_3 exposure and mortality.

Confounding by PM and PM Constituents

An important question in the evaluation of the association between short-term O_3 exposure and mortality is whether the relationship is confounded by particulate matter, particularly the PM chemical components that are found in the "summer haze" mixture which also contains O_3. However, because of the temporal correlation among these PM components and O_3, and their possible interactions, the interpretation of results from multipollutant models that attempt to disentangle the health effects associated with each pollutant is challenging.

The potential confounding effects of PM_{10} and $PM_{2.5}$ on the O_3-mortality relationship were examined by Bell et al. (2007) using data on 98 U.S. urban communities for the years 1987-2000 from the National Morbidity, Mortality, and Air Pollution Study (NMMAPS). In this analysis the authors included PM as a covariate in time-series models, and also examined $O_{3\text{-mo}}$rtality associations on days when O_3 concentrations were below a specified value. This analysis was limited by the small fraction of days when both PM and O_3 data were available, due to the every-3rd- or 6th-day sampling schedule for the PM indices, and the limited amount of city-specific data for $PM_{2.5}$ because it was only collected in most cities since 1999. As a result, of the 91 communities with $PM_{2.5}$ data, only 9.2% of days in the study period had data for both O_3 and $PM_{2.5}$, resulting in the use of only 62 communities in the $PM_{2.5}$ analysis. An examination of the correlation between PM (PM_{10} and $PM_{2.5}$) and O_3 across various strata of daily PM_{10} and $PM_{2.5}$ concentrations found that neither PM size fraction was highly correlated with O_3 across

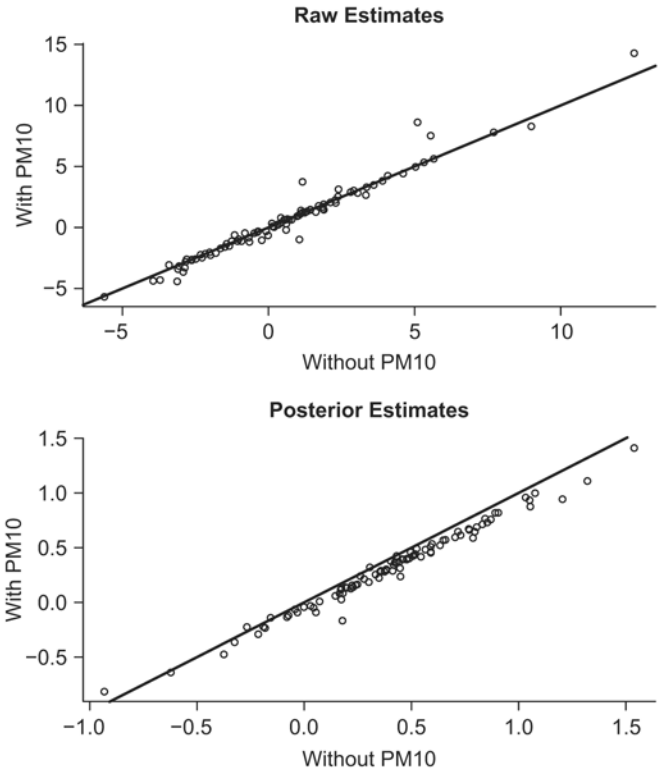
any of the strata examined. These results were also observed when using 8-h max and 1-h max O_3 exposure metrics. National and community-specific effect estimates of the association between short-term O_3 exposure and mortality were robust to inclusion of PM_{10} or $PM_{2.5}$ in time-series models through the range of O_3 concentrations (i.e., <10 ppb, 10-20, 20-40, 40-60, 60-80, and >80 ppb). For example, the percent increases in nonaccidental deaths per 10 ppb increase 24-h avg O_3 concentrations at lag 0-1 day were 0.22% (95% CI: -0.22, 0.65) without $PM_{2.5}$ and 0.21% (95% CI: -0.22, 0.64) with $PM_{2.5}$ in 62 communities.

Although no strong correlations between PM and O_3 were reported by Bell et al. (2007) the patterns observed suggest regional differences in their correlation. (Table 6-43). Both PM_{10} and $PM_{2.5}$ show positive correlations with O_3 in the Industrial Midwest, Northeast, Urban Midwest, and Southeast, especially in the summer months, presumably, because of the summer peaking sulfate. However, the mostly negative or weak correlations between PM and O_3 in the summer in the Southwest, Northwest, and southern California could be due to winter-peaking nitrate. Thus, the potential confounding effect of PM on the O_3-mortality relationship could be influenced by the relative contribution of sulfate and nitrate, which varies regionally and seasonally.

Table 6-43 Correlations between PM and ozone by season and region

	No. of Communities	Winter	Spring	Summer	Fall	Yearly
PM_{10}						
Industrial Midwest	19	0.37	0.44	0.44	0.39	0.41
Northeast	15	0.34	0.44	0.36	0.44	0.40
Urban Midwest	6	0.24	0.25	0.22	0.26	0.24
Southwest	9	0.00	0.02	-0.02	0.10	0.03
Northwest	11	-0.17	-0.20	-0.13	-0.11	-0.16
southern California	7	0.19	0.08	0.12	0.19	0.14
Southeast	25	0.33	0.35	0.31	0.31	0.32
U.S.	93	0.23	0.26	0.24	0.26	0.25
$PM_{2.5}$						
Industrial Midwest	19	0.18	0.39	0.43	0.44	0.36
Northeast	13	0.05	0.26	0.16	0.43	0.25
Urban Midwest	4	0.22	0.31	0.15	0.32	0.20
Southwest	9	-0.15	-0.08	-0.17	-0.15	-0.14
Northwest	11	-0.32	-0.34	-0.39	-0.24	-0.31
southern California	7	-0.25	-0.22	-0.25	-0.15	-0.23
Southeast	26	0.38	0.47	0.30	0.37	0.39
U.S.	90	0.09	0.21	0.12	0.22	0.16

Source: Bell et al. (2007).



Source: Reprinted with permission of Informa UK Ltd (Smith et al., 2009b).
The diagonal line indicates 1:1 ratio.

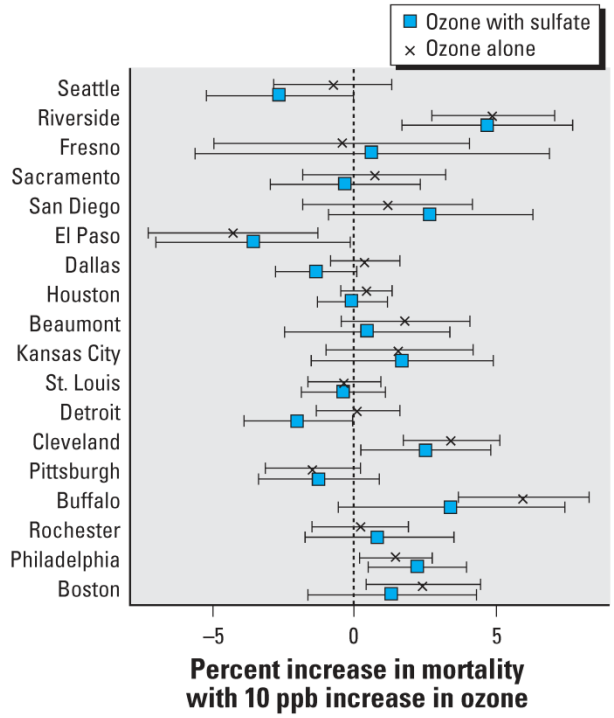
Figure 6-28 Scatter plots of ozone mortality risk estimates with versus without adjustment for PM_{10} in NMMAPS cities.

In an attempt to reassess a number of issues associated with the O_3-mortality relationship, including confounding, Smith et al. (2009b) re-analyzed the publicly available NMMAPS database for the years 1987-2000. The authors conducted a number of analyses using constrained distributed lag models and the average of 0- and 1-day lags. In addition, Smith et al. (2009b) examined the effect of different averaging times (24-h, 8-h, and 1-h max) on O_3-mortality regression coefficients, and whether PM_{10} confounded the O_3-mortality relationship. The authors reported that, in most cases, O_3 mortality risk estimates were reduced by between 22% and 33% in copollutant models with PM_{10}. This is further highlighted in Figure 6-28, which shows scatter plots of $O_{3\text{-mo}}$rtality risk estimates with adjustment for PM_{10} versus without adjustment for PM_{10}. Smith et al. (2009b) point out that a larger fraction (89 out of 93) of the posterior estimates lie below the diagonal line (i.e., estimates are smaller with PM_{10} adjustment) compared to the raw estimates (56 out of 93). This observation could be attributed to both sets of posterior estimates being calculated by "shrinking towards the mean." However, the most

prominent feature of these plots is that the variation of $O_{3\text{-}mo}$rtality risk estimates across cities is much larger than the impact of PM_{10} adjustment on the $O_{3\text{-}mo}$rtality relationship.

Franklin and Schwartz (2008) examined the sensitivity of O_3 mortality risk estimates to the inclusion of $PM_{2.5}$ or PM chemical components associated with secondary aerosols (e.g., sulfate [SO_4^{2-}], organic carbon [OC], and nitrate [NO_3-]) in copollutant models. This analysis consisted of between 3 and 6 years of data from May through September 2000-2005 from 18 U.S. communities. The association between O_3 and non-accidental mortality was examined in single-pollutant models and after adjustment for $PM_{2.5}$, sulfate, organic carbon, or nitrate concentrations. The single-city effect estimates were combined into an overall estimate using a random-effects model. In the single-pollutant model, the authors found a 0.89% (95% CI: 0.45, 1.33%) increase in nonaccidental mortality with a 10 ppb increase in same-day 24-h summertime O_3 concentrations across the 18 U.S. communities. Adjustment for $PM_{2.5}$ mass, which was available for 84% of the days, decreased the $O_{3\text{-}mo}$rtality risk estimate only slightly (from 0.88% to 0.79%), but the inclusion of sulfate in the model reduced the risk estimate by 31% (from 0.85% to 0.58%). However, sulfate data were only available for 18% of the days. Therefore, a limitation of this study is the limited amount of data for $PM_{2.5}$ chemical components due to the every-3rd-day or every-6th-day sampling schedule. For example, when using a subset of days when organic carbon measurements were available (i.e., 17% of the available days), O_3 mortality risk estimates were reduced to 0.51% (95% CI: -0.36 to 1.36) in a single-pollutant model.

Consistent with the studies previously discussed, the results from Franklin and Schwartz (2008) also demonstrate that the interpretation of the potential confounding effects of copollutants on O_3 mortality risk estimates is not straightforward. As presented in Figure 6-29, the regional and city-to-city variations in O_3 mortality risk estimates appear greater than the impact of adjusting for copollutants. In addition, in some cases, a negative O_3 mortality risk estimate becomes even more negative with the inclusion of sulfate (e.g., Seattle) in a copollutant model, or a null O_3 mortality risk estimate becomes negative when sulfate is included (e.g., Dallas and Detroit). Thus, the reduction in the overall O_3 mortality risk estimate (i.e., across cities) needs to be assessed in the context of the heterogeneity in the single-city estimates.



Source: Reprinted from Franklin and Schwartz (2008).

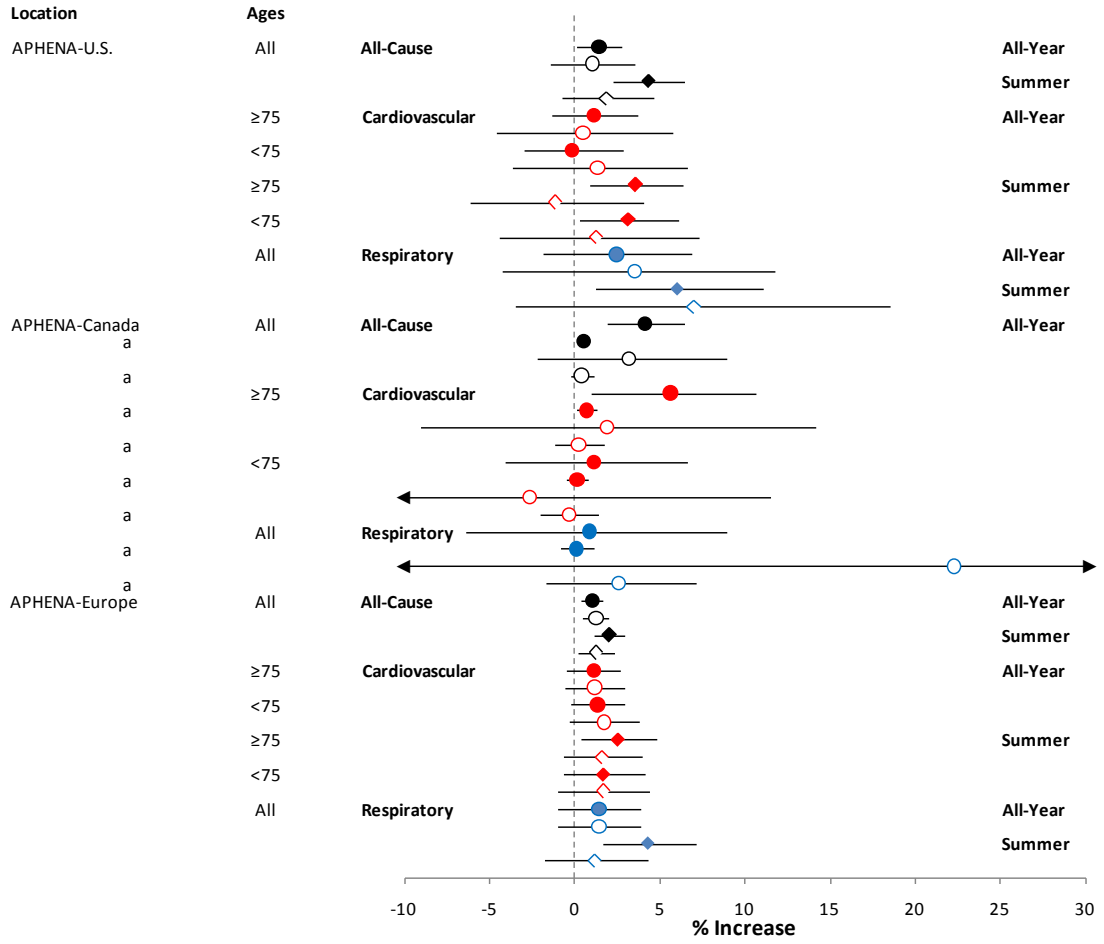
Figure 6-29 Community-specific ozone-mortality risk estimates for nonaccidental mortality per 10 ppb increase in same-day 24-h avg summertime ozone concentrations in single-pollutant models and copollutant models with sulfate.

In the APHENA study, the investigators from the U.S. (NMMAPS), Canadian, and European (APHEA2) multicity studies collaborated and conducted a joint analysis of PM_{10} and O_3 using each of these datasets (Katsouyanni et al., 2009). For mortality, each dataset consisted of a different number of cities and years of air quality data: U.S. encompassed 90 cities with daily O_3 data from 1987-1996 of which 36 cities had summer only O_3 measurements; Europe included 23 cities with 3-7 years of daily O_3 data during 1990-1997; and Canada consisted of 12 cities with daily O_3 data from 1987 to 1996. As discussed in Section 6.2.7.2, the APHENA study conducted extensive sensitivity analyses, of which the 8 df/year results for both the penalized spline (PS) and natural spline (NS) models are presented in the text for comparison purposes, but only the NS results are presented in figures because alternative spline models have previously been shown to result in similar effect estimates (HEI, 2003). Additionally, for the Canadian results, figures contain risk estimates standardized to both a 40 ppb increment for 1-h

max O_3 concentrations, consistent with the rest of the ISA, but also the approximate IQR across the Canadian cities as discussed previously (Section 6.2.7.2).

In the three datasets, the authors found generally positive associations between short-term O_3 exposure and all-cause, cardiovascular, and respiratory mortality. The estimated excess risks for O_3 were larger for the Canadian cities than for the U.S. and European cities. When examining the potential confounding effects of PM_{10} on O_3 mortality risk estimates, the sensitivity of the estimates varied across the data sets and age groups. In the Canadian dataset, adjusting for PM_{10} modestly reduced O_3 risk estimates for all-cause mortality for all ages in the PS (4.5% [95% CI: 2.2, 6.7%]) and NS (4.2% [95% CI: 1.9, 6.5%]) models to 3.8% (95% CI: -1.4, 9.8%) and 3.2% (95% CI: -2.2, 9.0%), respectively, at lag 1 for a 40 ppb increase in 1-h max O_3 concentrations (Figure 6-30; Table 6-44). However, adjusting for PM_{10} reduced O_3 mortality risk estimates in the ≥ 75-year age group, but increased the risk estimates in the <75-year age group. For cardiovascular and respiratory mortality more variable results were observed with O_3 risk estimates being reduced and increased, respectively, in copollutant models with PM_{10} (Figure 6-30; Table 6-44). Unlike the European and U.S. datasets, the Canadian dataset only conducted copollutant analyses at lag 1; as a result, to provide a comparison across study locations only the lag 1 results are presented for the European and U.S. datasets in this section.

In the European data, O_3 risk estimates were robust when adjusting for PM_{10} in the year-round data for all-cause, cardiovascular and respiratory mortality. When restricting the analysis to the summer months moderate reductions were observed in O_3 risk estimates for all-cause mortality with more pronounced reductions in respiratory mortality. In the U.S. data, adjusting for PM_{10} moderately reduced O_3 risk estimates for all-cause mortality in a year-round analysis at lag 1 (e.g., both the PS and NS models were reduced from 0.18% to 0.13%) (Figure 6-30; Table 6-44). Similar to the European data, when restricting the analysis to the summer months, adjusting for PM_{10} moderately reduced O_3 mortality risk estimates in the U.S. However, when examining cause-specific mortality risk estimates, consistent with the results from the Canadian dataset, which employed a similar PM sampling strategy (i.e., every-6th-day sampling), O_3 risk estimates for cardiovascular and respiratory mortality were more variable; reduced or increased in all-year and summer analyses. Overall, the estimated O_3 risks appeared to be moderately to substantially sensitive to inclusion of PM_{10} in copollutant models. Despite the multicity approach, the mostly every-6th-day sampling schedule for PM_{10} in the Canadian and U.S. datasets greatly reduced the sample size and limits the interpretation of these results.



Effect estimates are for a 40 ppb increase in 1-h max O_3 concentrations at lag 1. All estimates are for the 8 df/year model with natural splines. Circles represent all-year analysis results while diamonds represent summer season analysis results. Open circles and diamonds represent copollutant models with PM^{10}. Black = all-cause mortality; red = cardiovascular mortality; and blue = respiratory mortality. An "a" represents risk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O_3 concentrations (see explanation in Section 6.2.7.2).

Figure 6-30 Percent increase in all-cause (nonaccidental) and cause-specific mortality from the APHENA study for single- and copollutant models.

Table 6-44 Corresponding Effect Estimates for Figure 6-30

Location	Mortality	Ages	Season	Copollutant	% Increase (95% CI)
APHENA-U.S.	All-Cause	All	All-year		1.42 (0.08, 2.78)
				PM_{10}	1.02 (-1.40, 3.50)
			Summer		4.31 (2.22, 6.45)
				PM_{10}	1.90 (-0.78, 4.64)
	Cardiovascular	≥ 75	All-year		1.10 (-1.33, 3.67)
				PM_{10}	0.47 (-4.61, 5.79)
		<75			-0.16 (-3.02, 2.86)
				PM_{10}	1.34 (-3.63, 6.61)
		≥ 75	Summer		3.58 (0.87, 6.37)
				PM_{10}	-1.17 (-6.18, 4.07)
		<75			3.18 (0.31, 6.12)
				PM_{10}	1.26 (-4.46, 7.28)
	Respiratory	All	All-year		2.46 (-1.87, 6.86)
				PM_{10}	3.50 (-4.23, 11.8)
			Summer		6.04 (1.18, 11.1)
				PM_{10}	7.03 (-3.48, 18.5)
APHENA-Canada	All-Cause	All	All-year		4.15 (1.90, 6.45)
					0.52 (0.24, 0.80)a
				PM_{10}	3.18 (-2.18, 8.96)
				PM_{10}	0.40 (-0.28, 1.10)a
	Cardiovascular	≥ 75			5.62 (0.95, 10.7)
					0.70 (0.12, 1.30)a
				PM_{10}	1.90 (-9.03, 14.1)
				PM_{10}	0.24 (-1.20, 1.70)a
		<75			1.10 (-4.08, 6.61)
					0.14 (-0.53, 0.82)a
				PM_{10}	-2.64 (-14.7, 11.5)
				PM_{10}	-0.34 (-2.00, 1.40)a
	Respiratory	All			0.87 (-6.40, 8.96)
					0.11 (-0.84, 1.10)a
				PM_{10}	22.3 (-12.6, 71.3)
				PM_{10}	2.60 (-1.70, 7.10)a
APHENA-Europe	All-Cause	All	All-year		1.02 (0.39, 1.66)
				PM_{10}	1.26 (0.47, 1.98)
			Summer		2.06 (1.10, 2.94)
				PM_{10}	1.26 (0.16, 2.30)
	Cardiovascular	≥ 75	All-year		1.10 (-0.47, 2.70)
				PM_{10}	1.18 (-0.55, 2.94)
		<75			1.34 (-0.24, 2.94)
				PM_{10}	1.74 (-0.31, 3.75)
		≥75	Summer		2.54 (0.39, 4.80)
				PM_{10}	1.58 (-0.70, 3.99)
		<75			1.66 (-0.70, 4.15)
				PM_{10}	1.66 (-1.02, 4.40)
	Respiratory	All	All-year		1.42 (-1.02, 3.83)
				PM_{10}	1.42 (-1.02, 3.83)
			Summer		4.31 (1.66, 7.11)
				PM_{10}	1.18 (-1.79, 4.31)

[a]Risk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O_3 concentrations (see explanation in Section 6.2.7.2).

Stafoggia et al. (2010) examined the potential confounding effects of PM_{10} on the O_3-mortality relationship in individuals 35 years of age and older in 10 Italian cities from

2001 to 2005. In a time-stratified case-crossover analysis, using data for the summer months (i.e., April-September), the authors examined O_3-mortality associations across each city, and then obtained a pooled estimate through a random-effects meta-analysis. Stafoggia et al. (2010) found a strong association with nonaccidental mortality (9.2% [95% CI: 5.4, 13.0%] for a 30 ppb increase in 8-h max O_3 concentrations) in an unconstrained distributed lag model (lag 0-5) that persisted in copollutant models with PM_{10} (9.2% [95% CI: 5.4, 13.7%]). Additionally, when examining cause-specific mortality, the authors found positive associations between short-term O_3 exposure and cardiovascular (14.3% [95% CI: 6.7, 22.4%]), cerebrovascular (8.5% [95% CI: 0.1, 16.3%]), and respiratory (17.6% [95% CI: 1.8, 35.6%]) mortality in single-pollutant models. In copollutant models, O_3-mortality effect estimates for cardiovascular and cerebrovascular mortality were robust to the inclusion of PM_{10} (9.2% [95% CI: 5.4, 13.7%]) and 7.3% [95% CI: -1.2, 16.3%], respectively), and attenuated, but remained positive, for respiratory mortality (9.2% [95% CI: -6.9, 28.8%]). Of note, the correlations between O_3 and PM_{10} across cities were found to be generally low, ranging from (-0.03 to 0.49). The authors do not specify the sampling strategy used for PM_{10} in this analysis.

Confounding by Seasonal Trend

The APHENA study (Katsouyanni et al., 2009), mentioned above, also conducted extensive sensitivity analyses to identify the appropriate: smoothing method and basis functions to estimate smooth functions of time in city-specific models; and degrees of freedom to be used in smooth functions of time, to adjust for seasonal trends. Because O_3 peaks in the summer and mortality peaks in the winter, not adjusting or not sufficiently adjusting for the seasonal trend would result in an apparent negative association between the O_3 and mortality time-series. Katsouyanni et al. (2009) examined the effect of the extent of smoothing for seasonal trends by using models with 3 df/year, 8 df/year (the choice for their main model), 12 df/year, and df/year selected using the sum of absolute values of partial autocorrelation function of the model residuals (PACF) (i.e., choosing the degrees of freedom that minimizes positive and negative autocorrelations in the residuals). Table 6-45 presents the results of the degrees of freedom analysis using alternative methods to calculate a combined estimate: the Berkey et al. (1998) meta-regression and the two-level normal independent sampling estimation (TLNISE) hierarchical method. The results show that the methods used to combine single-city estimates did not influence the overall results, and that neither 3 df/year nor choosing the df/year by minimizing the sum of absolute values of PACF of regression residuals was sufficient to adjust for the seasonal negative relationship between O_3 and mortality. However, it should be noted, the majority of studies in the literature that examined the mortality effects of short-term O_3 exposure, particularly the multicity studies, used 7 or

8 df/year to adjust for seasonal trends, and in both methods a positive association was observed between O_3 exposure and mortality.

Table 6-45 Sensitivity of ozone risk estimates per 10 μg/m^3 increase in 24-h avg ozone concentrations at lag 0-1 to alternative methods for adjustment of seasonal trend, for all-cause mortality using Berkey MLE and TLNSE Hierarchical Models

Seasonality Control	Berkey	TLNISE
3 df/year	-0.54 (-0.88, 0.20)	-0.55 (-0.88, -0.22)
8 df/year	0.30 (0.11, 0.50)	0.31 (0.09, 0.52)
12 df/year	0.34 (0.15, 0.53)	0.33 (0.12, 0.54)
PACF	-0.62 (-1.01, -0.22)	-0.62 (-0.98, -0.27)

Source: Reprinted with permission of Health Effects Institute (2009).

6.6.2.2 Effect Modification

There have been several multicity studies that examined potential effect modifiers, or time-invariant factors, that may modify O_3 mortality risk estimates. These effect modifiers can be categorized into either individual-level or community-level characteristics, which are traditionally, examined in second stage regression models. The results from these analyses also inform upon whether certain populations are susceptible to O_3-related health effects (Chapter 8). In addition to potentially modifying the association between short-term O_3 exposure and mortality, both individual-level and community-level characteristics may also contribute to the apparent geographic pattern of spatial heterogeneity in O_3 mortality risk estimates. As a result, the geographic pattern of O_3 mortality risk estimates is also evaluated in this section.

Individual-Level Characteristics

Medina-Ramón and Schwartz (2008) conducted a case-only study in 48 U.S. cities to identify populations potentially susceptible to O_3-related mortality for the period 1989-2000 (May through September of each year [i.e., warm season]). A case-only design predicts the occurrence of time-invariant characteristics among cases as a function of the exposure level (Armstrong, 2003). For each potential effect modifier (time-invariant individual-level characteristics), city-specific logistic regression models were fitted, and the estimates were pooled across all cities. Furthermore, the authors examined potential differences in individual effect modifiers according to several city characteristics (e.g., mean O_3 level, mean temperature, households with central air

conditioning, and population density) in a meta-regression. Across cities the authors found a 1.96% (95% CI: 1.14-2.82%) increase in mortality at lag 0-2 for a 30 ppb increase in 8-h max O_3 concentrations. Additionally, Medina-Ramón and Schwartz (2008) examined a number of individual-level characteristics (e.g., age, race) and chronic conditions (e.g., secondary causes of death) as effect modifiers of the association between short-term O_3 exposure and mortality. The authors found that older adults (i.e., ≥ 65), women >60 years of age, black race, and secondary atrial fibrillation showed the greatest additional percent change in O_3-related mortality (Table 6-46). In addition, when examining city-level characteristics, the authors found that older adults, black race, and secondary atrial fibrillation had a larger effect on O_3 mortality risk estimates in cities with lower O_3 levels. Of note, a similar case-only study (Schwartz, 2005b) examined potential effect modifiers of the association between temperature and mortality, which would be expected to find results consistent with the Medina-Ramón and Schwartz (2008) study due to the high correlation between temperature and O_3. However, when stratifying days by temperature Schwartz (2005b) found strong evidence that diabetes modified the temperature-mortality association on hot days, which was not as evident when examining the O_3-mortality association in Medina-Ramón and Schwartz (2008). This difference could be due to the study design and populations included in both studies, a multicity study including all ages (Medina-Ramón and Schwartz, 2008) compared to a single-city study of individuals ≥ 65 years of age (Schwartz, 2005b). However, when examining results stratified by race, nonwhites were found to have higher mortality risks on both hot and cold days, which provide some support for the additional risk found for black race in Medina-Ramón and Schwartz (2008).

Individual-level factors that may result in susceptibility to O_3-related mortality were also examined by Stafoggia et al. (2010). As discussed above, using a time-stratified case-crossover analysis, the authors found an association between short-term O_3 exposure and nonaccidental mortality in an unconstrained distributed lag model in 10 Italian cities (9.2% [95% CI: 5.4, 13.0%; lag 0-5 for a 30 ppb increase in 8-h max O_3 concentrations). Stafoggia et al. (2010) conducted additional analyses to examine whether age, sex, income level, location of death, and underlying chronic conditions increased the risk of O_3-related mortality, but data were only available for nine of the cities for these analyses. Of the individual-level factors examined, the authors found the strongest evidence for increased risk of O_3-related mortality in individuals ≥ 85 years of age (22.4% [95% CI: 15.0, 30.2%]), women (13.7% [95% CI: 8.5, 19.7%]), and out-of-hospital deaths (13.0% [95% CI: 6.0, 20.4%]). When focusing specifically on out-of hospital deaths and the subset of individuals with chronic conditions, Stafoggia et al. (2010) found the strongest association for individuals with diabetes, which is consistent with the potentially increased susceptibility of diabetics on hot days observed in Schwartz (2005b).

Table 6-46 Additional percent change in ozone-related mortality for individual-level susceptibility factors

	Percentage	(95% CI)
Socio-demographic characteristics		
Age 65 yr or older	1.10	0.44, 1.77
Women	0.58	0.18, 0.98
Women <60 yr old[b]	-0.09	-0.76, 0.58
Women ≥ 60 yr old[b]	0.60	0.25, 0.96
Black race	0.53	0.19, 0.87
Low education	-0.29	-0.81, 0.23
Chronic conditions (listed as secondary cause)		
Respiratory system diseases		
Asthma	1.35	-0.31, 3.03
COPD	0.01	-0.49, 0.52
Circulatory system diseases		
Atherosclerosis	-0.72	-1.89, 0.45
Atherosclerotic CVD	0.74	-0.86, 2.37
Atherosclerotic heart disease	-0.38	-1.70, 0.96
Congestive heart disease	-0.04	-0.39, 0.30
Atrial fibrillation	1.66	0.03, 3.32
Stroke	0.17	-0.28, 0.62
Other diseases		
Diabetes	0.19	-0.46, 0.84
Inflammatory diseases	0.18	-1.09, 1.46

[a]These estimates represent the additional percent change in mortality for persons who had the characteristic being examined compared to persons who did not have the characteristic, when the mean O_3 level of the previous 3 days increased 10 ppb. These values were not standardized because they do not represent the actual effect estimate for the characteristic being evaluated, but instead, the difference between effect estimates for persons with versus without the condition.
[b]Compared with males in the same age group.

Source: Reprinted with permission from Lippincott Williams & Wilkins, Medina-Ramón and Schwartz (2008).

Additionally, Cakmak et al. (2011) examined the effect of individual-level characteristics that may modify the O_3-mortality relationship in 7 Chilean cities. In a time-series analysis using a constrained distributed lag of 0-6 days, Cakmak et al. (2011) found evidence for larger O_3 mortality effects in individuals > 75 years of age compared to younger ages, which is similar to Medina-Ramón and Schwartz (2008) and Stafoggia et al. (2010). Unlike the studies discussed above O_3-mortality risk estimates were found to be slightly larger in males (3.71% [95% CI: 0.79, 6.66] for a 40 ppb increase in max 8-h avg O_3 concentrations), but were not significantly different than those observed for females (3.00% [95% CI: 0.43, 5.68]). The major focus of Cakmak et al. (2011) is the examination of the influence of SES indicators (i.e., educational attainment, income level, and employment status) on the O_3-mortality relationship. The authors found the largest risk estimates in the lowest SES categories for each of the indicators examined this includes: primary school not completed when examining educational attainment; the lowest quartile of income level; and unemployed individuals when comparing employment status.

Overall, uncertainties exist in the interpretation of the potential effect modifiers, identified in Medina-Ramón and Schwartz (2008), Stafoggia et al. (2010), and Cakmak et

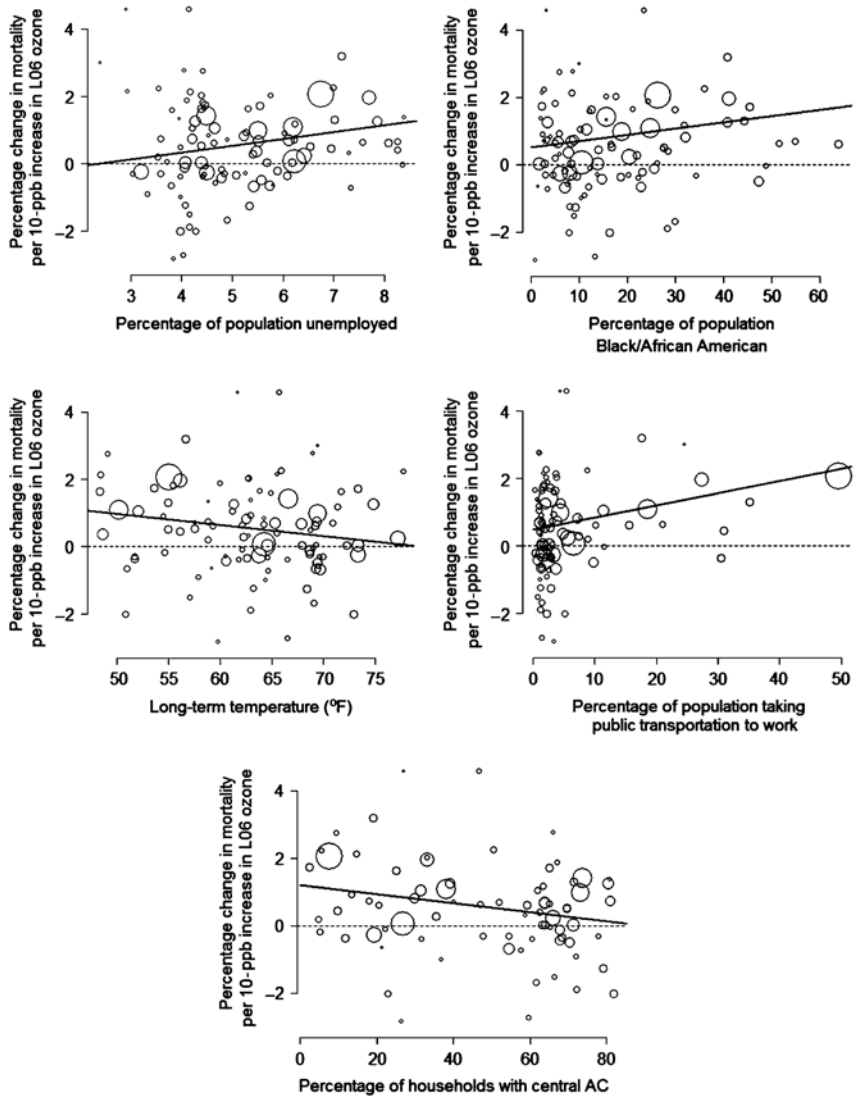
al. (2011) of the O_3-mortality relationship due to the expected heterogeneity in O_3 mortality risk estimates across cities as highlighted in Smith et al. (2009b) (Figure 6-28) and Franklin and Schwartz (2008) (Figure 6-29). For example, it is difficult to determine the relative importance of a susceptibility factor that results in an additional percent increase in mortality in a multicity analysis when analyses of the individual cities within the study did not indicate associations between O_3 and mortality. In addition, it is likely that individual-level susceptibility factors identified in Medina-Ramón and Schwartz (2008), Stafoggia et al. (2010), and Cakmak et al. (2011) only modify the O_3-mortality relationship. The factors identified span pollutants as is evident by older adults (i.e., $\geq$ 65) often being identified as an effect modifier of PM mortality risk estimates (U.S. EPA, 2009d).

Community-level Characteristics

Several studies also examined city-level (i.e., ecological) variables to explain city-to-city variation in estimated O_3 mortality risk estimates. Bell and Dominici (2008) investigated whether community-level characteristics, such as race, income, education, urbanization, transportation use, PM and O_3 levels, number of O_3 monitors, weather, and air conditioning use could explain the heterogeneity in O_3-mortality risk estimates across cities. The authors analyzed 98 U.S. urban communities from NMMAPS for the period 1987-2000. In the all-year regression model that included no community-level variables, a 20 ppb increase in 24-h avg O_3 concentrations during the previous week was associated with a 1.04% (95% CI: 0.56, 1.55) increase in mortality. Bell and Dominci (2008) found that higher $O_{3\text{-mo}}$rtality effect estimates were associated with higher: percent unemployment, fraction of the population Black/African-American, percent of the population that take public transportation to work; and with lower: temperatures and percent of households with central air conditioning (Figure 6-31). The modification of O_3-mortality risk estimates reported for city-specific temperature and prevalence of central air conditioning in this analysis confirm the result from the meta-analyses reviewed in the 2006 O_3 AQCD.

The APHENA project (Katsouyanni et al., 2009) examined potential effect modification of O_3 risk estimates in the Canadian, European, and U.S. data sets using a consistent set of city-specific variables. Table 6-47 presents the results from all age analyses for all-cause mortality using all-year O_3 data for the average of lag 0-1 day. While there are several significant effect modifiers in the U.S. data, the results are mostly inconsistent with the results from the Canadian and European data sets. The positive effect modification by percentage unemployed and the negative effect modification by mean temperature (i.e., a surrogate for air conditioning rate) are consistent with the results reported by Bell and Dominici (2008) discussed above. However, the lack of consistency across the data sets, even between the Canadian and U.S. data, makes it difficult to

interpret the results. Some of these associations may be due to coincidental correlations with other unmeasured factors that vary regionally (e.g., mean SO_2 tend to be higher in the eastern U.S.).



Source: Reprinted with permission of Johns Hopkins Bloomberg School of Public Health, Bell and Dominici (2008).

Figure 6-31 Ozone mortality risk estimates and community-specific characteristics, U.S., 1987-2000. The size of each circle corresponds to the inverse of the standard error of the community's maximum likelihood estimate. Risk estimates are for a 10 ppb increase in 24-h avg ozone concentrations during the previous week.

Table 6-47 Percent change in all-cause mortality, for all ages, associated with a 40ppb increase in 1-h max ozone concentrations at Lag 0–1 at the 25th and 75th percentile of the center-specific distribution of selected effect modifiers

	Canada			Europe			U.S.		
Effect Modifier	25th Percentile Estimate (95% CI)	75th Percentile Estimate (95% CI)	t Value	25th Percentile Estimate (95% CI)	75th Percentile Estimate (95% CI)	t Value	25th Percentile Estimate (95% CI)	75th Percentile Estimate (95% CI)	t Value
NO_2 CV	3.10 (1.90, 4.40)	3.99 (2.38, 5.62)	1.33	1.66 (0.71, 2.62)	1.34 (-0.08, 2.78)	-0.49	1.26 (0.47, 1.98)	0.08 (-0.78, 0.95)	-2.87
Mean SO_2	2.22 (0.71, 3.83)	4.72 (2.94, 6.61)	2.16	1.58 (0.47, 2.62)	1.66 (0.39, 2.86)	0.16	0.47 (-0.47, 1.42)	1.98 (1.10, 2.94)	2.79
O_3 CV	2.86 (0.79, 5.05)	3.50 (2.14, 4.89)	0.60	2.62 (1.50, 3.75)	1.10 (0.24, 1.98)	-2.65	0.16 (-0.70, 1.10)	1.50 (0.71, 2.22)	2.68
Mean NO_2/PM_{10}	3.91 (2.54, 5.29)	2.54 (0.95, 4.15)	-1.58	1.74 (0.87, 2.70)	1.50 (0.47, 2.62)	-0.43	-0.08 (-1.02, 0.95)	1.26 (0.47, 2.06)	2.64
Mean Temperature	2.86 (0.95, 4.72)	3.50 (2.22, 4.89)	0.83	1.58 (0.39, 2.86)	1.58 (0.31, 2.78)	-0.04	2.14 (1.34, 2.94)	0.00 (-0.78, 0.79)	-4.40
% ≥ 75 yr	2.22 (0.79, 3.58)	4.23 (3.02, 5.54)	2.68	1.50 (0.55, 2.46)	1.82 (0.55, 3.10)	0.52	1.02 (0.24, 1.90)	1.02 (0.31, 1.74)	-0.02
Age standardized Mortality	2.62 (0.79, 4.48)	4.07 (2.22, 5.87)	1.14	1.10 (-0.16, 2.38)	1.98 (0.79, 3.26)	1.07	0.00 (-0.94, 0.87)	1.58 (0.87, 2.38)	3.81
% Unemployed	2.78 (1.42, 4.07)	3.75 (2.54, 4.89)	1.88	1.42 (-0.47, 3.34)	1.34 (-0.47, 3.18)	-0.07	0.16 (-0.78, 1.18)	1.50 (0.71, 2.30)	2.45

Source: Adapted with permission of Health Effects Institute, Katsouyanni et al. (2009).

Regional Pattern of Ozone-Mortality Risk Estimates

In addition to examining whether individual- and community-level factors modify the $O_{3\text{-mo}}$rtality association, studies also examined whether these associations varied regionally within the U.S. Bell and Dominici (2008), in the study discussed above, also noted that O_3-mortality risk estimates were higher in the Northeast (1.44% [95% CI: 0.78, 2.10%]) and Industrial Midwest (0.73% [95% CI: 0.11, 1.35%]), while null associations were observed in the Southwest and Urban Midwest (Table 6-48). The regional heterogeneity in O_3-mortality risk estimates was further reflected by Bell and Dominici (2008) in a map of community-specific Bayesian O_3-mortality risk estimates (Figure 6-32). It is worth noting that in the analysis of PM_{10} using the same data set, Peng et al. (2005) also found that both the Northeast and Industrial Midwest showed particularly

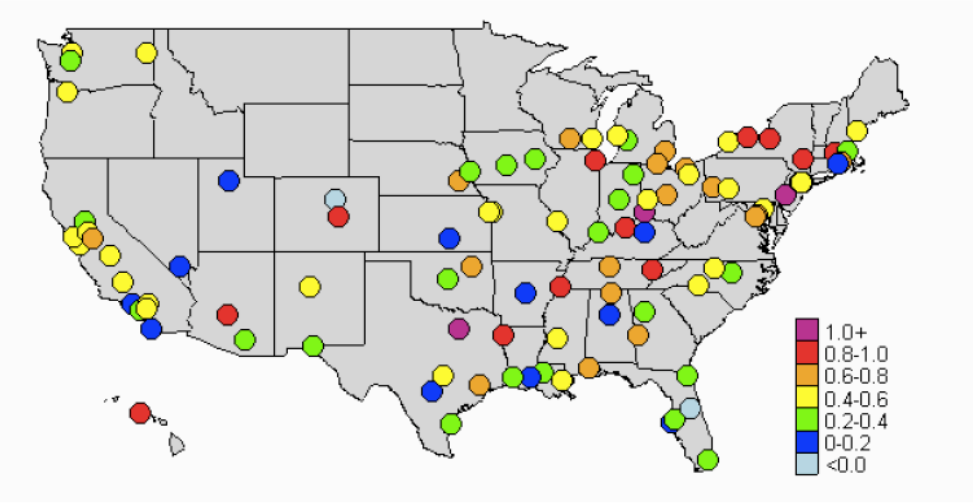
elevated effects, especially during the summer months. As mentioned above, although no evidence for confounding of O_3 mortality risk estimates by PM_{10} was observed, Bell et al. (2007) did find regional differences in the correlation between O_3 and PM_{10}. Thus, the heterogeneity in O_3 mortality risk estimates may need to be examined as a function of the correlation between PM and O_3.

Smith et al. (2009b), as discussed earlier, also examined the regional difference in O_3 mortality risk estimates across the same seven regions and similarly found evidence for regional heterogeneity. In addition, Smith et al. (2009b) constructed spatial maps of the risk estimates by an extension of a hierarchical model that allows for spatial auto-correlation among the city-specific random effects. Figure 6-31 presents the spatial map of O_3 mortality coefficients from the Smith et al. (2009b) analysis that used 8-h max O_3 concentrations during the summer. The results from the Bell and Dominici (2008) analysis (Figure 6-32) shows much stronger apparent heterogeneity in O_3-mortality risk estimates across cities than the smoothed map from Smith et al. (2009b) (Figure 6-33), but both maps generally show larger risk estimates in the eastern region of the U.S.

Table 6-48 Percentage increase in daily mortality for a 10 ppb increase in 24-h avg ozone concentrations during the previous week by geographic region in the U.S., 1987-2000

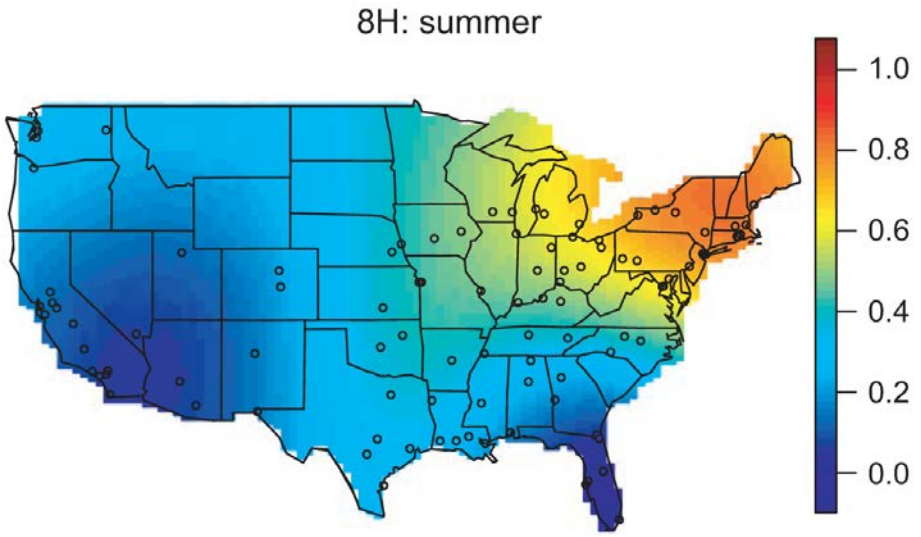
	No. of Communities	Regional Estimate	95% PI*
Regional results			
Industrial Midwest	20	0.73	0.11, 1.35
Northeast	16	1.44	0.78, 2.10
Northwest	12	0.08	-0.92, 1.09
southern California	7	0.21	-0.46, 0.88
Southeast	26	0.38	-0.07, 0.85
Southwest	9	-0.06	-0.92, 0.81
Urban Midwest	7	-0.05	-1.28, 1.19
National results			
All continental communities	97	0.51	0.27, 076
All communities	98	0.52	0.28, 0.77

Source: Used with permission from Johns Hopkins Bloomberg School of Public Health, Bell and Dominici (2008).



Source: Reprinted with permission of Johns Hopkins Bloomberg School of Public Health (Bell and Dominici, 2008).

Figure 6-32 Community-specific Bayesian ozone-mortality risk estimates in 98 U.S. communities.



Source: Reprinted with permission of Informa UK Ltd. (Smith et al., 2009b).

Figure 6-33 Map of spatially dependent ozone-mortality coefficients for 8-h max ozone concentrations using summer data.

6.6.2.3 Interaction

The terms effect modification and interaction are often used interchangeably, but theoretically they represent different concepts. Although interactions can lead to either antagonistic or synergistic effects, most studies attempt to identify potential factors that interact synergistically with O_3 to increase the risk of mortality. Within this section, interactive effects are defined as time-varying covariates, such as temperature and copollutants that are included in 1st stage time-series regression models. To date, only a few time-series studies have investigated the potential interaction between O_3 exposure and copollutants or weather variables. This can be attributed to the moderate to high correlation between O_3 and these covariates, which makes such investigations methodologically challenging.

Ren et al. (2008) examined the possible synergistic effect between O_3 and temperature on mortality in the 60 largest eastern U.S. communities from the NMMAPS data during the warm months (i.e., April to October) from 1987-2000. This analysis was restricted to the eastern areas of the U.S. (i.e., Northeast, Industrial Midwest and Southeast) because a previous study which focused specifically on the eastern U.S. found that temperature-mortality patterns differ between the northeast and southeast regions possibly due to climatic differences (Curriero et al., 2002). To examine possible geographic differences in the interaction between temperature and O_3, Ren et al. (2008) further divided the NMMAPS regions into the Northeast, which included the Northeast and Industrial Midwest regions (34 cities), and the Southeast, which included the Southeast region (26 cities). The potential synergistic effects between O_3 and temperature were examined using two different models. Model 1 included an interaction term in a Generalized Additive Model (GAM) for O_3 and maximum temperature (3-day avg values were used for both terms) to examine the bivariate response surface and the pattern of interaction between the two variables in each community. Model 2 consisted of a Generalized Linear Model (GLM) that used interaction terms to stratify by "low," "moderate," and "high" temperature days using the first and third quartiles of temperature as cut-offs to examine the percent increase in mortality in each community. Furthermore, a two-stage Bayesian hierarchical model was used to estimate the overall percent increase in all-cause mortality associated with short-term O_3 exposure across temperature levels and each region using model 2. The same covariates were used in both model 1 and 2. The bivariate response surfaces from model 1 suggest possible interactive effects between O_3 and temperature although the interpretation of these results is not straightforward due to the high correlation between these terms. The apparent interaction between temperature and O_3 as evaluated in model 2 varied across geographic regions. In the northeast region, a 20 ppb increase in 24-h avg O_3 concentrations at lag 0-2 was associated with an increase of 4.49% (95% posterior interval [PI]: 2.39, 6.36%), 6.21%

(95% PI: 4.47, 7.66%) and 12.8% (95% PI: 9.77, 15.7%) in mortality at low, moderate and high temperature levels, respectively. The corresponding percent increases in mortality in the southeast region were 2.27% (95% PI: -2.23, 6.46%) for low temperature, 3.02% (95% PI: 0.44, 5.70%) for moderate temperature, and 2.60% (95% PI: -0.66, 6.01%) for high temperature.

When examining the relationship between temperature and O_3-related mortality, the results reported by Ren et al. (2008) (i.e., higher O_3-mortality risks on days with higher temperatures) may appear to contradict the results of Bell and Dominici (2008) described earlier (i.e., communities with higher temperature have lower O_3-mortality risk estimates). However, the observed difference in results can be attributed to the interpretation of effect modification in a second-stage regression which uses long-term average temperatures, as was performed by Bell and Dominici (2008), compared to a first-stage regression that examines the interaction between daily temperature and O_3-related mortality. In this case, the second-stage regression results from Bell and Dominici (2008) indicate that a city with lower temperatures, on average, tend to show a stronger O_3 mortality effect, whereas, in the first-stage regression performed by Ren et al. (2008), the days with higher temperature tend to show a larger O_3-mortality effect. This observed difference may in part reflect the higher air conditioning use in communities with higher long-term average temperatures. Therefore, the findings from Ren et al. (2008) indicating generally lower O_3 risk estimates in the southeast region where the average temperature is higher than in the northeast region is consistent with the regional results reported by Bell and Dominici (2008). As demonstrated by the results from both Ren et al. (2008) and Bell and Dominici (2008) caution is required when interpreting results from studies that examined interactive effects using two different approaches because potential effect modification as suggested in a second-stage regression generally does not provide evidence for a short-term interaction examined in a first-stage regression. Overall, further examination of the potential interactive (synergistic) effects of O_3 and covariates in time-series regression models is required to more clearly understand the factors that may influence O_3 mortality risk estimates.

6.6.2.4 Evaluation of the Ozone-Mortality C-R Relationship and Related Issues

Evaluation of the O_3-mortality concentration-response relationship is not straightforward because the evidence from multicity studies (using log-linear models) suggests that O_3-mortality associations are highly heterogeneous across regions. In addition, there are numerous issues that may influence the shape of the O_3-mortality concentration-response relationship that warrant examination including: multi-day effects (distributed lags),

potential adaptation, mortality displacement (i.e., hastening of death by a short period), and the exposure metric used to compute risks (e.g., 1-h daily max versus 24-h avg). The following section presents the recent studies identified that conducted an initial examination of these issues.

Multiday Effects, Mortality Displacement, and Adaptation

The pattern of positive lagged associations followed by negative associations in a distributed lag model may be considered an indication of "mortality displacement" (i.e., deaths are occurring in frail individuals and exposure is only moving the day of death to a day slightly earlier). Zanobetti and Schwartz (2008b) examined this issue in 48 U.S. cities during the warm season (i.e., June-August) for the years 1989-2000. In an initial analysis, the authors applied a GLM to examine same-day O_3-mortality effects, and in the model included an unconstrained distributed lag for apparent temperature to take into account the effect of temperature on the day death occurred and the previous 7 days. To examine mortality displacement Zanobetti and Schwartz (2008b) refit models using two approaches: an unconstrained and a smooth distributed lag each with 21-day lags for O_3. In this study, all-cause mortality as well as cause-specific mortality (i.e., cardiovascular, respiratory, and stroke) were examined for evidence of mortality displacement. The authors found a 0.96% (95% CI: 0.60, 1.30%) increase in all-cause mortality across all 48 cities for a 30 ppb increase in 8-h max O_3 concentrations at lag 0 whereas the combined estimate of the unconstrained distributed lag model (lag 0-20) was 1.54% (95% CI: 0.15, 2.91%). Similarly, when examining the cause-specific mortality results (Table 6-49), larger risk estimates were observed for the distributed lag model compared to the lag 0 day estimates. However, for stroke a slightly larger effect was observed at lags 4-20 compared to lags 0-3 suggesting a larger window for O_3-induced stroke mortality. This is further supported by the sum of lags 0 through 20 days showing the greatest effect. Overall, these results suggest that estimating the mortality risk using a single day of O_3 exposure may underestimate the public health impact, but the extent of multi-day effects appear to be limited to a few days. This is further supported by the shape of the combined smooth distributed lag (Figure 6-34). It should be noted that the proportion of total variation in the effect estimates due to the between-cities heterogeneity, as measured by I^2 statistic, was relatively low (4% for the lag 0 estimates and 21% for the distributed lag), but 21 out of the 48 cities exhibited null or negative estimates. As a result, the estimated shape of the distributed lag cannot be interpreted as a general form of lag structure of associations applicable to all the cities included in this analysis.

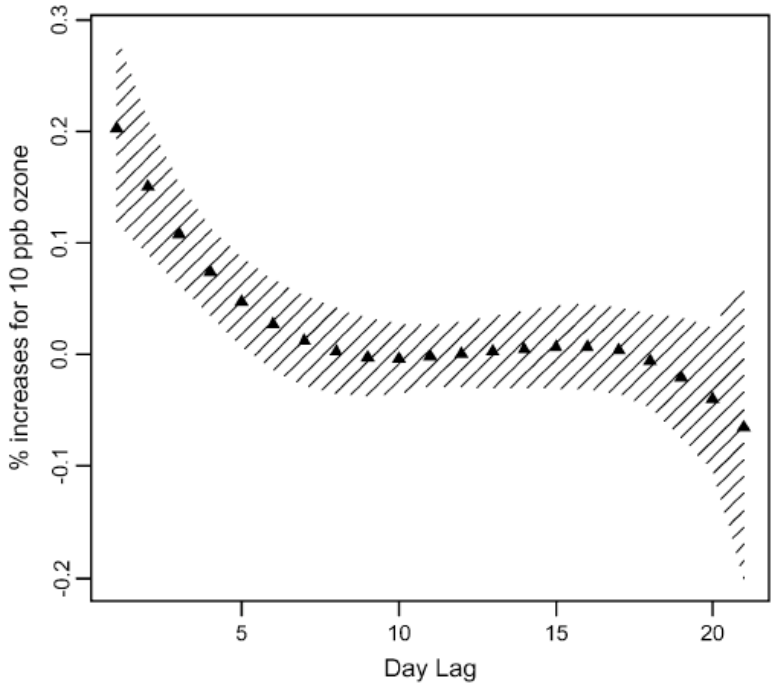
Table 6-49 Estimated effect of a 10 ppb increase in 8-h max ozone concentrations on mortality during the summer months for single-day and distributed lag models

	% (Percentage)	95% CI
Total mortality		
Lag 0	0.32	0.20, 0.43
Sum lags 0-20	0.51	0.05, 0.96
Sum lags 0-3	0.53	0.28, 0.77
Sum lags 4-20	-0.02	-0.35, 0.31
Cardiovascular mortality		
Lag 0	0.47	0.30, 0.64
Sum lags 0-20	0.49	-0.01, 1.00
Sum lags 0-3	0.80	0.48, 1.13
Sum lags 4-20	-0.23	-0.67, 0.22
Respiratory mortality		
Lag 0	0.54	0.26, 0.81
Sum lags 0-20	0.61	-0.41, 1.65
Sum lags 0-3	0.83	0.38, 1.28
Sum lags 4-20	-0.24	-1.08, 0.60
Stroke		
Lag 0	0.37	0.01, 0.74
Sum lags 0-20	2.20	0.76, 3.67
Sum lags 0-3	0.92	0.26, 1.59
Sum lags 4-20	1.26	0.05, 2.49

Source: Reprinted with permission from American Thoracic Society, Zanobetti and Schwartz (2008b).

Samoli et al. (2009) also investigated the temporal pattern of mortality effects in response to short-term exposure to O_3 in 21 European cities that were included in the APHEA2 project. Using a method similar to Zanobetti and Schwartz (2008b), the authors applied unconstrained distributed lag models with lags up to 21 days in each city during the summer months (i.e., June through August) to examine the effect of O_3 on all-cause, cardiovascular, and respiratory mortality. They also applied a generalized additive distributed lag model to obtain smoothed distributed lag coefficients. However, unlike Zanobetti and Schwartz (2008b), Samoli et al. (2009) controlled for temperature using a linear term for humidity and an unconstrained distributed lag model of temperature at lags 0-3 days. The choice of 0- through 3-day lags of temperature was based on a previous European multicity study (Baccini et al., 2008), which suggested that summer temperature effects last only a few days. Upon combining the individual city estimates across cities in a second stage regression, Samoli et al. (2009) found that the estimated effects on respiratory mortality were extended for a period of two weeks. However, for all-cause and cardiovascular mortality, the 21-day distributed lag models yielded null or (non-significant) negative estimates (Table 6-50). Figure 6-35 shows the distributed lag coefficients for all-cause mortality, which exhibit a declining trend and negative

coefficients beyond 5-day lags. The authors' interpretation of these results was that "using single-day exposures may have overestimated the effects on all-cause and cardiovascular mortality, but underestimated the effects on respiratory mortality." Thus, the results in part suggest evidence of mortality displacement for all-cause and cardiovascular mortality.



Source: Reprinted with permission of American Thoracic Society (Zanobetti and Schwartz, 2008b).

The triangles represent the percent increase in all-cause mortality for a 10 ppb increase in 8-h max ozone concentrations at each lag while the shaded areas are the 95% point-wise confidence intervals.

Figure 6-34 Estimated combined smooth distributed lag for 48 U.S. cities during the summer months.

Table 6-50 Estimated percent increase in cause-specific mortality (and 95% CIs) for a 10-μg/m^3 increase in maximum 8-h ozone during June-August, for the same day (lag 0), the average of the same and previous day (lag 0-1), the unconstrained distributed lag model for the sum of 0-20 days and the penalized distributed lag model (lag 0-20)

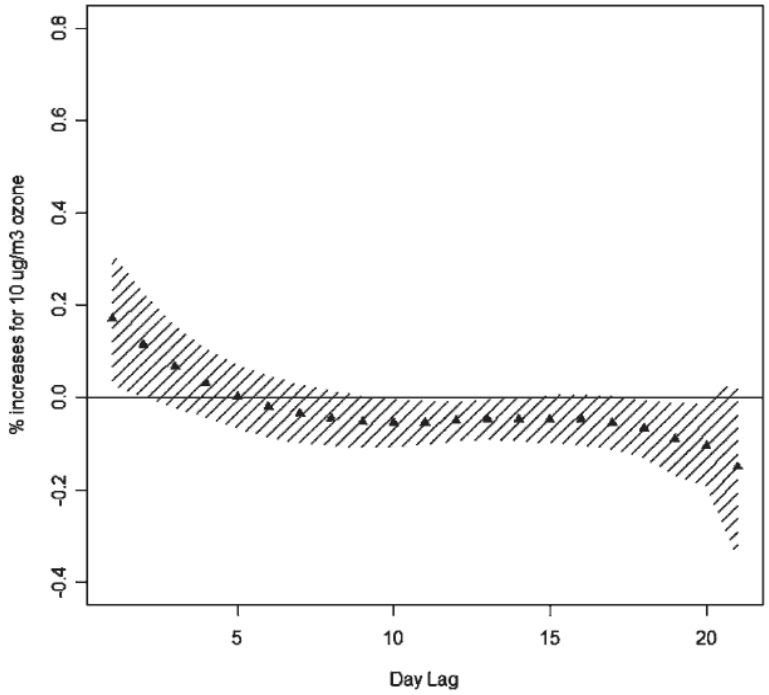
	Fixed effects	Random effects
	% (95% CI)	% (95% CI)
Total mortality		
Lag 0	0.28 (0.11, 0.45)	0.28 (0.07, 0.48)
Average lags 0-1	0.24 (0.15, 0.34)	0.22 (0.08, 0.35)
Sum lags 0-20, unconstrained	0.01 (-0.40, 0.41)	-0.54 (-1.28, 0.20)
Sum lags 0-20, penalized	0.01 (-0.41, 0.42)	-0.56 (-1.30, 0.19)
Cardiovascular mortality		
Lag 0	0.43 (0.18, 0.69)	0.37 (0.05, 0.69)
Average lags 0-1	0.33 (0.19, 0.48)	0.25 (0.03, 0.47)
Sum lags 0-20, unconstrained	-0.33 (-0.93, 0.29)	-0.62 (-1.47, 0.24)
Sum lags 0-20, penalized	-0.32 (-0.92, 0.28)	-0.57 (-1.39, 0.26)
Respiratory mortality		
Lag 0	0.36 (-0.21, 0.94)	0.36 (-0.21, 0.94)
Average lags 0-1	0.40 (0.11, 0.70)	0.40 (0.11, 0.70)
Sum lags 0-20, unconstrained	3.35 (1.90, 4.83)	3.35 (1.90, 4.83)
Sum lags 0-20, penalized	3.66 (2.25, 5.08)	3.66 (2.25, 5.08)

Source: Used with permission from BMJ Group (Samoli et al., 2009).

Although the APHENA project (Katsouyanni et al., 2009) did not specifically investigate mortality displacement and therefore did not consider longer lags (e.g., lag > 3 days), the study did present O_3 risk estimates for lag 0-1, lag 1, and a distributed lag model of 0-2 days in the Canadian, European, and U.S. datasets. Katsouyanni et al. (2009) found that the results vary somewhat across the regions, but, in general, there was no indication that the distributed lag model with up to a 2-day lag yielded meaningfully larger O_3 mortality risk estimates than the lag 0-1 and lag 1 results. For example, for all-cause mortality, using the model with natural splines and 8 df/year to adjust for seasonal trends, a reported percent excess risk for mortality for a 40 ppb increase in 1-h max O_3 concentrations for lag 0-1, lag 1, and the distributed lag model (lag 0-2) was 2.70% (95% CI: 1.02, 4.40%), 1.42% (95% CI: 0.08, 2.78%), and 3.02% (95% CI: 1.10, 4.89%), respectively. Thus, the observed associations appear to occur over a short time period, (i.e., a few days). Similarly, the Public Health and Air Pollution in Asia (PAPA) study (Wong et al., 2010) also examined multiple lag days (i.e., lag 0, lag 0-1, and lag 0-4), and although it did not specifically examine mortality displacement it does provide additional evidence regarding the timing of mortality effects proceeding O_3 exposure. In a combined analysis using data from all four cities examined (Bangkok, Hong Kong, Shanghai, and Wuhan), excess risk estimates at lag 0-4 were larger than those at lag 0 or lag 0-1 in both fixed and

random effect models (results not presented quantitatively). The larger risk estimates at lag 0-4 can primarily be attributed to the strong associations observed in Bangkok and Shanghai. However, it is worth noting that Bangkok differs from the three Chinese cities included in this analysis in that it has a tropical climate and does not exhibit seasonal patterns of mortality. As a result, Wong et al. (2010) examined the O_3-mortality associations at lag 0-1 in only the three Chinese cities and found that risk estimates were slightly reduced from 2.26% (95% CI: 1.36, 3.16) in the 4 city analysis to 1.84% (0.77, 2.86) in the 3 city analysis for a 30 ppb increase in 8-h max O_3 concentrations. Overall, the PAPA study further supports the observation of the APHENA study that associations between O_3 and mortality occur over a relatively short-time period, but also indicates that it may be difficult to interpret O_3-mortality associations across cities with different climates and mortality patterns.

When comparing the studies that explicitly examined the potential for mortality displacement in the O_3-mortality relationship, the results from Samoli et al. (2009), which provide evidence that suggests mortality displacement, are not consistent with those reported by Zanobetti and Schwartz (2008b). However, the shapes of the estimated smooth distributed lag associations are similar (Figure 6-34 and Figure 6-35). A closer examination of these figures shows that in the European data beyond a lag of 5 days the estimates remain negative whereas in the U.S. data the results remain near zero for the corresponding lags. These observed difference could be due the differences in the model specification between the 2 studies, specifically the use of: an unconstrained distributed lag model for apparent temperature up to 7 previous days (Zanobetti and Schwartz, 2008b) versus a linear term for humidity and an unconstrained distributed lag model of temperature up to 3 previous days (Samoli et al., 2009); and natural cubic splines with 2 df per season (Zanobetti and Schwartz, 2008b) versus dummy variables per month per year to adjust for season (Samoli et al., 2009). It is important to note, that these differences in model specification may have also influenced the city-to-city variation in risk estimates observed in these two studies (i.e., homogenous estimates across cities in Zanobetti and Schwartz (2008b) and heterogeneous estimates across cities in Samoli et al. (2009). Overall, the evidence of mortality displacement remains unclear, but Samoli et al. (2009), Zanobetti and Schwartz (2008b), and Katsouyanni et al. (2009) all suggest that the positive associations between O_3 and mortality are observed mainly in the first few days after exposure.



Source: Reprinted with permission of BMJ Group (Samoli et al., 2009).

The triangles represent the percent increase in all-cause mortality for a 10 μg/m^3 increase in 8-h max ozone concentrations at each lag; the shaded area represents the 95% CIs.

Figure 6-35 Estimated combined smooth distributed lag in 21 European cities during the summer (June-August) months.

Adaptation

Controlled human exposure studies have demonstrated an adaptive response to O_3 exposure for respiratory effects, such as lung function decrements, but this issue has not been examined in the epidemiologic investigation of mortality effects of O_3. Zanobetti and Schwartz (2008a) examined if there was evidence of an adaptive response in the O_3-mortality relationship in 48 U.S. cities from 1989 to 2000 (i.e., the same data analyzed in Zanobetti and Schwartz (2008b). The authors examined all-cause mortality using a case-crossover design to estimate the same-day (i.e., lag 0) effect of O_3, matched on referent days from every-3rd-day in the same month and year as the case. Zanobetti and Schwartz (2008a) examined O_3-mortality associations by: season, month in the summer season (i.e., May through September), and age categories in the summer season (Table 6-51). The estimated O_3 mortality risk estimate at lag 0 was found to be highest in the summer (1.51% [95% CI: 1.14, 1.87%]; lag 0 for a 30 ppb increase in 8-h max O_3 concentrations), and, within the warm months, the association was highest in July (1.96%

[95% CI: 1.42, 2.48%]; lag 0).[1] Upon further examination of the summer months, the authors also observed diminished effects in August (0.84% [95% CI: 0.33, 1.39%]; lag 0). Based on these results, the authors concluded that the mortality effects of O_3 appear diminished later in the O_3 season.

Table 6-51 Percent excess all-cause mortality per 10 ppb increase in daily 8-h max ozone on the same day, by season, month, and age groups

	%	95% CI
BY SEASON		
Winter	-0.13	-0.56, 0.29
Spring	0.35	0.16, 0.54
Summer	0.50	0.38, 0.62
Fall	0.05	-0.14, 0.24
BY MONTH		
May	0.48	0.28, 0.68
June	0.46	0.24, 0.68
July	0.65	0.47, 0.82
August	0.28	0.11, 0.46
September	-0.09	-0.35, 0.16
BY AGE GROUP		
0-20	0.08	-0.42, 0.57
21-30	0.10	-0.67, 0.87
31-40	0.07	-0.38, 0.52
41-50	0.08	-0.27, 0.43
51-60	0.54	0.19, 0.89
61-70	0.38	0.16, 0.61
71-80	0.50	0.32, 0.67
80	0.29	0.13, 0.44

Source: Reprinted with permission from BioMed Central Ltd. (Zanobetti and Schwartz, 2008a).

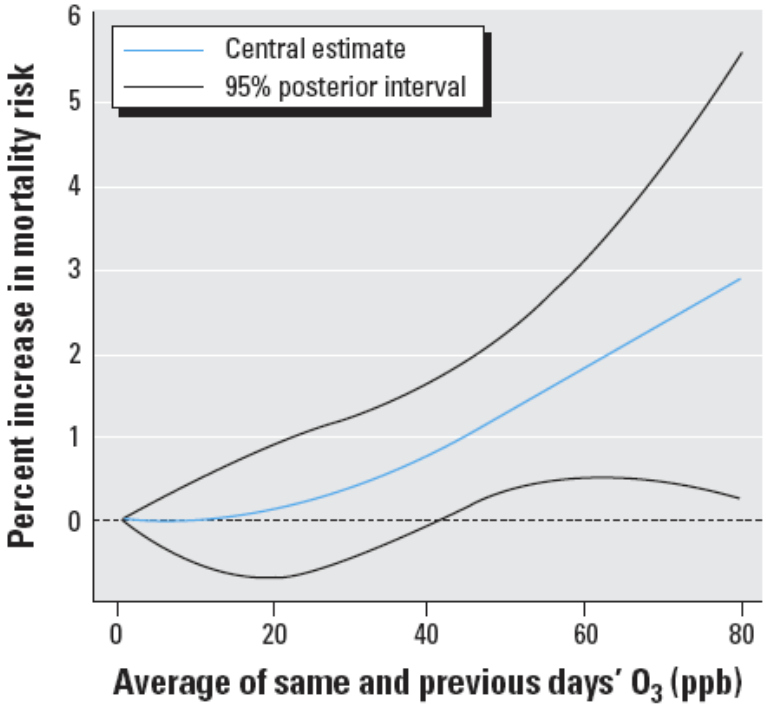
To further evaluate the potential adaptive response observed in Zanobetti and Schwartz (2008a) the distribution of the O_3 concentrations across the 48 U.S. cities during July and August was examined. Both July and August were found to have comparable means of 48.6 and 47.9 ppb with a reported maximum value of 97.9 and 96.0 ppb, respectively. Thus, the observed reduction in O_3-related mortality effect estimates in August (0.84%) compared to July (1.96%) appears to support the existence of an adaptive response. However, unlike an individual's adaptive response to decrements in lung function from short-term O_3 exposure, an examination of mortality prevents a direct observation of adaptation. Rather, for mortality the adaptation hypothesis is tested with a tacit assumption that, whatever the mechanism for O_3-induced mortality, the risk of death

[1] These values have been standardized to the increment used throughout the ISA for max 8-h avg increase in O_3 concentrations of 30 ppb. These values differ from those presented in Table 6-47 from Zanobetti and Schwartz (2008a) because the authors presented values for a 10 ppb increase in max 8-h avg O_3 concentrations.

from short-term O_3 exposure is reduced over the course of the summer months through repeated exposures. This idea would translate to a smaller population that would die from O_3 exposure towards the end of summer. This may complicate the interpretation of the distributed lag coefficients with long lag periods because the decreased coefficients may reflect diminished effects of the late summer, rather than diminished effects that are constant across the summer. These inter-twined issues need to be investigated together in future research.

Ozone-Mortality Concentration-Response Relationship and Threshold Analyses

Several of the recent studies evaluated have applied a variety of statistical approaches to examine the shape of the O_3-mortality C-R relationship and whether a threshold exists. The approach used by Bell et al. (2006) consisted of applying four statistical models to the NMMAPS data, which included 98 U.S. communities for the period 1987-2000. These models included: a linear analysis (i.e., any change in O_3 concentration can be associated with mortality) (Model 1); a subset analysis (i.e., examining O_3-mortality relationship below a specific concentration, ranging from 5 to 60 ppb) (Model 2); a threshold analysis (i.e., assuming that an association between O_3 and mortality is observed above a specific concentration and not below it, using the threshold values set at an increment of 5 ppb between 0 to 60 ppb and evaluating a presence of a local minima in AICs computed at each increment) (Model 3); and nonlinear models using natural cubic splines with boundary knots placed at 0 and 80 ppb, and interior knots placed at 20 and 40 ppb (Model 4). A two-stage Bayesian hierarchical model was used to examine these models and O_3-mortality risk estimates at the city-level in the first stage analysis and aggregate estimates across cities in the 2nd stage analysis using the average of 0- and 1-day lagged 24-h avg O_3 concentrations. The results from all of these models suggest that if a threshold exists it does so well below the current O_3 NAAQS. When restricting the analysis to all days when the current 8-h standard (i.e., 84 ppb daily 8-h max) is met in each community, Bell et al. (2006) found there was still a 0.60% (95% PI: 0.30, 0.90%) increase in mortality per 20 ppb increase in 24-h avg O_3 concentrations at lag 0-1. Figure 6-36 shows the combined C-R curve obtained using the nonlinear model (Model 4). Although these results suggest the lack of threshold in the $O_{3\text{-}mo}$rtality relationship, it is difficult to interpret such a curve because it does not take into consideration the heterogeneity in O_3-mortality risk estimates across cities.



Source: Bell et al. (2006).

Figure 6-36 Estimated combined C-R curve for ozone and nonaccidental mortality using the nonlinear (spline) model.

Using the same NMMAPS dataset as Bell et al. (2006), Smith et al. (2009b) further examined the O_3-mortality C-R relationship. Similar to Bell et al. (2006), Smith et al. (2009b) conduct a subset analysis, but instead of restricting the analysis to days with O_3 concentrations below a cutoff the authors only include days above a defined cutoff in the analysis. The results of this "reversed subset" approach are in line with those reported by Bell et al. (2006); consistent positive associations at all cutoff points up to a defined concentration where the total number of days with O_3 concentrations above a value are so limited that the variability around the central estimate is increased. In the Smith et al. (2009b) analysis this observation was initially observed at 45 ppb, with the largest variability at 60 ppb; however, unlike Bell et al. (2006) where 73% of days are excluded when subsetting the data to less than 20 ppb, the authors do not detail the number of days of data included in the subset analyses at higher concentrations. In addition to the subset analysis, Smith et al. (2009b) examined the shape of the C-R curve using a piecewise linear approach with cutpoints at 40 ppb, 60 ppb, and 80 ppb. Smith et al. (2009b) found that the shape of the C-R curve is similar to that reported by Bell et al. (2006) (Figure 6-36), but argue that slopes of the β for each piece of the curve are highly variable with

the largest variation in the 60-80 ppb range. However, the larger variability around the β between 60-80 would be expected due to the small number of days with O_3 concentrations within that range in an all-year analysis. This result is consistent with that observed by Bell et al. (2006), which is presented in Figure 6-36.

The APHENA project (Katsouyanni et al., 2009) also analyzed the Canadian and European datasets (the U.S. data were analyzed for PM_{10} only) for evidence of a threshold, using the threshold analysis method (Model 3) applied in Bell et al.'s (2006) study described above. There was no evidence of a threshold in the Canadian data (i.e., the pattern of AIC values for each increment of a potential threshold value varied across cities, most of which showed no local minima). Likewise, the threshold analysis conducted using the European data also showed no evidence of a threshold.

The PAPA study, did not examine whether a threshold exists in the O_3-mortality C-R relationship, but instead the shape of the C-R curve individually for each city (Bangkok, Hong Kong, Shanghai, and Wuhan) (Wong et al., 2010). Using a natural spline smoother with 3df for the O_3 term, Wong et al. (2010) examined whether non-linearity was present by testing the change in deviance between this smoothed, non-linear, model and an unsmoothed, linear, model with 1 df. For each of the cities, both across the full range of the O_3 distribution and specifically within the range of the 25th to 75th percentile of each city's O_3 concentrations (i.e., a range of 9.7 ppb to 60.4 ppb across the cities) there was no evidence of a non-linear relationship in the O_3-mortality C-R curve. It should be noted that the range of the 25^{th} to 75^{th} percentiles in all of the cities, except Wuhan, was lower than that observed in the U.S. using all-year data where the range from the 25^{th} to 75^{th} percentiles is 30 ppb to 50 ppb (Table 3-6).

Additional threshold analyses were conducted using NMMAPS data, by Xia and Tong (2006) and Stylianou and Nicolich (2009). Both studies used a new statistical approach developed by Xia and Tong (2006) to examine thresholds in the O_3 mortality C-R relationship. The approach consisted of an extended GAM model, which accounted for the cumulative and nonlinear effects of air pollution using a weighted cumulative sum for each pollutant, with the weights (non-increasing further into the past) derived by a restricted minimization method. The authors did not use the term distributed lag model, but their model has the form of distributed lag model, except that it allows for nonlinear functional forms. Using NMMAPS data for 1987-1994 for 3 U.S. cities (Chicago, Pittsburgh, and El Paso), Xia and Tong (2006) found that the extent of cumulative effects of O_3 on mortality were relatively short. While the authors also note that there was evidence of a threshold effect around 24-h avg concentrations of 25 ppb, the threshold values estimated in the analysis were sometimes in the range where data density was low. Thus, this threshold analysis needs to be replicated in a larger number of cities to confirm

this observation. It should be noted that the model used in this analysis did not include a smooth function of days to adjust for unmeasured temporal confounders, and instead adjusted for season using a temperature term. As a result, these results need to be viewed with caution because some potential temporal confounders (e.g., influenza) do not always follow seasonal patterns of temperature.

Stylianou and Nicolich (2009) examined the existence of thresholds following an approach similar to Xia and Tong (2006) for all-cause, cardiovascular, and respiratory mortality using data from NMMAPS for nine major U.S. cities (i.e., Baltimore, Chicago, Dallas/Fort Worth, Los Angeles, Miami, New York, Philadelphia, Pittsburgh, and Seattle) for the years 1987-2000. The authors found that PM_{10} and O_3 were the two important predictors of mortality. Stylianou and Nicolich (2009) found that the estimated O_3-mortality risks varied across the nine cities with the models exhibiting apparent thresholds, in the 10-45 ppb range for O_3. However, given the city-to-city variation in risk estimates, combining the city-specific estimates into an overall estimate complicates the interpretation of a threshold. Unlike the Xia and Tong (2006) analysis, Stylianou and Nicolich (2009) included a smooth function of time to adjust for seasonal/temporal confounding, which could explain the difference in results between the two studies.

In conclusion, the evaluation of the O_3-mortality C-R relationship did not find any evidence that supports a threshold in the relationship between short-term exposure to O_3 and mortality within the range of O_3 concentrations observed in the U.S. Additionally, recent evidence suggests that the shape of the O_3-mortality C-R curve remains linear across the full range of O_3 concentrations. However, the studies evaluated demonstrated that the heterogeneity in the O_3-mortality relationship across cities (or regions) complicates the interpretation of a combined C-R curve and threshold analysis. Given the effect modifiers identified in the mortality analyses that are also expected to vary regionally (e.g., temperature, air conditioning prevalence), a national or combined analysis may not be appropriate to identify whether a threshold exists in the O_3-mortality C-R relationship. Overall, the studies evaluated support a linear O_3-mortality C-R relationship and continue to support the conclusions from the 2006 O_3 AQCD, which stated that "if a population threshold level exists in O_3 health effects, it is likely near the lower limit of ambient O_3 concentrations in the United States" (U.S. EPA, 2006b).

6.6.2.5 Associations of Cause-Specific Mortality and Short-term Ozone Exposure

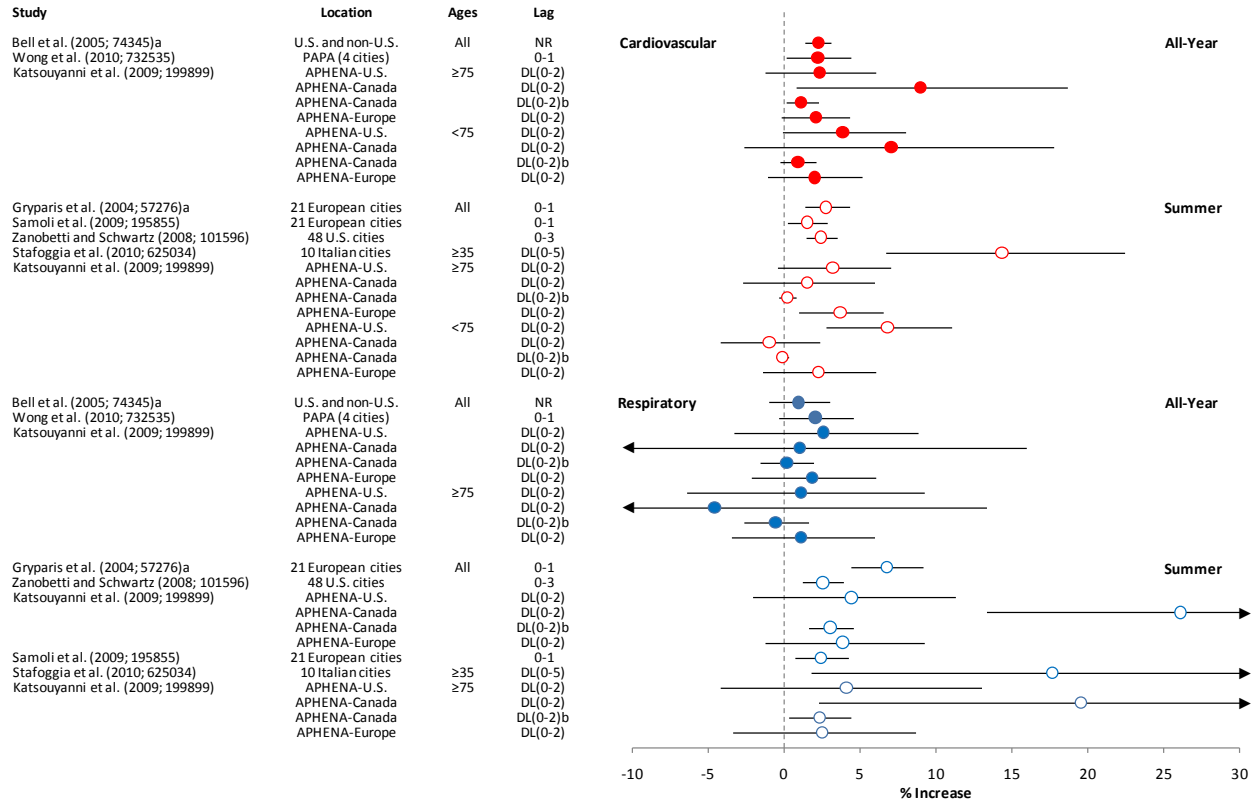
In the 2006 O_3 AQCD, an evaluation of studies that examined cause-specific mortality found consistent positive associations between short-term O_3 exposure and

cardiovascular mortality, with less consistent evidence for associations with respiratory mortality. The majority of the evidence for associations between O_3 exposure and cause-specific mortality were from single-city studies, which had small daily mortality counts and subsequently limited statistical power to detect associations.

New multicity studies evaluated in this review build upon and confirm the associations between short-term O_3 exposure and cause-specific mortality identified in the 2006 O_3 AQCD (U.S. EPA, 2006b) (Figure 6-37; Table 6-52). In APHENA, a multicontinent study that consisted of the NMMAPS, APHEA2 and Canadian multicity datasets, consistent positive associations were reported for both cardiovascular and respiratory mortality in all-year analyses when focusing on the natural spline model with 8 df/year (Section 6.6.2.1). The associations between O_3 exposure and cardiovascular and respiratory mortality in all-year analyses were further supported by the multicity PAPA study (Wong et al., 2010). Cardiovascular mortality associations persisted in analyses restricted to the summer season with evidence for stronger respiratory mortality associations compared to those observed in all-year analyses (Figure 6-37; Table 6-52). Additional multicity studies from the U.S. (Zanobetti and Schwartz, 2008b) and Europe (Stafoggia et al., 2010; Samoli et al., 2009) that conducted summer season analyses also found strong associations between O_3 exposure and cardiovascular and respiratory mortality.

Of the studies evaluated, only the APHENA study (Katsouyanni et al., 2009) and an Italian multicity study (Stafoggia et al., 2010) conducted an analysis of the potential for copollutant confounding of the O_3 cause-specific mortality relationship. When focusing on the natural spline model with 8 df/year and lag 1 results (as discussed in Section 6.6.2.1), the APHENA study found that O_3 cause-specific mortality risk estimates were fairly robust to the inclusion of PM_{10} in copollutant models in the European dataset with more variability in the U.S. and Canadian datasets (i.e., copollutant risk estimates increased and decreased for respiratory and cardiovascular mortality). In summer season analyses cardiovascular O_3 mortality risk estimates were robust in the European dataset and attenuated but remained positive in the U.S. datasets; whereas, respiratory O_3 mortality risk estimates were attenuated in the European dataset and robust in the U.S. dataset. The authors did not examine copollutant models during the summer season in the Canadian dataset (Figure 6-30; Table 6-49). Interpretation of these results requires caution; however, due to the different PM sampling schedules employed in each of these study locations (i.e., primarily every-6th day in the U.S. and Canadian datasets and every-day in the European dataset). The results of the summer season analyses from the APHENA study (Katsouyanni et al., 2009) are consistent with those from a study of 10 Italian cities during the summer months (Stafoggia et al., 2010). Stafoggia et al. (2010) found that cardiovascular (14.3% [95% CI: 6.7, 22.4%]) and cerebrovascular (8.5% [95%

CI: 0.06, 16.3%]) mortality O_3 effect estimates were robust to the inclusion of PM_{10} in copollutant models (14.3% [95% CI: 6.7, 23.1%] and 7.3% [95% CI: -1.2, 16.3], respectively), while respiratory mortality O_3 effects estimates (17.6% [95% CI: 1.8, 35.5%]) were attenuated, but remained positive (9.2% [95% CI: -6.9, 28.8%]).



Effect estimates are for a 20 ppb increase in 24-h avg; 30 in 8-h max; and 40ppb increase in 1-h max ozone concentrations. Red = cardiovascular; blue = respiratory; closed circles = all-year analysis; and open circles = summer-only analysis. An "a" represents studies from the 2006 ozone AQCD. A "b" represents risk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in ozone concentrations (Section 6.2.7.2).

Figure 6-37 Percent increase in cause-specific mortality.

Table 6-52 Corresponding effect estimates for Figure 6-37

Study	Location	Ages	Lag	Avg Time	%Increase (95% CI)
Cardiovascular					
All-year					
Bell et al. (2005)[a]	U.S. and non-U.S.	All	NR	24-h avg	2.23 (1.36,3.08)
Wong et al. (2010)	PAPA (4 cities)		0-1	8-h max	2.20 (0.06, 4.37)
Katsouyanni et al. (2009)	APHENA-U.S.	≥ 75	DL(0-2)	1-h max	2.30 (-1.33, 6.04)
	APHENA-Canada		DL(0-2)		8.96 (0.75,18.6)
	APHENA-Canada		DL(0-2)[b]		1.1 (0.10,2.20)
	APHENA-Europe		DL(0-2)		2.06 (-0.24, 4.31)
	APHENA-U.S.	<75	DL(0-2)		3.83 (-0.16, 7.95)
	APHENA-Canada		DL(0-2)		7.03 (-2.71, 17.7)
	APHENA-Canada		DL(0-2)[b]		0.87 (-0.35, 2.10)
	APHENA-Europe		DL(0-2)		1.98 (-1.09, 5.13)
Summer					
Gryparis et al. (2004)[a]	21 European cities	All	0-1	8-h max	2.7 (1.29,4.32)
Samoli et al. (2009)	21 European cities		0-1	8-h max	1.48 (0.18, 2.80)
Zanobetti and Schwartz (2008b)	48 U.S. cities		0-3	8-h max	2.42 (1.45, 3.43)
Stafoggia et al. (2010)	10 Italian cities	≥ 35	DL(0-5)	8-h max	14.3 (6.65, 22.4)
Katsouyanni et al. (2009)	APHENA-U.S.	≥ 75	DL(0-2)	1-h max	3.18 (-0.47, 6.95)
	APHENA-Canada		DL(0-2)		1.50 (-2.79, 5.95)
	APHENA-Canada		DL(0-2)[b]		0.19 (-0.36, 0.74)
	APHENA-Europe		DL(0-2)		3.67 (0.95, 6.53)
	APHENA-U.S.	<75	DL(0-2)		6.78 (2.70, 11.0)
	APHENA-Canada		DL(0-2)		-1.02 (-4.23, 2.30)
	APHENA-Canada		DL(0-2)[b]		-0.13 (-0.55, 0.29)
	APHENA-Europe		DL(0-2)		2.22 (-1.48, 6.04)
Respiratory					
All-years					
Bell et al. (2005)[a]	U.S. and non-U.S.	All	NR	24-h avg	0.94 (-1.02, 2.96)
Wong et al. (2010)	PAPA (4 cities)		0-1	8-h max	2.02 (-0.41, 4.49)
Katsouyanni et al. (2009)	APHENA-U.S.		DL(0-2)	1-h max	2.54 (-3.32, 8.79)
	APHENA-Canada		DL(0-2)		1.02 (-11.9, 15.9)
	APHENA-Canada		DL(0-2)[b]		0.13 (-1.60, 1.90)
	APHENA-Europe		DL(0-2)		1.82 (-2.18, 6.04)
	APHENA-U.S.	≥ 75	DL(0-2)		1.10 (-6.48, 9.21)
	APHENA-Canada		DL(0-2)		-4.61 (-19.3, 13.3)
	APHENA-Canada		DL(0-2)[b]		-0.60 (-2.70, 1.60)
	APHENA-Europe		DL(0-2)		1.10 (-3.48, 5.95)
Summer					
Gryparis et al. (2004)[a]	21 European cities	All	0-1	8-h max	6.75 (4.38, 9.10)
Zanobetti and Schwartz (2008b)	48 U.S. cities		0-3	8-h max	2.51 (1.14, 3.89)
Katsouyanni et al. (2009)	APHENA-U.S.		DL(0-2)	1-h max	4.40 (-2.10, 11.3)
	APHENA-Canada		DL(0-2)		26.1 (13.3, 41.2)
	APHENA-Canada		DL(0-2)[b]		3.00 (1.60, 4.50)
	APHENA-Europe		DL(0-2)		3.83 (-1.33, 9.21)
Samoli et al. (2009)	21 European cities		0-1	8-h max	2.38 (0.65, 4.19)
Stafoggia et al. (2010)	10 Italian cities	≥ 35	DL(0-5)	8-h max	17.6 (1.78, 35.5)
Katsouyanni et al. (2009)	APHENA-U.S.	≥ 75	DL(0-2)	1-h max	4.07 (-4.23, 13.0)
	APHENA-Canada		DL(0-2)		19.5 (2.22, 40.2)
	APHENA-Canada		DL(0-2)[b]		2.30 (0.28, 4.40)
	APHENA-Europe		DL(0-2)		2.46 (-3.40, 8.62)

[a]Studies from the 2006 O_3 AQCD.
[b]Risk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O_3 concentrations (Section 6.2.7.2).

Collectively, the results from the new multicity studies provide evidence of associations between short-term O_3 exposure and cardiovascular and respiratory mortality with additional evidence indicating these associations persist, and in the case of respiratory mortality are strengthened, in the summer season. Although copollutant analyses of cause-specific mortality are limited, the APHENA study found that O_3 cause-specific

mortality risk estimates were fairly robust to the inclusion of PM_{10} in copollutant models in the European dataset, which is supported by the results from Stafoggia et al. (2010). Additionally, APHENA found that O_3 cause-specific mortality risk estimates were moderately to substantially sensitive (e.g., increased or attenuated) to inclusion of PM_{10} in the U.S. and Canadian datasets. However, the mostly every-6th-day sampling schedule for PM_{10} in the U.S. and Canadian datasets greatly reduced their sample size and limits the interpretation of these results.

6.6.3 Summary and Causal Determination

The evaluation of new multicity studies that examined the association between short-term O_3 exposure and mortality found evidence which supports the conclusions of the 2006 O_3 AQCD. These new studies reported consistent positive associations between short-term O_3 exposure and all-cause (nonaccidental) mortality, with associations being stronger during the warm season, as well as additional support for associations between O_3 exposure and cardiovascular and respiratory mortality.

New studies further examined potential confounders (e.g., copollutants and seasonality) of the O_3-mortality relationship. Because the PM-O_3 correlation varies across regions, due to the difference in PM chemical constituents, interpretation of the combined effect of PM on the relationship between O_3 and mortality is not straightforward. Unlike previous studies that were limited to primarily examining the confounding effects of PM_{10}, the new studies expanded their analyses to include multiple PM indices (e.g., PM_{10}, $PM_{2.5}$, and PM components). An examination of copollutant models found evidence that associations between O_3 and all-cause mortality were robust to the inclusion of PM_{10} or $PM_{2.5}$ (Stafoggia et al., 2010; Katsouyanni et al., 2009; Bell et al., 2007), while other studies found evidence for a modest reduction (~20-30%) when examining PM_{10} (Smith et al., 2009b). Additional evidence suggests potential sensitivity (e.g., increases and attenuation) of O_3 mortality risk estimates to copollutants by age group or cause-specific mortality (e.g., respiratory and cardiovascular) (Stafoggia et al., 2010; Katsouyanni et al., 2009). An examination of PM components, specifically sulfate, found evidence for reductions in O_3-mortality risk estimates in copollutant models (Franklin and Schwartz, 2008). Overall, across studies, the potential impact of PM indices on O_3-mortality risk estimates tended to be much smaller than the variation in O_3-mortality risk estimates across cities suggesting that O_3 effects are independent of the relationship between PM and mortality. Although some studies suggest that O_3-mortality risk estimates may be confounded by PM or its chemical components the interpretation of these results requires caution due to the limited PM datasets used as a result of the every-3rd- and 6th-day PM sampling schedule. When examining the potential for seasonal confounding of the

O_3-mortality relationship it was observed that the extent of smoothing or the methods used for adjustment can influence O_3 risk estimates because of the opposing seasonal trends of O_3 and mortality when not instituting enough degrees of freedom to control for temporal/seasonal trends (Katsouyanni et al., 2009).

The multicity studies evaluated in this review also examined the regional heterogeneity observed in O_3-mortality risk estimates. These studies provide evidence which suggests generally higher O_3-mortality risk estimates in northeastern U.S. cities with some regions showing no associations between O_3 exposure and mortality (e.g., Southwest, Urban Midwest) (Smith et al., 2009b; Bell and Dominici, 2008). Multicity studies that examined individual- and community-level characteristics identified characteristics that may explain the observed regional heterogeneity in O_3-mortality risk estimates as well as characteristics of populations potentially susceptible to O_3-related health effects. An examination of community-level characteristics found an increase in the O_3-mortality risk estimates in cities with higher unemployment, percentage of the population Black/African-American, percentage of the working population that uses public transportation, lower temperatures, and lower prevalence of central air conditioning (Medina-Ramón and Schwartz, 2008). Additionally, a potential interactive, or synergistic, effect on the O_3-mortality relationship was observed when examining differences in the O_3-mortality association across temperature levels (Ren et al., 2008). An examination of individual-level characteristics found evidence that older age, female sex, Black race, having atrial fibrillation, SES indicators (i.e., educational attainment, income level, and employment status), and out-of hospital deaths, specifically in those individuals with diabetes, are modify O_3-mortality associations (Cakmak et al., 2011; Stafoggia et al., 2010; Medina-Ramón and Schwartz, 2008), and may increase susceptibility to O_3-related mortality. Overall, additional research is warranted to further confirm whether these characteristics, individually or in combination, can explain the observed regional heterogeneity.

Additional studies were evaluated that examined factors, such as multi-day effects, mortality displacement, adaptation, and whether a threshold exists in the O_3-mortality relationship, which may influence the shape of the O_3-mortality C-R curve. An examination of multiday effects in a U.S. and European multicity study found conflicting evidence for mortality displacement, but both studies suggest that the positive associations between O_3 and mortality are observed mainly in the first few days after exposure (Samoli et al., 2009; Zanobetti and Schwartz, 2008b). A U.S. multicity study found evidence of an adaptive response to O_3 exposure, with the highest risk estimates earlier in the O_3 season (i.e., July) and diminished effects later (i.e., August) (Zanobetti and Schwartz, 2008a). However, the evidence of adaptive effects has an implication for the interpretation of multi-day effects, and requires further analysis. Analyses that

specifically focused on the O_3-mortality C-R relationship supported a linear O_3-mortality relationship and found no evidence of a threshold within the range of O_3 concentrations in the U.S., but did observe evidence for potential differences in the C-R relationship across cities (Katsouyanni et al., 2009; Stylianou and Nicolich, 2009; Bell et al., 2006). Collectively, these studies support the conclusions of the 2006 O_3 AQCD that "if a population threshold level exists in O_3 health effects, it is likely near the lower limit of ambient O_3 concentrations in the U.S."

In conclusion, the new epidemiologic studies build upon and confirm the associations reported in the 2006 O_3 AQCD. Additionally, these new studies have provided additional information regarding key uncertainties previously identified including the potential confounding effects of copollutants and seasonal trend, individual- and community-level factors that may lead to increased risk of O_3-induced mortality and the heterogeneity in O_3-mortality risk estimates, and continued evidence of a linear no-threshold C-R relationship. Although some uncertainties still remain, the collective body of evidence is sufficient to conclude that **there is likely to be a causal relationship between short-term O_3 exposure and mortality.**

6.7 Overall Summary

The evidence reviewed in this chapter describes the recent findings regarding the health effects of short-term exposure to ambient O_3 concentrations. Table 6-53 provides an overview of the causal determinations for each of the health categories evaluated.

Table 6-53 Summary of causal determinations for short-term exposures to ozone

Health Category	Causal Determination
Respiratory Effects	Causal relationship
Cardiovascular Effects	Suggestive of a causal relationship
Central Nervous System Effects	Suggestive of a causal relationship
Effects on Liver and Xenobiotic Metabolism	Inadequate to infer a causal relationship
Effects on Cutaneous and Ocular Tissues	Inadequate to infer a causal relationship
Mortality	Likely to be a causal relationship

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7 INTEGRATED HEALTH EFFECTS OF LONG-TERM OZONE EXPOSURE

7.1 Introduction

This chapter reviews, summarizes, and integrates the evidence on relationships between health effects and long-term exposures to O_3. Both epidemiologic and toxicological studies provide a basis for examining long-term O_3 exposure health effects for respiratory effects, cardiovascular effects, reproductive and developmental effects, central nervous system effects, cancer outcomes, and mortality. Long-term exposure has been defined as a duration of approximately 30 days (1 month) or longer.

Conclusions from the 2006 O_3 AQCD are summarized briefly at the beginning of each section, and the evaluation of evidence from recent studies builds upon what was available during the previous review. For each health outcome (e.g., respiratory disease, lung function), results are summarized for studies from the specific scientific discipline, i.e., epidemiologic and toxicological studies. The major sections (i.e. respiratory, cardiovascular, mortality, reproductive/developmental, cancer) conclude with summaries of the evidence for the various health outcomes within that category and integration of the findings that lead to conclusions regarding causality based upon the framework described in Chapter 1. Determination of causality is made for the overall health effect category, such as respiratory effects, with coherence and plausibility being based on evidence from across disciplines and also across the suite of related health outcomes, including cause-specific mortality.

7.2 Respiratory Effects

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

Several studies (Horak et al., 2002; Frischer et al., 1999) collectively indicated that O_3 exposure over several summer months was associated with smaller increases in lung function growth in children. For longer time periods (annual), the definitive analysis in the Child Health Study (CHS) reported by Gauderman et al. (2004) provided little evidence that such long-term exposure to ambient O_3 was associated with significant deficits in the growth rate of lung function in children in contrast to the effects observed with other pollutants such as acid vapor, NO_2, and $PM_{2.5}$. Asthmatic children with GSTM1 null genotype were found to be more susceptible to the impact of O_3 exposure (over a 12 week study period) on small airways function in Mexico (Romieu et al., 2004a). Limited epidemiologic research examined the relationship between long-term O_3 exposures and inflammation. Evidence of inflammation and allergic responses consistent with known effects of O_3 exposure (30 day mean) such as increased eosinophil levels were observed in an Austrian study (Frischer et al., 2001). The cross-sectional surveys available for the 2006 O_3 AQCD detected no associations between long-term O_3 exposures and asthma prevalence, asthma-related symptoms or allergy to common aeroallergens in children after controlling for covariates.

New evidence presented below reports consistent associations between long-term O_3 exposure and new-onset asthma related to genotype in U.S. cohorts in multi-community studies. Related studies report coherent relationships between respiratory symptoms among asthmatics and long-term O_3 exposure. Short-term exposure to O_3 is associated with increases in respiratory symptoms and asthma medication use, as summarized in Section 6.2.4.2. A new line of evidence reports a positive exposure response relationship between first asthma hospitalization and long-term O_3 exposure. Results from recent studies examining pulmonary function, inflammation, and allergic responses are also presented.

7.2.1 New Onset Asthma

Risk for new-onset asthma is related in part to genetic susceptibility, behavioral factors and environmental exposure (Gilliland et al., 1999). Complex chronic diseases, such as asthma, are partially the result of a sequence of biochemical reactions involving exposures to various environmental agents metabolized by a number of different genes (Conti et al., 2003). Understanding the relation between genetic polymorphisms and environmental exposure can help identify high-risk subgroups in the population and provide better insight into pathway mechanisms for these complex diseases. Oxidative stress likely underlies these mechanistic hypotheses (Gilliland et al., 1999). Susceptibility genes act through modification of disease risk associated with environmental factors. Epidemiologic investigation of hypotheses of possible mechanisms involving the gene-

environmental (GxE) interaction involves statistical analysis of these interactions for the risk of new-onset asthma in children being influenced by exposure to air pollution (Gauderman, 2002, 2001; Gilliland et al., 1999).

Evidence for the potential importance of genetic susceptibility and behavioral factors on new onset asthma are provided by several recent studies (Himes et al., 2009; Islam et al., 2008; Li et al., 2008; Hanene et al., 2007; Ercan et al., 2006; Li et al., 2006a; Tamer et al., 2004; Gilliland et al., 2002). Evidence for a gene-pollution interaction in the pathogenesis of asthma are supported by recent study findings (Islam et al., 2009; Islam et al., 2008; Oryszczyn et al., 2007; Lee et al., 2004b; Gilliland et al., 2002).

Evidence for associations between long-term exposure to O_3 and new-onset asthma is provided by new studies from the CHS. Initiated in the early 1990's, the CHS was originally designed to examine whether long-term exposure to ambient pollutants was related to chronic respiratory outcomes in children in 12 communities in southern California (Peters et al., 1999a; Peters et al., 1999b). About 10 years later, the CHS inaugurated a series of genetic studies (Gilliland et al., 1999) nested within the CHS cohort by obtaining biological samples from the study subjects (buccal cells). These new studies examined the relationship between health outcomes, genetic susceptibility, behavioral factors and environmental exposure.

First, the hypothesis that the functional polymorphisms of HMOX-1 [(GT)n repeat], CAT (-262C > T -844C > T0, and MNSOD (Ala-9Val) are associated with new-onset asthma was evaluated, and then whether the effects of these variants varied by exposure to O_3 (Islam et al., 2008). HMOX1 [heme oxygenase (decycling) 1] is a human gene that encodes for the enzyme heme oxygenase. Heme oxygenase 1 (HO-1) is an enzyme that catalyzes the metabolism of heme. The heme iron serves as a source or sink of electrons during electron transfer or redox chemistry, so the presence of the HMOX1 gene, and therefore the generation of heme oxygenase, protects against oxidative stress in the body. The authors observed that functional promoter variants in CAT and HMOX-1 showed ethnicity-specific associations with new-onset asthma and that oxidant gene protection was restricted to children living in low-O_3 communities.

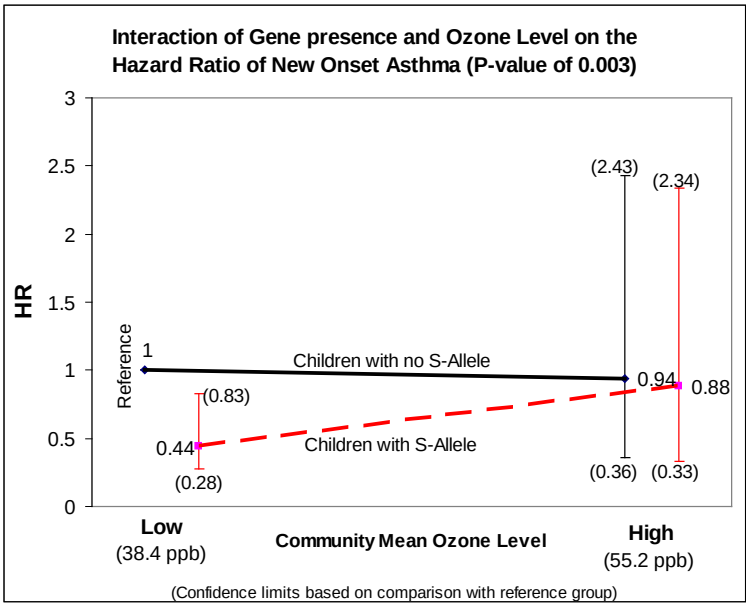
The subjects were drawn from the CHS cohort. Children with a history of asthma or wheeze were excluded from this analysis. Analyses were restricted to children of Hispanic (n = 576) or non-Hispanic white ethnicity (n = 1,125). New-onset asthma was classified as having no prior history of asthma at study entry with subsequent report of physician-diagnosed asthma at follow-up with the date of onset assigned to be the midpoint of the interval between the interview date when asthma diagnosis was first reported and the previous interview date. As a sensitivity analysis, the asthma definition was restricted to those new-onset asthma cases who also used an inhaler (n = 121). They

calculated long-term mean pollutant levels (1994 – 2003) to assign exposure to children in each community for use in the statistical analysis. The effect of ambient air pollution on the relationship between genetic polymorphism and new-onset asthma was assessed using models where the community specific average air pollution levels were fitted as a continuous variable together with the appropriate interaction terms for genes and air pollutants (Berhane et al., 2004). Cox proportional hazard regression models were fitted to the data. A stratified analysis for the two independent fourth-grade cohorts of the study population recruited in 1993 and 1996 was conducted to assess whether the results could be replicated in independent groups of children.

Over the follow-up period, 160 new cases of asthma were diagnosed (Islam et al., 2008). The evidence indicated that the effect of variation in the HMOX-1 gene on risk of new-onset asthma differed by ambient O_3 level. An interaction P value was reported of 0.003 from the hierarchical two stage Cox proportional hazard model fitting the community-specific O_3 and PM_{10} levels (continuous) and controlling for random effect of the communities. Average O_3 levels showed low correlation with the other monitored pollutants. The interaction indicated a greater effect (association) of community O_3 level among children with the gene than with children without the gene. Alleles with 23 or fewer (GT)n repeats are categorized as short (S). The S-allele variant of this protective enzyme is more readily induced than those with more numerous repeats. The largest protective effect of the (GT)n repeat polymorphism of HMOX-1 was observed for children who were S-allele carriers and resided in low-O_3 communities with Hazard Ratio (HR) of 0.44 (95% CI: 0.23, 0.83). The ratio of HR of S-allele carriers who resided in high O_3 communities (HR=0.88; [95% CI: 0.33, 2.34]) was twofold greater than in those who resided in the low-O_3 communities (HR=0.44). The non-parallelism of the two lines in An interaction p-value of 0.003 was obtained from the hierarchical two stage Cox proportional hazard model fitting the community specific O3 and controlling for random effect of the communities. The interaction indicates there is a greater effect (association) of community O3 level on children with the gene than with children without the gene. The HRs are off-set as opposed to overlapping in the figure to allow clearer presentation of the results.

Figure 7-1 illustrates the interaction: Children with the S-allele have protection against the onset of asthma; however, in high- O_3 communities, this protection is attenuated. The results from sensitivity analyses on the two fourth-grade cohorts, and the inhaler definition for asthma were both consistent with the main results. An analysis related to children's participation in sports or time spent outdoors produced the same outcome. No significant interactions were observed between PM_{10} or other pollutants and the HMOX - 1 gene; quantitative results were not presented. A potential concern for not adjusting for multiple testing was considered by the authors as not a factor in this analysis because the

selection of the genes was based on a priori hypotheses defined by a well-studied biological pathway. Thus in this cohort in southern California, Islam et al. (2008) related new-onset asthma to O_3 exposure in genetically susceptible children.



Source: Developed by EPA with data from Islam et al. (2008) (used by permission of American Thoracic Society).

An interaction p-value of 0.003 was obtained from the hierarchical two stage Cox proportional hazard model fitting the community specific O_3 and controlling for random effect of the communities. The interaction indicates there is a greater effect (association) of community O_3 level on children with the gene than with children without the gene. The HRs are off-set as opposed to overlapping in the figure to allow clearer presentation of the results.

Figure 7-1 Interaction of gene presence and O_3 level on the Hazard Ratio (HR) of new-onset asthma in the 12 Children's Health Study communities.

Related to the findings in Islam et al. (2008) discussed above, Islam et al. (2009) examined whether GSTP1, GSTM1, exercise and O_3 exposure have interrelated effects on the pathogenesis of asthma. A modifying role of air pollution on the association between Ile105Val and asthma in a cohort of children had been observed (Lee et al., 2004b), but the study did not examine O_3 specifically or consider exercise. A primary conclusion that the authors (Islam et al., 2009) reported was that the common functional variants of GSTP1 and GSTM1 null genotypes modulate the risk of new onset asthma during adolescence. Children who had the GSTM1 null genotype were at 1.6-fold (95% CI: 1.2, 2.2) increased risk of developing new onset asthma compared with those without the null genotype. Further, the CHS investigators examined the complex interrelationship

of antioxidant defenses with asthma risk with increasing doses of O_3, resulting from increasing ventilation associated with vigorous exercise characterized by the number of team sports played. In an earlier analysis, McConnell et al. (2002) had reported that the risk of new onset asthma was associated with outdoor exercise, especially in high O_3 communities but did not consider genetic variants. In this new study, Islam et al. (2009) find a six fold increased risk of asthma (HR=6.15, [95% CI: 2.2, 7.4]) for children who were homozygous for Ile105, participated in three or more team sports and lived in high-O_3 communities, demonstrating the potential importance of a combination of genetic variability, O_3 exposure and behavior on asthma risk.

Epidemiologic evidence of associations of arginase variants with asthma are limited (Li et al., 2006a). Asthmatic subjects have higher arginase activity than non-asthmatic subjects (Morris et al., 2004). NO is a mediator of nitrosative stress synthesized from L-arginine by nitric oxide synthases. In the CHS, Salam et al. (2009) examined whether arginase variants (ARG1 and ARG2 genes) were associated with asthma and whether atopy and exposures to smoking and air pollution influence the associations. The modifying effect of O_3 and atopy on the association between haplotypes and asthma were evaluated using likelihood ratio tests with appropriate interaction terms. They found that both ARG1 and ARG2 genetic loci were associated with childhood-onset asthma. The effect of the ARG1 haplotype varied by the child's history of atopy and ambient O_3. Among atopic children living in high O_3 communities, those carrying the ARG1 haplotype had reduced asthma risk (Odds Ratio [OR] per ARG1h4 haplotype copy = 0.12; [95% CI: 0.04, 0.43]; P heterogeneity across atopy/O_3 categories = 0.008).

Further, the CHS presents results examining the relationship of new onset asthma with traffic-related pollution near homes and schools (McConnell et al., 2010). Asthma risk increased with modeled traffic-related pollution exposure from roadways near homes and near schools. The HR was 0.76 (95% CI: 0.38, 1.54) across the range of ambient O_3 exposure in the communities. With adjustment for school and residential non-freeway traffic-related exposure, the estimated HR for O_3 was 1.01 (95% CI: 0.49, 2.11). Gene variants were not evaluated in this study.

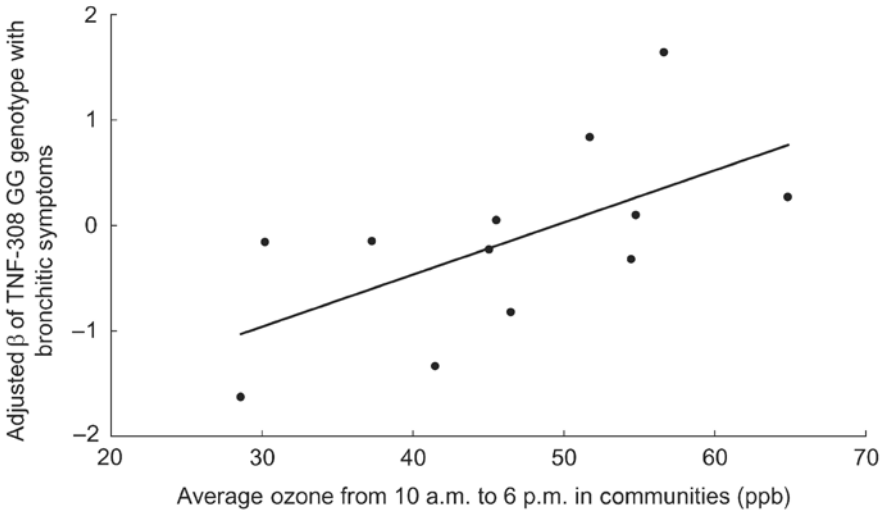
Some cross-sectional studies reviewed in the 2006 O_3 AQCD observed positive relationships between chronic exposure to O_3 and prevalence of asthma and asthmatic symptoms in school children (Ramadour et al., 2000; Wang et al., 1999) while others (Kuo et al., 2002; Charpin et al., 1999) did not. Recent studies provide additional evidence.

In a cross-sectional nationwide study of 32,672 Taiwanese school children, Hwang et al. (2005) assessed the effects of air pollutants on the risk of asthma. The study population was recruited from elementary and middle schools within 1 km of air monitoring stations.

The risk of asthma was related to O_3 in the one-pollutant model. The addition of other pollutants (NO_x, CO_2, SO_2, and PM_{10}), in two-pollutant and three-pollutant models, increased the O_3 risk estimates. The prevalence of childhood asthma was assessed in Portugal by contrasting the risk of asthma between a high O_3 rural area and an area with low O_3 levels (Sousa et al., 2011; Sousa et al., 2009; Sousa et al., 2008). The locations were selected to provide a difference in O_3 levels without the confounding effects of other pollutants. Both evaluation for asthma symptoms and FEV_1 suggested that O_3 increased asthma prevalence. Clark et al. (2010) investigated the effect of exposure to ambient air pollution *in utero* and during the first year of life on risk of subsequent incidence asthma diagnosis up to 3-4 years of age in a population-based nested case-control study for all children born in southwestern British Columbia in 1999 and 2000 (n=37,401; including 3,482 [9.3%] with asthma). Air pollution exposure for each subject was estimated based on their residential address history using regulatory monitoring data, land use regression modeling, and proximity to stationary pollutant sources. Daily values from the three closest monitors within 50 km were used to calculate exposures. Traffic-related pollutants were associated with the highest risk. Ozone was inversely correlated with the primary traffic-related pollutants (r = -0.7 to -0.9). The low reliability of asthma diagnosis in infants makes this study difficult to interpret (Martinez et al., 1995). In a cross-sectional analysis, Akinbami et al. (2010) examined the association between chronic exposure to outdoor pollutants (12-month avg levels by county) and asthma outcomes in a national sample of children ages 3-17 years living in U.S. metropolitan areas (National Health Interview Survey, N = 34,073). A 5-ppb increase in estimated 8-h max O_3 concentration (annual average) yielded a positive association for both currently having asthma and for having at least 1 asthma attack in the previous year; while the adjusted odds ratios for other pollutants were not statistically significant. Models in which pollutant value ranges were divided into quartiles produced comparable results. Multi-pollutant models (SO_2 and PM) produced similar results. The median value for 12-month avg O_3 levels was 39.5 ppb and the IQR was 35.9-43.7 ppb. The adjusted odds for current asthma for the highest quartile (49.9-59.5 ppb) of estimated O_3 exposure was 1.56 (95% CI: 1.15, 2.10) with a positive dose-response relationship apparent from the lowest quartile to the highest. Thus, this cross-sectional analysis and Hwang et al. (2005) provides further evidence relating O_3 exposure and the risk of asthma.

The occurrence of bronchitic symptoms among children with asthma was investigated in the CHS examining the role of gene-environment interactions and long-term O_3 exposure. Lee et al. (2009b) studied associations of TNF-308 genotype with bronchitis symptoms among asthmatic children and investigated whether associations vary with ambient O_3 exposure since increased airway TNF may be related to inflammation. Asthmatic children with the GG genotype had a lower prevalence of bronchitic symptoms compared with children carrying at least one A-allele (e.g., GA or AA). Low-versus high-

O_3 strata were defined as less than or greater than 50- ppb O_3 avg. Asthmatic children with TNF-308 GG genotype had a significantly reduced risk of bronchitic symptoms with low-O_3 exposure (OR=0.53; [95% CI: 0.31, 0.91]). The risk was not reduced in children living in high-O_3 communities (OR=1.42; [95% CI: 0.75, 2.70]). The difference in genotypic effects between low- and high-O_3 environments was statistically significant among asthmatics (P for interaction = 0.01), but insignificant among non-asthmatic children. Using indicator variables for each category based on genotype and O_3 exposure, Lee et al. (2009b) calculated the effect of TNF-308 GG genotype on the occurrence of bronchitic symptoms among children with asthma. Figure 7-2 presents adjusted O_3 community-specific beta-coefficients plotted against ambient O_3 concentration, using weights proportional to the inverse variance. They further report that they found no substantial differences in the effect of the GG genotype in asthmatic children in relation to exposure to PM_{10}, $PM_{2.5}$, NO_2, acid vapor or second-hand smoke exposure. These results suggest a role of gene-environment interactions such as long-term O_3 exposure on the occurrence of bronchitic symptoms among children with asthma.



Source: Reprinted with permission of John Wiley & Sons (Lee et al., 2009b).

Figure 7-2 Ozone modifies the effect of TNF G-308A genotype on bronchitic symptoms among children with asthma in the CHS. Using indicator variables for each category based on genotype and O_3 exposure, betas were calculated of TNF-308 GG genotype on the occurrence of bronchitic symptoms among children with asthma.

The French Epidemiology study on Genetics and Environment of Asthma (EGEA) investigated the relationship between ambient air pollution and asthma severity in a cohort in five French cities (Paris, Lyon, Marseille, Montpellier, and Grenoble) (Rage et al., 2009a). In this cross-sectional study, asthma severity over the past 12 months was assessed among 328 adult asthmatics using two methods: (1) a four-class severity score that integrated clinical events and type of treatment; and (2) a five-level asthma score based only on symptoms. Two measures of exposure were also assessed: (1 [first method]) closest monitor data from 1991 to 1995 where a total of 93% of the subjects lived within 10 km of a monitor, but where 70% of the O_3 concentrations were back-extrapolated values; and (2 [second method]) a validated spatial model that used geostatistical interpolations and then assigned air pollutants to the geocoded residential addresses of all participants and individually assigned exposure to ambient air pollution estimates. Higher asthma severity scores were significantly related to both the 8-h avg O_3 during April-September and the number of days with 8-h O_3 avgs above 55 ppb. Both exposure assessment methods and severity score methods resulted in very similar findings. Effect estimates of O_3 were similar in three-pollutant models. No PM data were available. Since these estimates were not sensitive to the inclusion of ambient NO_2 in the three-pollutant models, the authors viewed the findings not to be explained by particles which usually have substantial correlations between PM and NO_2. Effect estimates for O_3 in three-pollutant models including O_3, SO_2, and NO_2 yielded OR for O_3-days of 2.74 (95% CI: 1.68, 4.48) per IQR days of 10-28 (+18) ppb. The effect estimates for SO_2 and NO_2 in the three-pollutant model were 1.33 (95% CI: 0.85, 2.11) and 0.94 (95% CI: 0.68, 1.29) respectively. Taking into account duration of residence did not change the result. This study suggests that a higher asthma severity score is related to long-term O_3 exposure.

An EGEA follow-up study (Jacquemin et al., In Press), examines the relationship between asthma and O_3, NO_2, and PM_{10}. New aspects considered include: 1) examination of three domains of asthma control (symptoms, exacerbations, and lung function); 2) levels of asthma control (controlled, partially controlled, and uncontrolled asthma); and 3) PM_{10} and multi-pollutant analysis. In this cross-sectional analysis, EGEA2 studied 481 adult subjects with current asthma from 2003 to 2007. The IQRs were 11 (41-52) $\mu g/m^3$ for annual O_3 and 13 (25-38) $\mu g/m^3$ for summer (April-September) O_3. The association between asthma control and air pollutants was expressed by ORs (reported for one IQR of the pollutant), derived from multinomial logistic regression. For each factor, the simultaneous assessment of the risk for uncontrolled asthma and for partly controlled asthma was compared with controlled asthma using a composite of the three domains. In crude and adjusted models, O_3-sum and PM_{10} were positively associated with partly controlled and uncontrolled asthma, with a clear gradient

from controlled, partly controlled (OR=1.53, 95%CI: 1.01, 2.33) and uncontrolled (OR=2.14, 95% CI: 1.34, 3.43) (from the multinomial logistic regression).

Separately, they used a composite asthma control classification that used the ordinal logistic regression for risk comparing controlled to partly controlled asthma and comparing partly controlled to uncontrolled asthma. For these two pollutants, the ORs assessed using the ordinal logistic regression were significant (ORs were 1.69 (95% CI: 1.22, 2.34) and 1.35 (95% CI: 1.13, 1.64) for O_3-sum and PM_{10}, respectively). For two pollutant models using the ordinal logistic regression, the adjusted ORs for O_3-sum and PM_{10} included simultaneously in a unique model were 1.50 (95% CI: 1.07, 2.11) for O_3-sum and 1.28 (95% CI: 1.06, 1.55) for PM_{10}, respectively. This result suggests that the effects of both pollutants are independent.

The analysis of the associations between air pollution for all asthma subjects and each one of the three asthma control domains showed the following: 1) for lung function defined dichotomously as % predicted FEV_1 value < or > =80 (OR=1.35, 95%CI: 0.80, 2.28 for adjusted O_3-sum); 2) for symptoms defined as asthma attacks or dyspnoea or woken by asthma attack or shortness of breath in the past three months (OR=1.59, 95%CI: 1.10, 2.30 for adjusted O_3-sum); and for exacerbations defined at least one hospitalizations or ER visits in the last year or oral corticosteroids in the past three months (OR=1.58, 95%CI: 0.97, 2.59 for adjusted O_3-sum). Since the estimates for both pollutants were more stable and significant when using the integrated measure of asthma control, this indicates that the results are not driven by one domain. These results support an effect of long-term exposure to O_3 on asthma control in adulthood in subjects with pre-existing asthma.

The interrelationships between variants in catalase (CAT) and myeloperoxidase (MPO) genes, ambient pollutants, and acute respiratory illness were investigated in a national U.S. cohort (Wenten et al., 2009). Health information, air pollution, and incident respiratory-related school absences were ascertained in January-June 1996 for 1,136 Hispanic and non-Hispanic white U.S. elementary schoolchildren as part of the prospective Air Pollution and Absence Study, a population based cohort study conducted as part of the CHS. A related earlier study (Gilliland et al., 2001), which was discussed in the 2006 O_3 AQCD, examined the effects of ambient air pollution on school absenteeism due to respiratory illness without a genetic aspect to the study. In a new study Wenten et al. (2009) hypothesized that variation in the level or function of these enzymes would modulate respiratory illness risk, especially under high levels of oxidative stress. The joint effect of these two genes on respiratory illness was examined. Risk of respiratory-related school absences was elevated for children with the CAT (G/G) and MPO (G/A or A/A) genes (relative risk = 1.35, [95% CI: 1.03, 1.77]; P-interaction = 0.005). To assess

effects of long-term average levels of O_3 on acute effects, communities were divided into high and low exposure groups by median levels (46.9 ppb O_3). The epistatic effect of CAT and MPO variants was evident in communities exhibiting high ambient O_3 levels (P-interaction = 0.03). The association of respiratory-illness absences with functional variants in CAT and MPO that differ by air pollution levels illustrates the need to consider genetic epistasis in assessing gene-environment interactions. In high O_3 communities, CAT/MPO genotypes that resulted in decreased oxidative stress were associated with a decreased risk of respiratory related school absences compared with the CAT/MPO wild-type genotype (Relative Risk [RR] = 0.42, [95% CI: 0.20, 0.89]).

7.2.2 Asthma Hospital Admissions and ED Visits

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

An ecologic study (Moore et al., 2008) evaluated time trends in associations between declining warm-season O_3 concentrations and hospitalization for asthma in children in California's South Coast Air Basin who ranged in age from birth to 19 years. Quarterly average concentrations from 195 spatial grids, 10×10 km, were used. Ozone was the only pollutant associated with increased hospital admissions over the study period. A linear relation was observed for asthma hospital discharges (Moore et al., 2008). A matched case-control study (Karr et al., 2007) was conducted of infant bronchiolitis (ICD 9, code 466.1) hospitalization and two measures of long-term pollutant exposure (the month prior to hospitalization and the lifetime average) for O_3 in the South Coast Air Basin of southern California among 18,595 infants born between 1995 and 2000. Ozone was associated with reduced risk in the single-pollutant model, but this relation did not persist in multi-pollutant models (CO, NO_2 and $PM_{2.5}$).

In a cross-sectional study, Meng et al. (2010) examined associations between air pollution and asthma morbidity in the San Joaquin Valley in California by using the 2001 California Health Interview Survey data from subjects ages 1 to 65+ who reported physician-diagnosed asthma (n = 1,502). Subjects were assigned annual average concentrations for O_3 based on residential ZIP code and the closet air monitoring station

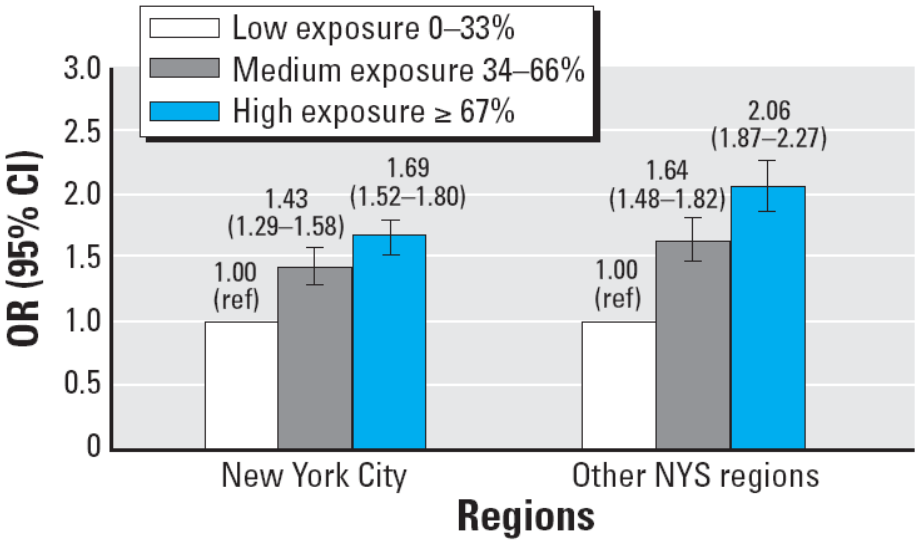
within 8 km but did not have data on duration of residence. Multi-pollutant models for O_3 and PM did not differ substantially from single-pollutant estimates, indicating that pollutant multi-collinearity is not a problem in these analyses. The authors reported increased asthma-related ED visits or hospitalizations for O_3 (OR=1.49; [95% CI: 1.05, 2.11] per 10 ppb) for all ages. Positive associations were obtained for symptoms but 95% CIs included null values. Associations for symptoms for adults (ages 18 +) were observed (OR=1.40; [95% CI: 1.02, 1.91] per 10 ppb).

Associations between air pollution and poorly controlled asthma among adults in Los Angeles and San Diego Counties, were investigated using the California Health Interview Survey data collected between November 2000 and September 2001 (Meng et al., 2007). Each respondent was assigned an annual average concentration measured at the nearest station within 5 miles of the residential cross-street intersection. Poorly controlled asthma was defined as having daily or weekly asthma symptoms or at least one ED visit or hospitalization because of asthma during the past 12 months. This cross-sectional study reports an OR of 3.34 (95% CI: 1.01, 11.09) for poorly controlled asthma when comparing those 65 years of age and older above the 90th percentile (28.7 ppb) level to those below that level. Multi-pollutant (PM) analysis produced similar results.

Evidence associating long-term O_3 exposure to first asthma hospital admission in a concentration-response relationship is provided in a retrospective cohort study (Lin et al., 2008b). This study investigated the association between chronic exposure to O_3 and childhood asthma admissions (defined as a principal diagnosis of ICD9, code 493) by following a birth cohort of 1,204,396 eligible births born in New York State during 1995-1999 to first asthma admission or until 31 December 2000. There were 10,429 (0.87%) children admitted to the hospital for asthma between 1 and 6 years of age. The asthma hospitalization rate in New York State in 1993 was 2.87 per 1,000 (Lin et al., 1999). Three annual indicators (all 8-h max from 10:00 a.m. to 6:00 p.m.) were used to define chronic O_3 exposure: (1) mean concentration during the follow-up period (41.06 ppb); (2) mean concentration during the O_3 season (50.62 ppb); and (3) proportion of follow-up days with O_3 levels >70 ppb. In this study the authors aimed to predict the risk of having asthma admissions in a birth cohort, but the time to the first admission in children that is usually analyzed in survival models was not their primary interest. The effects of co-pollutants were assessed and controlled for using the Air Quality Index (AQI). Interaction terms were used to assess potential effect modifications. A positive association between chronic exposure to O_3 and childhood asthma hospital admissions was observed indicating that children exposed to high O_3 levels over time are more likely to develop asthma severe enough to be admitted to the hospital. The various factors were examined and differences were found for younger children (1-2 years), poor neighborhoods, Medicaid/self-paid births, geographic region and others. As shown in

Adjusted for child's sex, age, birth weight, and gestational age; maternal race, ethnicity, age, education, insurance, and smoking status during pregnancy; and regional poverty level and temperature. ORs by low, medium, and high exposure are shown for New York City (NYC: low [37.3 ppb], medium [37.3 - 38.11] ppb, high [38.11 + ppb]) and other New York State regions (Other NYS regions: low [42.58 ppb], medium [42.58-45.06 ppb], high [45.06+ ppb]) for first asthma hospital admission.

Figure 7-3, positive concentration-response relationships were observed. Asthma admissions were significantly associated with increased O_3 levels for all chronic exposure indicators (ORs, 1.16-1.68). When estimating the O_3 effect using the exceedance proportion, an increase was observed (OR=1.68; [95% CI: 1.64, 1.73]) in hospital admissions with an IQR (2.51%) increase in O_3. A proportional hazards model for the New York City data was run as a sensitivity analysis and it yielded similar results between asthma admissions and chronic exposure to O_3 (Cox model: HR = 1.14, [95% CI: 1.124, 1.155] is similar to logistic model results: OR = 1.16 (95% CI: 1.15, 1.17) (Lin, 2010). Thus, this study provides evidence associating long-term O_3 exposure to first asthma hospital admission in a concentration-response relationship.



Adjusted for child's sex, age, birth weight, and gestational age; maternal race, ethnicity, age, education, insurance, and smoking status during pregnancy; and regional poverty level and temperature. ORs by low, medium, and high exposure are shown for New York City (NYC: low [37.3 ppb], medium [37.3 - 38.11] ppb, high [38.11 + ppb]) and other New York State regions (Other NYS regions: low [42.58 ppb], medium [42.58-45.06 ppb], high [45.06+ ppb]) for first asthma hospital admission.

Figure 7-3 Ozone-asthma concentration-response relationship using the mean concentration during the entire follow-up period.

7.2.3 Pulmonary Structure and Function

The definitive 8-year follow-up analysis of the first cohort of the CHS, which is discussed in Section 7.2 (Gauderman et al., 2004), provided little evidence that long-term exposure to ambient O_3 was associated with significant deficits in the growth rate of lung function in children. A later CHS study (Islam et al., 2007) examined relationships between air pollution, lung function, and new onset asthma and reported no substantial differences in the effect of O_3 on lung function. Ozone concentrations from the least to most polluted communities (mean annual average of 8-h avg O_3) ranged from 30 to 65 ppb, as compared to the ranges observed for the other pollutants, which had four- to eightfold differences in concentrations. In a more recent CHS study, Breton et al. (2011) hypothesized that genetic variation in genes on the glutathione metabolic pathway may influence the association between ambient air pollutant exposures and lung function growth in children. They investigated whether genetic variation in glutathione genes GSS, GSR, GCLC, and GCLM was associated with lung function growth in healthy children using data collected on 2,106 children over an 8-year time-period as part of the Children's Health Study. Breton et al. (2011) found that variation in the GSS locus was associated with differences in susceptibility of children for lung function growth deficits associated with NO_2, PM_{10}, $PM_{2.5}$, elemental carbon, organic carbon, and O_3. The negative effects of air pollutants were largely observed within participants who had a particular GSS haplotype. The effects ranged from -124.2 to -149.1 mL for FEV_1, -92.9 to -126.7 mL for FVC and -193.9 to -277.9 mL/s for MMEF for all pollutants except O_3, for which some positive associations were reported: 25.9 mL for FEV_1; 0.1 mL for FVC, and 166.5 mL/s for MMEF. Ozone was associated with larger decreases in lung function in children without this haplotype, when compared to the other pollutants with values of -76.6 mL for FEV_1, -17.2 mL for FVC, and -200.3 mL/s for MMEF, but only the association with MMEF was statistically significant.

As discussed in the 2006 O_3 AQCD, a study of freshman students at the University of California, Berkeley reported that lifetime exposure to O_3 was associated with decreased measures of small airways (<2 mm) function (FEF_{75} and FEF_{25-75}) (Tager et al., 2005). There was an interaction with the FEF_{25-75}/FVC ratio, a measure of intrinsic airway size. Subjects with a large ratio were less likely to have decreases in FEF_{75} and FEF_{25-75} for a given estimated lifetime exposure to O_3. Kinney and Lippmann (2000) examined 72 nonsmoking adults (mean age 20 years) from the second-year class of students at the U.S. Military Academy in West Point, NY, and reported results that appear to be consistent with a decline in lung function that may in part be due to O_3 exposures over a period of several summer months. Ilhorst et al. (2004) examined 2,153 children with a median age of 7.6 years and reported pulmonary function results which indicated that significantly lower FVC and FEV_1 increases were associated with higher O_3 exposures over the

medium-term of several summer months, but not over several months in the winter. Semi-annual mean O_3 concentrations ranged from 22 to 54 ppb during the summer months and 4 to 36 ppb during the winter months. However, over the longer-term 3.5-year period Ilhorst et al. (2004) found no associations between increases in lung function and mean summer months O_3 levels for FVC and FEV_1, in contrast to the significant medium-term effects. Frischer et al. (1999) showed results similar to the Ilhorst et al. (2004) study.

Mortimer et al. (2008a, b) examined the association of prenatal and lifetime exposures to air pollutants with pulmonary function and allergen sensitization in a subset of asthmatic children (ages 6-11) included in the Fresno Asthmatic Children's Environment Study (FACES). Monthly means of pollutant levels for the years 1989-2000 were created and averaged separately across several important developmental time-periods, including: the entire pregnancy, each trimester, the first 3 years of life, the first 6 years of life, and the entire lifetime. In the first analysis (Mortimer et al., 2008a), negative effects on pulmonary function were found for exposure to PM_{10}, NO_2, and CO during key neonatal and early life developmental periods. The authors did not find a negative effect of exposure to O_3 within this cohort. In the second analysis (Mortimer et al., 2008b), sensitization to at least one allergen was associated, in general, with higher levels of CO and PM_{10} during the entire pregnancy and second trimester, and higher PM_{10} during the first 2 years of life. Lower exposure to O_3 during the entire pregnancy or second trimester was associated with an increased risk of allergen sensitization. Although the pollutant metrics across time periods were correlated, the strongest associations with the outcomes were observed for prenatal exposures. Though it may be difficult to disentangle the effect of prenatal and postnatal exposures, the models from this group of studies suggest that each time period of exposure may contribute independently to different dimensions of school-aged children's pulmonary function. For 4 of the 8 pulmonary-function measures (FVC, FEV_1, PEF, FEF_{25-75}), prenatal exposures were more influential on pulmonary function than early-lifetime metrics, while, in contrast, the ratio of measures (FEV_1/FVC and FEF_{25-75}/FVC) were most influenced by postnatal exposures. When lifetime metrics were considered alone, or in combination with the prenatal metrics, the lifetime measures were not associated with any of the outcomes. This suggests that the timing of the O_3 exposure may be more important than the overall dose, and prenatal exposures are not just markers for lifetime or current exposures.

Latzin et al. (2009) examined whether prenatal exposure to air pollution was associated with lung function changes in the newborn. Tidal breathing, lung volume, ventilation inhomogeneity and eNO were measured in 241 unsedated, sleeping neonates (age = 5 weeks). Consistent with the previous studies, no association was found for prenatal exposure to O_3 and lung function.

In a cross-sectional study of adults, Qian et al. (2005) examined the association of long-term exposure to O_3 and PM_{10} with pulmonary function from data of 10,240 middle-aged subjects who participated in the Atherosclerosis Risk in Communities (ARIC) study in four U.S. communities. A surrogate for long-term O_3 exposure from daily data was determined at the individual level. Ozone was significantly and negatively associated with measures of pulmonary function.

To determine the extent to which long-term exposure to outdoor air pollution accelerates adult decline in lung function, Forbes et al. (2009b) studied the association between chronic exposure to outdoor air pollution and lung function in approximately 42,000 adults aged 16 and older who were representatively sampled cross-sectionally from participants in the Health Survey for England (1995, 1996, 1997, and 2001). FEV_1 was not associated with O_3 concentrations. In contrast to the results for PM_{10}, NO_2, and SO_2; combining the results of all the survey years showed that a 5-ppb difference in O_3 was counter-intuitively associated with a higher FEV_1 by 22 mL.

In a prospective cohort study consisting of school-age, non-asthmatic children in Mexico City (n = 3,170) who were 8 years of age at the beginning of the study, Rojas-Martinez et al. (2007) evaluated the association between long-term exposure to O_3, PM_{10} and NO_2 and lung function growth every 6 months from April 1996 through May 1999. Exposure data were provided by 10 air quality monitor stations located within 2 km of each child's school. Over the study period, 8-h O_3 concentrations ranged from 60 ppb (SD, ±25) in the northeast area of Mexico City to 90 ppb (SD, ±34) in the southwest, with an overall mean of 69.8 ppb. In multi-pollutant models, an IQR increase in mean O_3 concentration of 11.3 ppb was associated with an annual deficit in FEV_1 of 12 mL in girls and 4 mL in boys. Single-pollutant models showed an association between ambient pollutants (O_3, PM_{10} and NO_2) and deficits in lung function growth. While the estimates from copollutant models were not substantially different than single pollutant models, independent effects for pollutants could not be estimated accurately because the traffic-related pollutants were correlated. To reduce exposure misclassification, microenvironmental and personal exposure assessments were conducted in a randomly selected subsample of 60 children using passive O_3 samplers. Personal O_3 concentrations were correlated ($p < 0.05$) with the measurements obtained from the fixed-site air monitoring stations.

In the 2006 O_3 AQCD, few studies had investigated the effect of chronic O_3 exposure on pulmonary function. The strongest evidence was for medium-term effects of extended O_3 exposures over several summer months on lung function in children, i.e., reduced lung function growth being associated with higher ambient O_3 levels. Longer-term studies, investigating the association of chronic O_3 exposure on lung function such as the CHS,

were inconclusive. Short-term O_3 exposure studies presented in Section 6.2.1.2 provide a cumulative body of epidemiologic evidence that strongly supports associations between ambient O_3 exposure and decrements in lung function among children. For new studies of long-term O_3 exposure relationship to pulmonary function, one study, where O_3 and other pollutant levels were higher (90 ppb at high end of the range) than those in the CHS, observes a relationship between O_3 concentration and pulmonary function declines in school-aged children. Two studies of adult cohorts provide mixed results where long-term exposures were at the high end of the range with levels of 49.5 ppb in one study and 27 ppb IQR in the other. Thus there is little new evidence to build upon the very limited studies from the 2006 O_3 AQCD.

7.2.3.1 Pulmonary Structure and Function: Evidence from Toxicological Studies

As reviewed in the 1996 and 2006 O_3 AQCDs, there are both qualitative and quantitative uncertainties in the extrapolation of data generated by rodent toxicology studies to the understanding of health effects observed in humans, as documented by epidemiologic and controlled exposure studies. Chief among these data extrapolation issues are the differences between rodent and human respiratory physiology, cellular makeup, dosimetry, and morphometry (see Chapter 5). However, important evidence is available from O_3-inhalation studies performed in nonhuman primates whose respiratory system most closely resembles that of the human. A long series of studies have used nonhuman primates to examine the effect of O_3 alone or in combination with an inhaled allergen, house dust mite antigen, on morphology and lung function. These studies, by Plopper and colleagues, have demonstrated changes in pulmonary function and airway morphology in adult and infant nonhuman primates repeatedly exposed to environmentally relevant concentrations of O_3 (Joad et al., 2008; Carey et al., 2007; Plopper et al., 2007; Fanucchi et al., 2006; Joad et al., 2006; Evans et al., 2004; Larson et al., 2004; Tran et al., 2004; Evans et al., 2003b; Schelegle et al., 2003; Fanucchi et al., 2000; Hyde et al., 1989; Harkema et al., 1987a; Harkema et al., 1987b; Fujinaka et al., 1985). The findings of these nonhuman primate studies have also been observed in rodent studies discussed at the end of this section and included in Table 7-1.

Since publication of the 1996 and 2006 O_3 AQCDs, the initial observations in adult nonhuman primates have been expanded in a series of experiments using infant rhesus monkeys repeatedly exposed to 0.5 ppm O_3 starting at 1 month of age (Plopper et al., 2007). Many of the observations found in adult monkeys have also been noted in infant rhesus monkeys, although a direct comparison of the degree of effects between adult and infant monkeys has not been reported. In terms of pulmonary function changes, after

several episodic exposures of infant monkeys to O_3 (each cycle: 5 days of 0.5 ppm O_3 at 8 h/day, followed by 9 days of filtered air exposure), they observed more than a doubling in the baseline airway resistance, which was accompanied by a small increase in airway responsiveness to inhaled histamine (Schelegle et al., 2003), although neither measurement was statistically different from filtered air control values. Exposure of animals to inhaled house dust mite antigen alone also produced small but not statistically significant changes in baseline airway resistance and airway responsiveness, whereas the combined exposure to both (O_3 + antigen) produced statistically significant and greater than additive changes in both functional measurements. This nonhuman primate evidence of an O_3-induced change in airway responsiveness supports the biologic plausibility of long-term exposure to O_3 contributing to the effects of asthma in children. To understand which conducting airways and inflammatory mechanisms are involved in O_3-induced airway hyperresponsiveness in the infant rhesus monkey, a follow-up study examined airway responsiveness ex vivo in lung slices (Joad et al., 2006). Using video microscopy to morphometrically evaluate the response of bronchi and respiratory bronchioles to methacholine, (a bronchoconstricting agent commonly used to evaluate airway responsiveness in asthmatics), the investigators observed differential effects for the two airway sizes. While episodic exposure to O_3 alone (0.5 ppm) had little effect on ex vivo airway responsiveness in bronchi and respiratory bronchioles, exposure to dust mite antigen alone produced airway hyperresponsiveness in the large bronchi, whereas O_3 + antigen produced significant increases in airway hyperresponsiveness only in the respiratory bronchioles. These results suggest that ozone's effect on airway responsiveness occurs predominantly in the smaller bronchioles, where dosimetric models indicate the dose would be higher.

The functional changes in the conducting airways of infant rhesus monkeys exposed to either O_3 alone or O_3 + antigen were accompanied by a number of cellular and morphological changes, including a significant fourfold increase in eosinophils, (a cell type important in allergic asthma), in the bronchoalveolar lavage of infant monkeys exposed to O_3 alone. Thus, these studies demonstrate both functional and cellular changes in the lung of infant monkeys after cyclic exposure to 0.5 ppm O_3. This concentration, while higher than those used in controlled human exposure studies, provides relevant information to understanding the adverse effects of ambient O_3 exposure on the respiratory tract of humans. No concentration-response data, however, are available from these nonhuman primate studies.

In addition to these functional and cellular changes, significant structural changes in the respiratory tract have been observed in infant rhesus monkeys exposed to O_3. During normal respiratory tract development, conducting airways increase in diameter and length in the infant rhesus monkey. Exposure to O_3 alone (5 days of 0.5 ppm O_3 at 8 h/day,

followed by 9 days of filtered air exposures for 11 cycles), however, markedly affected the growth pattern of distal conducting airways (Fanucchi et al., 2006). Whereas the first alveolar outpocketing occurred at airway generation 13 or 14 in filtered air-control infant monkeys, the most proximal alveolarized airways occurred at an average of 10 airway generations in O_3-exposed monkeys. Similarly, the diameter and length of the terminal and respiratory bronchioles were significantly decreased in O_3-exposed monkeys. Importantly, the O_3-induced structural pathway changes persisted after recovery in filtered air for 6 months after cessation of the O_3 exposures. These structural effects were accompanied by significant increases in mucus goblet cell mass, alterations in smooth muscle orientation in the respiratory bronchioles, epithelial nerve fiber distribution, and basement membrane zone morphometry. These latter effects are significant because of their potential contribution to airway obstruction and airway hyperresponsiveness which are central features of asthma.

As noted above, a significant increase in airway responsiveness to inhaled histamine occurred in infant rhesus monkeys exposed to O_3 + house dust mite antigen, but not to O_3 alone (Schelegle et al., 2003). To study the underlying mechanisms of this airway hyperresponsiveness, these investigators evaluated the effect of exposure to O_3 alone and in combination with (+) antigen on non-specific airway responsiveness to methacholine at different airway generations. After exposure to filtered air, O_3, antigen, or O_3 + antigen, the bronchi and respiratory bronchioles of 6-month-old monkeys were challenged ex vivo with methacholine. Exposure to O_3 alone had no significant effect on airway responsiveness to methacholine in either airway, whereas O_3 + antigen produced a significant increase in airway responsiveness in the respiratory bronchioles but not the larger bronchi.

Because many cellular and biochemical factors are known to contribute to allergic asthma, the effect of exposure to O_3 alone or O_3 + antigen on immune system parameters was also examined in infant rhesus monkeys. Mast cells, which contribute to asthma via the release of potent proteases, were elevated in animals exposed to antigen alone but O_3 alone had little effect on mast cell numbers and the response of animals exposed to O_3 + antigen was not different from that of animals exposed to antigen alone; thus suggesting that mast cells played little role in the interaction between O_3 and antigen in this model of allergic asthma (Van Winkle et al., 2010). Increases in CD4+ and CD8+ lymphocytes were observed at 6 months of age in the blood and bronchoalveolar lavage fluid of infant rhesus monkeys exposed to O_3 + antigen but not in monkeys exposed to either agent alone (Miller et al., 2009). Activated lymphocytes (i.e., CD25+ cells) were morphometrically evaluated in the airway mucosa and significantly increased in infant monkeys exposed to antigen alone or O_3 + antigen. Although O_3 alone had no effect on CD25+ cells, it did alter the anatomic distribution of CD25+ cells within the airways.

Ozone had only a small effect on these sets of immune cells and did not produce a strong interaction with an inhaled allergen in this nonhuman primate model.

In addition to alterations in the immune system, nervous system interactions with epithelial cells are thought to play a contributing role to airway hyperresponsiveness. As noted in the 2006 O_3 AQCD, exposure of infant rhesus monkeys altered the normal development of neural innervation in the epithelium of the conducting airways (Larson et al., 2004). Whereas, a significant reduction in airway innervation occurred after exposure to O_3 alone, a significantly greater reduction occurred in monkeys exposed to O_3 + antigen. This reduction in overall airway innervation was accompanied, however, by an increase in the abundance of protein gene product 9.5, a nonspecific neural marker. Significant increases in protein gene product 9.5 were still observed in O_3 alone- and O_3 + antigen-exposed infant monkeys after a 6-month recovery protocol (Kajekar et al., 2007). Thus, in addition to structural, immune, and inflammatory effects, exposure to O_3 produces alterations in airway innervation which may contribute to O_3-induced exacerbation of asthma.

A number of studies in both nonhuman primates and rodents demonstrate that O_3 exposure can increase collagen synthesis and deposition, inducing fibrotic-like changes in the lung (Last et al., 1994; Chang et al., 1992; Moffatt et al., 1987; Reiser et al., 1987; Last et al., 1984). Increased collagen content is often associated with elevated abnormal cross links that appear to be irreversible (Reiser et al., 1987). Generally changes in collagen content have been observed in rats exposed to 0.5 ppm O_3 or higher, although extracellular matrix thickening has been observed in the lungs of rats exposed to an urban pattern of O_3 with daily peaks of 0.25 ppm for 38 weeks (Chang et al., 1992; Chang et al., 1991). A more recent study using an urban pattern of exposure to 0.5 ppm O_3 demonstrated that O_3-induced collagen deposition in mice is dependent on the activity of TGF-β (Katre et al., 2011). Sex differences have been observed with respect to increased centriacinar collagen deposition and crosslinking, which was observed in female but not male rats exposed to 0.5 and 1.0 ppm O_3 for 20 months (Last et al., 1994). Few other long-term exposure morphological studies have presented sex differences and most only evaluated males. It is unclear what the long-term effects of these structural changes may be. A number of studies indicate that structural changes in the respiratory system are persistent or irreversible. For example, O_3-induced hyperplasia was still evident in the nasal epithelia of rats 13 weeks after recovery from 0.5 ppm O_3 exposure (Harkema et al., 1999). In a study of episodic exposure to 0.25 ppm O_3, Chang et al. (1992) observed no reversal of basement membrane thickening in rat lungs up to 17 weeks post-exposure. Episodic exposure (0.25 ppm O_3, every other month) of monkeys induced equivalent morphological changes compared to continuously exposed animals, even though they

were exposed for half the time and evaluation occurred a month after exposure ceased as opposed to immediately (Tyler et al., 1988).

Table 7-1 Respiratory effects in nonhuman primates and rodents resulting from long-term O_3 exposure

Study	Model	O_3 (ppm)	Exposure Duration	Effects
Catalano et al. (1995a; 1995b); Chang et al. (1995); Harkema et al. (1997a; 1997b; 1994); Last et al. (1994); Pinkerton et al. (1995); Plopper et al.(1994); Stockstill et al. (1995); Pinkerton et al. (1998)	Rat, male and female, Fischer F344, 6-8 weeks old	0.12 0.5 1.0	6 h/day, 5 days/week for 20 months	Effects similar to (or a model of) early fibrotic human disease were greater in the periacinar region than in terminal bronchioles. Thickened alveolar septa observed in rats exposed to 0.12 ppm O_3. Other effects (e.g., mucous cell metaplasia in the nose and mild fibrotic response in the parenchyma, increased collagen in CAR of females) observed at 0.5 to 1.0 ppm. Some morphometric changes such as epithelial thickening and bronchiolarization occurred after 2 or 3 months of exposure to 1.0 ppm.
Herbert et al. (1996)	Mice, male and female, B6C3F1, 6-7 weeks old,	0.12 0.50 1.0	6 h/day, 5 days/week for 24 and 30 months	Similar to the response of rats in the same study (see rat above). Effects were seen in the nose and centriacinar region of the lung at 0.5 and 1.0 ppm.
Chang et al. (1991)	Rat, male, F344, 6 weeks old	Continuous: 0.12 or 0.25 Episodic/urban: baseline 0.06; peak 0.25	Continuous: 12 h/day for 6 weeks Simulated urban pattern; slow rise to peak 9 h/day, 5 days/week, 13 weeks	Increased Type 1 and 2 epithelial volume assessed by TEM. Linear relationship observed between increases in Type 1 epithelial cell volume and concentration x time product. Degree of injury not related to pattern of exposure (continuous or episodic).
Chang et al. (1992)	Rat, male, F344, 6 weeks old	baseline 0.06; peak 0.25	Slow rise to peak 9 h/day, 5 days/week, 13 and 78 weeks Recovery in filtered air for 6 or 17 weeks	Progressive epithelial hyperplasia, fibroblast proliferation, and interstitial matrix accumulation observed using TEM. Interstitial matrix thickening due to deposition of basement membrane and collagen fibers. Partial recovery of interstitial matrix during follow-up periods in air; but no resolution of basement membrane thickening.
Barry et al. (1985, 1983)	Rat, male, 1 day old or 6 weeks old	0.12 (adults only) 0.25	12 h/day for 6 weeks	Lung and alveolar development not significantly affected. Increased Type 1 and 2 epithelial cells and AM in CAR alveoli, thickened Type 1 cells with smaller volume and less surface coverage as assessed by TEM (adults and juveniles). In adults, smaller but statistically significant similar changes at 0.12 ppm, suggesting linear concentration-response relationship. No statistically significant age-related effects observed.
Tyler et al. (1988)	Monkey; male, Macaca fascicularis, 7 mo old	0.25	8 h/day, 7 days/week, Daily for 18 mo or episodically every other mo for 18 mos Episodic group evaluated 1 mo post exposure	Increased collagen content, chest wall compliance, and inspiratory capacity in episodic group only. Respiratory bronchiolitis in both groups. Episodically exposed group incurred greater alterations in physiology and biochemistry and equivalent changes in morphometry even though exposed for half the time as the daily exposure group.
Harkema et al. (1999)	Rat, male, Fischer F344/N HSD, 10-14 weeks old	0.25 0.5	8 h/day, 7 days/week for 13 weeks	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.
Van Bree et al. (2002)	Rat, male, Wistar, 7 weeks old, n = 5/group	0.4	23.5 h/day for 1, 3, 7, 28,or 56 days	Acute inflammatory response in BALF reached a maximum at day 1 and resolved within 6 days during exposure. Centriacinar region inflammatory responses throughout O_3 exposure with increased collagen and bronchiolization still present after a recovery period.
Katre et al. (2011)	Mice; male, C57BL/6, 6-8 week sold	0.5	8 h/day, [5 days/week O3, and 2 days filtered air] for 5 or 10 cycles	Sustained elevation in TGF-β and PAI-1 in lung (5 or 10 cycles); elevated α-SMA and increased collagen deposition in airway walls (after 10 cycles). Collagen increase shown to depend on TGF-β.

Study	Model	O_3 (ppm)	Exposure Duration	Effects
Schelegle et al. (2003);	Monkey; Rhesus, 30 days old*	0.5	8 h/day for 5 days, every 5 days for a total of 11 episodes	Goblet cell metaplasia, increased AHR, and increased markers of allergic asthma (e.g., eosinophilia) were observed, suggesting that episodic exposure to O_3 alters postnatal morphogenesis and epithelial differentiation and enhances the allergic effects of house dust mite allergen in the lungs of infant primates.
Larson et al. (2004)	Monkey;Macaca mulatta, 30 days old*	0.5	11 episodes of 5 days each, 8 h/day followed by 9 days of recovery	O_3 or O_3 + house dust mite antigen caused changes in density and number of airway epithelial nerves in small conducting airways. Suggests episodic O_3 alters pattern of neural innervation in epithelial compartment of developing lungs.
Plopper et al. (2007)	Monkey; Rhesus, 30 days old*	0.5	5 months of episodic exposure; 5 days O_3 followed by 9 days of filtered air, 8h/day.	Non-significant increases airway resistance and airway responsiveness with O_3 or inhaled allergen alone. Allergen + O_3 produced additive changes in both measures.
Fanucchi et al. (2006)	Monkey; male Rhesus,30 days old	0.5	5 months of episodic exposure; 5 days O_3 followed by 9 days of filtered air, 8h/day.	Cellular changes and significant structural changes in the distal respiratory tract in infant rhesus monkeys exposed to O_3 postnatally.
Reiser et al. (1987)	Monkey; male and female Cynomolgus 6-7 mo old	0.61	8 h/day for 1 year	Increased lung collagen content associated with elevated abnormal cross links that were irreversibly deposited.

* sex not reported

Collectively, evidence from animal studies strongly suggests that chronic O_3 exposure is capable of damaging the distal airways and proximal alveoli, resulting in lung tissue remodeling and leading to apparent irreversible changes. Potentially, persistent inflammation and interstitial remodeling play an important role in the progression and development of chronic lung disease. Further discussion of the modes of action that lead to O_3-induced morphological changes can be found in Section 5.3.7. The findings reported in chronic animal studies offer insight into potential biological mechanisms for the suggested association between seasonal O_3 exposure and reduced lung function development in children as observed in epidemiologic studies (see Section 7.2.3). Discussion of mechanisms involved in lifestage susceptibility and developmental effects can be found in Section 5.4.2.4.

7.2.4 Pulmonary Inflammation, Injury, and Oxidative Stress

The 2006 O_3 AQCD stated that the extensive human clinical and animal toxicological evidence, together with the limited epidemiologic evidence available, suggests a causal role for O_3 in inflammatory responses in the airways. Short-term exposure epidemiologic studies discussed earlier in Section 6.2.3.2 show consistent associations of O_3 exposure and increased airway inflammation and oxidative stress. Further discussion of the mechanisms underlying inflammation and oxidative stress responses can be found in Section 5.3.3. Though the majority of recent studies focus on short-term exposures,

several epidemiologic and toxicology studies of long-term exposure add to observations of O_3-induced inflammation and injury.

Inflammatory markers and peak expiratory pulmonary function were examined in 37 allergic children with physician-diagnosed mild persistent asthma in a highly polluted urban area in Italy and then again 7 days after relocation to a rural location with significantly lower pollutant levels (Renzetti et al., 2009). The authors observed a fourfold decrease in nasal eosinophils and a statistically significant decrease in fractional exhaled nitric oxide along with an improvement in lower airway function. Several pollutants were examined, including PM_{10}, NO_2, and O_3, though pollutant-specific results were not presented. These results are consistent with studies showing that traffic-related exposures are associated with increased airway inflammation and reduced lung function in children with asthma and contribute to the notion that this negative influence may be rapidly reversible. Exhaled NO (eNO) has been shown to be a useful biomarker for airway inflammation in large population-based studies (Linn et al., 2009). Thus, while the time scale of 7 days between examinations for eNO needs to be evaluated for appropriateness, the results suggest that inflammatory responses are reduced when O_3 levels are decreased.

Chest radiographs (CXR) of 249 children in Mexico City who were chronically exposed to O_3 and $PM_{2.5}$ were analyzed by Calderón-Garcidueñas et al. (2006). They reported an association between chronic exposures to O_3 and other pollutants and a significant increase in abnormal CXR's and lung CTs suggestive of a bronchiolar, peribronchiolar, and/or alveolar duct inflammatory process, in clinically healthy children with no risk factors for lung disease. These CXR and CT results should be viewed with caution because it is difficult to attribute effects to O_3 exposure.

In a cross-sectional study, Wood et al. (2009) examined the association of outdoor air pollution with respiratory phenotype (PiZZ type) in alpha 1-Antitrypsin deficiency (α-ATD) from the U.K. α-ATD registry. In total, 304 PiZZ subjects underwent full lung function testing and quantitative high-resolution computed tomography to identify the presence and severity of COPD – emphysema. Mean annual air pollution data for 2006 was matched to the location of patients' houses and used in regression models to identify phenotypic associations with pollution controlling for covariates. Relative trends in O_3 levels were assessed to validate use of a single year's data to indicate long-term exposure and validation; data showed good correlations between modeled and measured data (Stedman and Kent, 2008). Regression models showed that estimated higher exposure to O_3 exposure was associated with worse gas transfer and more severe emphysema, albeit accounting for only a small proportion of the lung function variability. This suggests that a gene-specific group demonstrates a long-term O_3 exposure effect.

The similarities of nonhuman primates to humans make them attractive models in which to study the effects of O_3 on the respiratory tract. The nasal mucous membranes, which protect the more distal regions of the respiratory tract, are susceptible to injury from O_3. Carey et al. (2007) conducted a study of O_3 exposure in infant rhesus macaques, whose nasal airways closely resemble that of humans. Monkeys were exposed either acutely for 5 days (8 h/day) to 0.5 ppm O_3, or episodically for several biweekly cycles alternating 5 days of 0.5 ppm O_3 with 9 days of filtered air (0 ppm O_3), designed to mimic human exposure (70 days total). All monkeys acutely exposed to O_3 had moderate to marked necrotizing rhinitis, with focal regions of epitheliar exfoliation, numerous infiltrating neutrophils, and some eosinophils. The distribution, character, and severity of lesions in episodically exposed monkeys were similar to that of acutely exposed animals. Neither group exhibited mucous cell metaplasia proximal to the lesions, a protective adaptation observed in adult monkeys exposed continuously to 0.3 ppm O_3 in another study (Harkema et al., 1987a). Adult monkeys also exhibit attenuation of inflammatory responses with continued daily exposure (Harkema et al., 1987a), but inflammation did not resolve over time in young episodically exposed monkeys(Carey et al., 2011). Inflammation in conducting airways has also been observed in rats chronically exposed to O_3. Using an agar-based technique to fill the alveoli so that only the rat bronchi are lavaged, a 90-day exposure of rats to 0.8 ppm O_3 (8 h/day) elicited significantly elevated pro-inflammatory eicosanoids PGE_2 and 12-HETE in the conducting airway compared to filtered air-exposed rats (Schmelzer et al., 2006).

7.2.5 Allergic Responses

The association of air pollutants with childhood respiratory allergies was examined in the U.S. using the 1999-2005 National Health Interview Survey of approximately 70,000 children, and ambient air pollution data from the U.S. EPA, with monitors within 20 miles of each child's residential block (Parker et al., 2009). The authors examined the associations between the reporting of respiratory allergy or hay fever and medium-term exposure to O_3 over several summer months, controlling for demographic and geographic factors. Increased respiratory allergy/hay fever was associated with increased O_3 levels (adjusted OR per 10 ppb = 1.20; [95% CI: 1.15, 1.26]). These associations persisted after stratification by urban-rural status, inclusion of multiple pollutants (O_3, SO_2, NO_2, PM), and definition of exposure by differing exposure radii; smaller samples within 5 miles of monitors were remarkably similar to the primary results. No associations between the other pollutants and the reporting of respiratory allergy/hay fever were apparent. Ramadour et al. (2000) reported no relationship between O_3 levels and rhinitis symptoms and hay fever. Hwang et al. (2006) report the prevalence of allergic rhinitis (adjusted OR

per 10 ppb = 1.05; [95% CI: 0.98, 1.12]) in a large cross-sectional study in Taiwan. In a large cross-sectional study in France, Penard-Morand et al. (2005) reported a positive relationship between lifetime allergic rhinitis and O_3 exposure in a two-pollutant model with NO_2. These studies related positive outcomes of allergic response and O_3 exposure but with variable strength for the effect estimates. A toxicological study reported that five weeks of continuous exposure to 0.4 ppm O_3 (but not 0.1 or 0.2 ppm O_3) augmented sneezing and nasal secretions in a guinea pig model of nasal allergy (Iijima and Kobayashi, 2004). Nasal eosinophils, which participate in allergic disease and inflammation, and allergic antibody levels in serum were also elevated by exposure to concentrations as low as 0.2 ppm (Iijima and Kobayashi, 2004).

Nasal eosinophils were observed to decrease by fourfold in 37 atopic, mildly asthmatic children 7 days after relocation from a highly polluted urban area in Italy to a rural location with significantly lower pollutant levels (Renzetti et al., 2009). Inflammatory and allergic effects of O_3 exposure (30 day mean) such as increased eosinophil levels were observed in children in an Austrian study (Frischer et al., 2001). Episodic exposure of infant rhesus monkeys to 0.5 ppm O_3 for 5 months appears to significantly increase the number and proportion of eosinophils in the blood and airways (lavage) [protocol described above in 7.2.3.1 for Fanucchi et al. (2006)] (Maniar-Hew et al., 2011). These changes were not evident at 1 year of age (6 months after O_3 exposure ceased). Increased eosinophils levels have also been observed after acute or prolonged exposures to O_3 in adult bonnet and rhesus monkeys (Hyde et al., 1992; Eustis et al., 1981).

Total IgE levels were related to air pollution levels in 369 adult asthmatics in five French centers using generalized estimated equations (GEE) as part of the EGEA study described earlier (Rage et al., 2009b). Geostatistical models were performed on 4×4 km grids to assess individual outdoor air pollution exposure that was assigned to subject's home address. Ozone concentrations were positively related to total IgE levels and an increase of 5 ppb of O_3 resulted in an increase of 20.4% (95% CI: 3.0, 40.7) in total IgE levels. Nearly 75% of the subjects were atopic. In two-pollutant models including O_3 and NO_2, the O_3 effect estimate was decreased by 25% while the NO_2 effect estimate was decreased by 57%. Associations were not sensitive to adjustment for covariates or the season of IgE measurements. These cross-sectional results suggest that exposure to O_3 may increase total IgE in adult asthmatics.

Although very few toxicological studies of long-term exposure examining allergy are available, short-term exposure studies in rodents and nonhuman primates demonstrate allergic skewing of immune responses and enhanced IgE production. Due to the persistent nature of these responses, the short-term toxicological evidence lends

biological plausibility to the limited epidemiologic findings of an association between long-term O_3 exposure and allergic outcomes.

7.2.6 Host Defense

Short-term exposures to O_3 have been shown to cause decreases in host defenses against infectious lung disease in animal models. However, acute O_3-induced suppression of alveolar phagocytosis and immune functions observed in animals appears to be transient and attenuated with continuous or repeated exposures. Chronic exposures (weeks, months) of 0.1 ppm do not cause greater effects on infectivity than short exposures, due to defense parameters becoming reestablished with prolonged exposures, although chronic exposure has been shown to slow alveolar clearance. No detrimental effects were seen with a 120-day exposure to 0.5 ppm O_3 on acute lung injury from influenza virus administered immediately before O_3 exposure started. However, O_3 was shown to increase the severity of postinfluenzal alveolitis and lung parenchymal changes (Jakab and Bassett, 1990). Little new evidence has become available to address the effects of long-term exposure on host defense mechanisms. However, a recent study by Maniar-Hew et al. (2011) demonstrated that the immune system of infant rhesus monkeys episodically exposed to 0.5 ppm O_3 for 5 months[1] appeared to be altered in ways that could diminish host defenses. Reduced numbers of circulating leukocytes were observed, particularly polymorphonuclear leukocytes (PMNs) and lymphocytes, which were decreased in the blood and airways (bronchoalveolar lavage). These changes did not persist at 1 year of age (6 months postexposure); rather, increased numbers of monocytes were observed at that time point. Challenge with LPS, a bacterial ligand that activates monocytes and other innate immune cells, elicited lower responses in O_3-exposed animals even though the relevant reactive cell population was increased. This was observed in both an in vivo inhalation challenge and an ex vivo challenge of peripheral blood mononuclear cells. Thus a decreased ability to respond to pathogenic signals was observed six months after O_3 exposure ceased, in both the lungs and periphery.

7.2.7 Respiratory Mortality

A limited number of epidemiologic studies have assessed the relationship between long-term exposure to O_3 and mortality. The 2006 O_3 AQCD concluded that an insufficient amount of evidence existed "to suggest a causal relationship between chronic O_3 exposure and increased risk for mortality in humans" (U.S. EPA, 2006b). Though total

[1] Exposure protocol is described above in Section 7.2.3.1 for Fanucchi et al. (2006)

and cardio-pulmonary mortality were considered in these studies, respiratory mortality was not specifically considered. In the most recent follow-up analysis of the ACS cohort (Jerrett et al., 2009), cardiopulmonary deaths were subdivided into respiratory and cardiovascular, separately, as opposed to combined in the Pope et al. (2002) work. A 10-ppb increment in exposure to O_3 elevated the risk of death from respiratory causes and this effect was robust to the inclusion of $PM_{2.5}$. The association between increased O_3 concentrations and increased risk of death from respiratory causes was insensitive to the use of a random-effects survival model allowing for spatial clustering within the metropolitan area and state of residence, and to adjustment for several ecologic variables considered individually. Additionally, a recent study (Zanobetti and Schwartz, In Press) observed an association between long-term exposure to O_3 and elevated risk of mortality among Medicare enrollees that had previously experienced an emergency hospital admission due to COPD.

7.2.8 Summary and Causal Determination

The epidemiologic studies reviewed in the 2006 O_3 AQCD detected no associations between long-term (annual) O_3 exposures and asthma-related symptoms, asthma prevalence, or allergy to common aeroallergens among children after controlling for covariates. Little evidence was available to relate long-term exposure to current ambient O_3 concentrations to deficits in the growth rate of lung function in children. Additionally, limited evidence was available evaluating the relationship between long-term O_3 levels and pulmonary inflammation and other endpoints. From toxicological studies, it appeared that O_3-induced inflammation tapered off during long-term exposures, but that hyperplastic and fibrotic changes remained elevated and in some cases even worsened after a postexposure period in clean air. Episodic exposures were also known to cause more severe pulmonary morphologic changes than continuous exposure (U.S. EPA, 2006b).

The new epidemiologic evidence base consists of studies using a variety of designs and analysis methods evaluating the relationship between long-term annual measures of exposure to ambient O_3 and measures of respiratory morbidity conducted by different research groups in different locations. See Table 7-2 for O_3 concentrations associated with selected studies. The positive results from various designs and locations support an association between long-term O_3 concentrations and respiratory morbidity.

New studies examined the relationship between long-term O_3 exposure and new onset asthma in children. Studies have provided evidence for a relationship between different genetic variants (HMOX, GST, ARG) that, in combination with O_3 exposure, are related

to new onset asthma (Islam et al., 2009; Salam et al., 2009; Islam et al., 2008). These studies involve two separate cohorts in 12 California communities of the CHS. These prospective cohort studies represent strong evidence because they are methodologically rigorous epidemiology studies. The stratified analysis for the two independent fourth-grade cohorts of the study population recruited in 1993 and 1996 yielded consistent results and provided replication in independent groups of children.

Table 7-2 Summary of selected key new studies examining annual ozone exposure and respiratory health effects

Study; Health Effect; Location	Annual Mean O_3 Concentration (ppb)	O_3 Range (ppb) Percentiles
Akinbami et al. (2010); current asthma United States	12 month median 39.8	IQR 35.9 to 43.7
Hwang et al. (2005); prevalence of asthma Taiwan	Mean 23.14	Range 18.65 to 31.17
Islam et al.(2008); new-onset asthma; CHS	55.2 high vs. 38.4 low communities 10:00 a.m. to 6:00 p.m.	See left
Islam et al. (2009); new-onset asthma; CHS	55.2 high vs. 38.4 low communities 10:00 a.m. to 6:00 p.m.	See left
Salam et al. (2009); childhood onset asthma; CHS	O_3 greater than or less than 50 ppb	See left
Lin et al. (2008b); first asthma hospital admission; New York State - 10 regions	Range of mean O3 concentrations over the 10 New York Regions 37.51 to 47.78	See left
Moore et al. (2008); asthma hospital admissions; South Coast Basin	Median 87.8 ppb	Range 28.6 to 199.9
Meng et al. (2010); asthma ED visits or hospitalizations; San Joaquin Valley, CA	Median 30.3 ppb	25-75% range 27.1 to 34.0
Lee et al. (2009b); bronchitic symptoms in asthmatic children; CHS	Above and below 50 ppb	See left
Rage et al. (2009b); asthma severity; five French cities	Mean 30 ppb	25th-75th 21-36
Jacquemin et al. (In Press); asthma control in adults; five French cities	Median 46.9 ppb;	25th-75th 41-52
Wenten et al. (2009); respiratory school absence, U.S.	Median 46.9 ppb; 10:00 a.m. – 6:00 p.m.	Min-Max 27.6-65.3

Studies using a cross-sectional design provide support for a relationship between long-term O_3 exposure and health effects in asthmatics. A long-term O_3 exposure study relates bronchitic symptoms to TNF-308 genotype asthmatic children with ambient O_3 exposure in the CHS (Lee et al., 2009b). A study in five French cities reports effects on asthma severity related to long-term O_3 exposure (Rage et al., 2009a). A follow-up study of this cohort (Jacquemin et al., In Press) supports an effect of long-term O_3-sum exposure on asthma control in adulthood in subjects with pre-existing asthma. Akinbami et al. (2010) and Hwang et al. (2005) provides further evidence relating O_3 exposures and the risk of asthma. For the respiratory health of a cohort based on the general U.S. population, risk

of respiratory-related school absences was elevated for children with the CAT and MPO variant genes related to communities with high ambient O_3 levels (Wenten et al., 2009).

Chronic O_3 exposure was related to first childhood asthma hospital admissions in a positive concentration-response relationship in a New York State birth cohort (Lin et al., 2008b). A separate hospitalization cross-sectional study in San Joaquin Valley in California reports similar findings (Meng et al., 2010). Another study relates asthma hospital admissions to quarterly average O_3 in the South Coast Air Basin of California (Moore et al., 2008).

Information from toxicological studies indicates that long term exposure to O_3 during gestation or development can result in irreversible morphological changes in the lung, which in turn can influence pulmonary function. Studies by Plopper and colleagues have demonstrated changes in pulmonary function and airway morphology in adult and infant nonhuman primates repeatedly exposed to environmentally relevant concentrations of O_3 (Fanucchi et al., 2006; Joad et al., 2006; Schelegle et al., 2003; Harkema et al., 1987b). This nonhuman primate evidence of an O_3-induced change in airway responsiveness supports the biologic plausibility of long term exposure to O_3 contributing to the adverse effects of asthma in children. Results from epidemiologic studies examining long-term O_3 exposure and pulmonary function effects are inconclusive with some new studies relating effects at higher exposure levels. The results from the CHS described in the 2006 O_3 AQCD remain the definitive line of evidence. Other cross-sectional studies provide mixed results.

Table 7-3 Studies providing evidence concerning potential confounding by PM for available endpoints

Study Endpoint	Exposure	Single Pollutant O_3	Single Pollutant PM	O_3 with PM	PM with O_3
Hwang et al. (2005) Asthma risk in children	10 ppb O_3	1.138 (1.001, 1.293	0.934 (0.909, 0.960)	PM_{10} 1.253 (1.089, 1.442)	0.925 (0.899, 0.952)
Jacquemin et al. (In Press) Asthma control in adults	IQR 25-38 ppb O_3 summer	1.69 (1.22, 2.34)	1.33 (1.06, 1.67)	PM_{10} 1.50 (1.07, 2.11)	1.28 (1.06, 1.55)
Lin et al. (2008b) Asthma admissions in children	IQR 2.5%	1.16 (1.15, 1.17)	NA	Air Quality Index 1.24 (1.23, 1.25)	NA
Akinbami et al. (2010) Asthma prevalence in children	IQR 35.9-43.7 ppb	1.56 (1.15, 2.10)	$PM_{2.5}$ 1.43 (0.98, 2.10)	Adjusted for SO_2,$PM_{2.5}$,PM_{10} 1.86 (1.02-3.40) Adjusted for $PM_{2.5}$, PM_{10} 1.36 (0.91-2.02)	$PM_{2.5}$ 1.24 (0.70-2.21) $PM_{2.5}$ 1.26 (0.80-1.98)
Lee et al. (2009b) Bronchitic symptoms asthmatics	High O_3 >50 ppb	1.42 (0.75, 2.70)	NA	No substantial differences PM_{10}, $PM_{2.5}$	NA
Rage et al. (2009a) Asthma severity in adults	IQR 28.5-33.9 ppb	2.53 (1.69, 3.79)	NA	No PM data Three pollutant (O_3, NO_2, SO_2) 2.74 (1.68, 4.48)	NA
Meng et al. (2007) Asthma control	1 ppm	1.70 (0.91, 3.18)	PM_{10} 2.06 (1.17, 3.61) women	Did not differ	NA
Meng et al. (2010) Asthma ED visits, Hospitalization	10 ppb	1.49 (1.05, 2.11)	PM10 1.29 (0.99, 1.69)	Did not differ	NA
Karr et al. (2007) Bronchiolitis Hospitalization	10 ppb	0.92 (0.88, 0.96)	1.09 (1.04, 1.14)	$PM_{2.5}$ 1.02 (0.94, 1.10)	1.09 (1.03, 1.15)
Rojas-Martinez et al. (2007) FEV_1 (mL) Deficit Girls	11.3 ppb IQR	-24 (-30, -19)	PM_{10} IQR 36.4 ug/m3 -29(-36, -21)	-17 (-23, -12)	-24 (-31, -16)
Parker et al. (2009) Respiratory allergy	10 ppb	1.24 (1.15, 1.34)	1.23 (1.04, 1.46)	Multi-pollutant 1.18 (1.09, 1.27)	1.29 (1.07, 1.56)

The highest quartile is shown for all results.

NA = not available

Several studies (see Table 7-3) provide results from studies that adjusted for potential confounders, presenting results for both O_3 and PM (single and multipollutant models) as well as other pollutants where PM effects were not provided. As shown in the table, O_3 associations are generally robust to adjustment for potential confounding by PM.

The 2006 O_3 AQCD concluded that the extensive human clinical and animal toxicological evidence, together with the limited epidemiologic evidence available,

suggests a causal role for short-term O_3 exposure in inflammatory responses in the airways. Though the majority of recent studies focus on short-term exposures, several epidemiologic and toxicological studies of long-term exposure add to observations of O_3-induced inflammation and injury. Toxicological studies in rodents and nonhuman primates indicate that chronic O_3 exposure causes structural changes in the respiratory tract, and simulated seasonal exposure studies suggest that such exposures might have cumulative impacts. The strongest epidemiologic evidence for a relationship between long-term O_3 exposure and respiratory morbidity is provided by new studies that demonstrate associations between long-term measures of O_3 exposure and new-onset asthma in children and increased respiratory symptom effects in asthmatics. While there are currently a limited number of studies in this data base, the U.S. multi-community prospective cohort studies are methodologically rigorous epidemiologic studies. Asthma risk is related to complex relationships between genetic variability, environmental O_3 exposure, and behavior. The genes, evaluated in these studies, are both key candidates in the oxidative stress pathway and have been shown to play an important role in asthma development. Reduced risk for asthma development is reported in some studies in children living in low- O_3 communities. Mean O_3 concentrations in the studies (10:00 a.m. to 6:00 p.m.) ranged from 28.6 to 45.5 ppb in low O_3 communities (mean = 38.4 ppb) and from 46.5 to 64.9 ppb in high O_3 communities (mean = 55.2 ppb). These CHS multi-community studies form a foundation for the evidence base in which findings for several genes indicate the breath of the evidence across different gene variants. The several other studies with different designs, analysis, locations and researchers provide a cumulative collective body of evidence informing these relationships. The other studies in the new data base provide coherent evidence for long-term O_3 exposure and respiratory morbidity effects such as first asthma hospitalization and respiratory symptoms in asthmatics. Studies considering other pollutants provide data suggesting that the effects related to O_3 are independent from potential effects of the other pollutants. Some studies provide evidence for a positive concentration-response relationship. Short-term studies provide supportive evidence with increases in respiratory symptoms and asthma medication use, hospital admissions and ED visits for all respiratory outcomes and asthma, and decrements in lung function in children. The above discussion of the recent epidemiologic and toxicological data base provides a compelling case to support the hypothesis that a relationship exists between long-term exposure to ambient O_3 and measures of respiratory morbidity. The 2006 O_3 AQCD concluded the evidence was suggestive but inconclusive at that time. **The new epidemiological data base, combined with toxicological studies in rodents and nonhuman primates, provides biologically plausible evidence that there is likely to be causal relationship between long-term exposure to O_3 and respiratory morbidity.**

7.3 Cardiovascular Effects

7.3.1 Cardiovascular Disease

7.3.1.1 Cardiovascular Epidemiology

Long-term exposure to O_3 and its effects on cardiovascular morbidity were not considered in the 2006 O_3 AQCD. However, recent studies have assessed the chronic effects of O_3 exposure on cardiovascular morbidity (Chuang et al., 2011; Forbes et al., 2009a; Chen et al., 2007). The association between O_3 exposure and markers of lipid peroxidation and antioxidant capacity was examined among 120 nonsmoking healthy college students, aged 18-22 years, from the University of California, Berkeley (Feb-Jun 2002) (Chen et al., 2007). By design, students were chosen from geographic areas so they had experienced different levels of O_3 over their lifetimes and during recent summer vacation in either greater Los Angeles (LA) or the San Francisco Bay Area (SF). A marker of lipid peroxidation, 8-isoprostane (8-iso-PGF) in plasma, was assessed. This marker is formed continuously under normal physiological conditions but has been found at elevated concentrations in response to environmental exposures. A marker of overall antioxidant capacity, ferric reducing ability of plasma (FRAP), was also measured. The lifetime O_3 exposure estimates (estimated monthly average) did not show much overlap between the two geographic areas [median (range): LA, 42.9 ppb (28.5-65.3); SF, 26.9 ppb (17.6-33.5)]. Estimated lifetime O_3 exposure was related to 8-iso-PGF [$\beta = 0.025$ (pg/mL)/8-h ppb O_3, $p = 0.0007$]. For the 17-ppb cumulative lifetime O_3 exposure difference between LA and SF participants, there was a 17.41-pg/mL (95% CI: 15.43, 19.39) increase in 8-iso-PGF. No evidence of association was observed between lifetime O_3 exposure and FRAP [$\beta = -2.21$ (pg/mL)/8-h ppb O_3, $p = 0.45$]. The authors note that O_3 was highly correlated with $PM_{10-2.5}$ and NO_2 in this study population; however, their inclusion in the O_3 models did not substantially modify the magnitude of the associations with O_3. Because the lifetime exposure results were supported by shorter-term exposure results from analyses considering O_3 concentrations up to 30 days prior to sampling, the authors conclude that persistent exposure to O_3 can lead to sustained oxidative stress and increased lipid peroxidation. However, because there was not much overlap in lifetime O_3 exposure estimates between LA and SF, it is possible that the risk estimates involving the lifetime O_3 exposures could be confounded by unmeasured factors related to other differences between the two cities.

Forbes et al. (2009a) used the annual average exposures to assess the relationship between chronic ambient air pollution and levels of fibrinogen and C-reactive protein

(CRP) in a cross-sectional study conducted in England. Data were collected from the Health Survey of England for 1994, 1998, and 2003. The sampling strategy was designed to obtain a representative sample of the English population; however, due to small group sizes, only data from white ethnic groups were analyzed. For analyses, the annual concentrations of O_3 were averaged for the year of data collection and the previous year with the exception of 1994 (because pollutant data were not available for 1993). Median O_3 concentrations were 26.7 ppb, 25.4 ppb, and 28 ppb for 1994, 1998, and 2003, respectively. Year specific adjusted effect estimates were created and combined in a meta-analysis. No evidence of association was observed for O_3 and levels of fibrinogen or CRP (e.g., the combined estimates for the percent change in fibrinogen and CRP for a 10 ppb increase in O_3 were -0.28 [95% CI: -2.43, 1.92] and -3.05 [95% CI: -16.10, 12.02], respectively).

A study was performed in Taiwan to examine the association between long-term O_3 concentrations and blood pressure and blood markers using the Social Environment and Biomarkers of Aging Study (SEBAS) (Chuang et al., 2011). Individuals included in the study were 54 years of age and older. The mean annual O_3 concentration during the study period was 22.95 ppb (SD 6.76 ppb). Positive associations were observed between O_3 concentrations and both systolic and diastolic blood pressure [changes in systolic and diastolic blood pressure were 21.51mmHg (95% CI: 16.90, 26.13) and 20.56 mmHg (95% CI: 18.14, 22.97) per 8.95 ppb increase in O_3, respectively). Increased O_3 concentrations were also associated with increased levels of total cholesterol, fasting glucose, hemoglobin A1c, and neutrophils. No associations were observed between O_3 concentrations and triglyceride and IL-6 levels. The observed associations were reduced when other pollutants were added to the models. Further research will be important for understanding the effects, if any, of chronic O_3 exposure on cardiovascular morbidity risk.

7.3.1.2 Cardiovascular Toxicology

Three new studies have investigated the cardiovascular effects of long-term exposure to O_3 in animal models (See Table 7-4 for study details). In addition to the short-term exposure effects described in Section 6.3.3, a recent study found that O_3 exposure in genetically hyperlipidemic mice enhanced aortic atherosclerotic lesion area compared to air exposed controls (Chuang et al., 2009). Chuang et al. (2009) not only provided evidence for increased atherogenesis in susceptible mice, but also reported an elevated vascular inflammatory and redox state in wild-type mice and infant primates (Section 6.3.3.2). This study is compelling in that it identifies biochemical and cellular events responsible for transducing the airway epithelial reactions of O_3 into

proinflammatory responses that are apparent in the extrapulmonary vasculature (Cole and Freeman, 2009).

Another recent study provides further evidence for increased vascular inflammation and oxidation and long term effects in the extrapulmonary space. Rats episodically exposed to O_3 for 16 weeks presented marked increases in gene expression of biomarkers of oxidative stress, thrombosis, vasoconstriction, and proteolysis (Kodavanti et al., 2011). Ozone exposure upregulated aortic mRNA expression of heme oxygenase-1 (HO-1), tissue plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor (vWf), thrombomodulin, endothelial nitric oxide synthase (eNOS), endothelin-1 (ET-1), matrix metalloprotease-2 (MMP-2), matrix metalloprotease-3 (MMP-3), and tissue inhibitor of matrix metalloprotease-2 (TIMP-2). In addition, O_3 exposure depleted some cardiac mitochondrial phospholipid fatty acids (C16:0 and C18:1), which may be the result of oxidative modifications. The authors speculate that oxidatively modified lipids and proteins produced in the lung and heart promote vascular pathology through activation of lectin-like oxidized-low density lipoprotein receptor-1 (LOX-1). Activated LOX-1 induces expression of a number of the biomarkers induced by O_3 exposure and is considered pro-atherogenic. Both LOX-1 mRNA and protein were increased in mouse aorta after O_3 exposure. This study provides a possible pathway and further support to the observed O_3 induced atherosclerosis.

Vascular occlusion resulting from atherosclerosis can block blood flow through vessels causing ischemia. The restoration of blood flow or reperfusion can cause injury to the tissue from subsequent inflammation and oxidative damage. Ozone exposure enhanced the sensitivity to myocardial ischemia-reperfusion (I/R) injury in rats while increasing oxidative stress levels and pro-inflammatory mediators and decreasing production of anti-inflammatory proteins (Perepu et al., 2010). Both long- and short-term O_3 exposure decreased the left ventricular developed pressure, rate of change of pressure development, and rate of change of pressure decay and increased left ventricular end diastolic pressure in isolated perfused hearts (Section 6.3.3.2 for short-term exposure discussion). In this ex vivo heart model, O_3 induced oxidative stress by decreasing SOD enzyme activity and increasing malondialdehyde levels. Ozone also elicited a proinflammatory state evident by an increase in TNF-α and a decrease in the anti-inflammatory cytokine IL-10. The authors conclude that O_3 exposure will result in a greater I/R injury.

Table 7-4 Characterization of study details for Section 7.3.1.2

Study	Model	O_3 (ppm)	Exposure Duration	Effects
Chuang et al. (2009)	Mice; ApoE-/-; M; 6 weeks	0.5	8 wks, 5 days/week, 8 h/day	Enhanced aortic atherosclerotic lesion area compared to air controls.
Kodavanti et al. (2011)	Rat; Wistar; M; 10-12 weeks	0.4	16 wks, 1 day/week, 5 h/day	Increased vascular inflammation and oxidative stress, possibly through activation of LOX-1 signaling.
Perepu et al. (2010)	Rat; Sprague-Dawley; Weight: 50-75 g	0.8	56 days, 8 h/day	Enhanced the sensitivity to myocardial I/R injury while increasing oxidative stress and pro-inflammatory mediators and decreasing production of anti-inflammatory proteins.

No previous studies investigated cardiovascular effects from long-term exposure to O_3.

7.3.2 Cardiac Mortality

A limited number of epidemiologic studies have assessed the relationship between long-term exposure to O_3 and mortality. The 2006 O_3 AQCD concluded that an insufficient amount of evidence existed "to suggest a causal relationship between chronic O_3 exposure and increased risk for mortality in humans" (U.S. EPA, 2006b). Though total and cardio-pulmonary mortality were considered in these studies, cardiovascular mortality was not specifically considered. In the most recent follow-up analysis of the ACS cohort (Jerrett et al., 2009), cardiopulmonary deaths were subdivided into respiratory and cardiovascular, separately, as opposed to combined in the Pope et al. (2002) work. A 10-ppb increment in exposure to O_3 elevated the risk of death from the cardiopulmonary, cardiovascular, and ischemic heart disease. Inclusion of $PM_{2.5}$ as a copollutant attenuated the association with exposure to O_3 for all of the cardiovascular endpoints to become null. Additionally, a recent study (Zanobetti and Schwartz, In Press) observed an association between long-term exposure to O_3 and elevated risk of mortality among Medicare enrollees that had previously experienced an emergency hospital admission due to congestive heart failure (CHF) or myocardial infarction (MI).

7.3.3 Summary and Causal Determination

Previous AQCDs did not address the cardiovascular effects of long-term O_3 exposure due to limited data availability. The evidence remains limited; however the emerging data is supportive of a role for O_3 in chronic cardiovascular diseases. Few epidemiologic studies have investigated cardiovascular morbidity after long-term O_3 exposure, and the majority only assessed cardiovascular disease related biomarkers. A study on O_3 and cardiovascular mortality reported no association after adjustment for $PM_{2.5}$ levels.

Further epidemiologic studies on cardiovascular morbidity and mortality after long-term exposure have not been published.

Toxicological evidence on long-term O_3 exposure is also limited but three strong toxicological studies have been published since the previous AQCD. These studies provide evidence for O_3 enhanced atherosclerosis and I/R injury, corresponding with development of a systemic oxidative, proinflammatory environment. Further discussion of the mechanisms that may lead to cardiovascular effects can be found in Section 5.3.8. Although questions exist for how O_3 inhalation causes systemic effects, a recent study proposes a mechanism for development of vascular pathology that involves activation of LOX-1 by O_3 oxidized lipids and proteins. This activation may also be responsible for O_3 induced changes in genes involved in proteolysis, thrombosis, and vasoconstriction. Taking into consideration the findings of toxicological studies, and the emerging evidence from epidemiologic studies, the generally limited body of evidence **is suggestive of a causal relationship between long-term exposures to O_3 and cardiovascular effects.**

7.4 Reproductive and Developmental Effects

Although the body of literature is growing, the research focusing on adverse birth outcomes is small. Among these studies, various measures of birth weight and fetal growth, such as low birth weight (LBW), small for gestational age (SGA), and intrauterine growth restriction (IUGR), and preterm birth (<37-week gestation; [PTB]) have received more attention in air pollution research, while congenital malformations are less studied. There are also new studies on reproductive and developmental effects.

Infants and fetal development processes may be particularly susceptible to O_3-induced health effects, and although the physical mechanisms are not fully understood, several hypotheses have been proposed; these include: oxidative stress, systemic inflammation, vascular dysfunction and impaired immune function (Section 5.3). Study of these outcomes can be difficult given the need for detailed exposure data and potential residential movement of mothers during pregnancy. Air pollution epidemiologic studies reviewed in the 2006 O_3 AQCD examined impacts on birth-related endpoints, including intrauterine, perinatal, postneonatal, and infant deaths; premature births; intrauterine growth retardation; very low birth weight (weight <1,500 grams) and low birth weight (weight <2,500 grams); and birth defects. However, in the limited number of studies that investigated O_3, no associations were found between O_3 and birth outcomes, with the possible exception of birth defects.

Several recent articles have reviewed methodological issues relating to the study of outdoor air pollution and adverse birth outcomes (Chen et al., 2010a; Woodruff et al., 2009; Ritz and Wilhelm, 2008; Slama et al., 2008). Some of the key challenges to interpretation of these study results include the difficulty in assessing exposure as most studies use existing monitoring networks to estimate individual exposure to ambient air pollution; the inability to control for potential confounders such as other risk factors that affect birth outcomes (e.g., smoking); evaluating the exposure window (e.g., trimester) of importance; and limited evidence on the physiological mechanism of these effects (Ritz and Wilhelm, 2008; Slama et al., 2008). Recently, an international collaboration was formed to better understand the relationships between air pollution and adverse birth outcomes and to examine some of these methodological issues through standardized parallel analyses in datasets from different countries (Woodruff et al., 2010). Initial results from this collaboration have examined PM and birth weight (Parker et al., 2011); work on O_3 has not yet been performed. Although early animal studies (Kavlock et al., 1980) found that exposure to O_3 in the late gestation of pregnancy in rats led to some abnormal reproductive performances for neonates, to date human studies have reported inconsistent results for the association of ambient O_3 on birth outcomes.

7.4.1 Effects on Sperm

A limited amount of research has been conducted to examine the association between air pollution and male reproductive outcomes, specifically semen quality. To date, the epidemiologic studies have considered various exposure durations before semen collection that encompass either the entire period of spermatogenesis (i.e., 90 days) or key periods of sperm development that correspond to epididymal storage, development of sperm motility, and spermatogenesis. In an analysis conducted as part of the Teplice Program, 18-year-old men residing in the heavily polluted district of Teplice in the Czech Republic were found to be at greater risk of having abnormalities in sperm morphology and chromatin integrity than men of similar age residing in Prachatice, a less polluted district (Selevan et al., 2000; Sram et al., 1999). A follow-up longitudinal study conducted on a subset of the same men from Teplice revealed associations between total episodic air pollution and abnormalities in sperm chromatin (Rubes et al., 2005). A limitation of these studies is that they did not identify specific pollutants and their concentrations.

More recent epidemiologic studies conducted in the U.S. have also reported associations between ambient air pollution and sperm quality for individual air pollutants, including O_3 and $PM_{2.5}$. In a repeated measures study in Los Angeles, CA, Sokol et al. (2006) reported a reduction in average sperm concentration during three exposure windows (0-9,

10-14, and 70-90 days before semen collection) associated with high ambient levels of O_3 in healthy sperm donors. This effect persisted under a joint additive model for O_3, CO, NO_2 and PM_{10}. The authors did not detect a reduction in sperm count. Hansen et al. (2010) investigated the effect of exposure to O_3 and $PM_{2.5}$ (using the same exposure windows used by Sokol et al. (2006) on sperm quality in three southeastern counties (Wake County, NC; Shelby County, TN; Galveston County, TX). Outcomes included sperm concentration and count, morphology, DNA integrity and chromatin maturity. Overall, the authors found both protective and adverse effects, although some results suggested adverse effects on sperm concentration, count and morphology.

The biological mechanisms linking ambient air pollution to decreased sperm quality have yet to be determined, though O_3-induced oxidative stress, inflammatory reactions, and the induction of the formation of circulating toxic species have been suggested as possible mechanisms (see Section 5. 3.8). Decremental effects on testicular morphology have been demonstrated in toxicological studies with histological evidence of O_3-induced depletion of germ cells in testicular tissue and decreased seminiferous tubule epithelial layer. Jedlinska-Krakowska et al. (2006) demonstrated histopathological evidence of impaired spermatogenesis (round spermatids/ spermatocytes, giant spermatid cells, and focal epithelial desquamation with denudation to the basement membrane). The exposure protocol used five month old adult rats exposed to O_3 as adults (0.5 ppm, 5 h/day for 50 days). This degeneration could be rescued by vitamin E administration, indicating an antioxidant effect. Vitamin C administration had no effect at low doses of ascorbic acid and exacerbated the O_3-dependent damage at high doses, as would be expected as vitamin C can be a radical generator instead of an antioxidant at higher doses. In summary, this study provided toxicological evidence of impaired spermatogenesis with O_3 exposure that was rescued with certain antioxidant supplementation.

Overall, there is limited epidemiologic evidence for an association with O_3 concentration and decreased sperm concentration. A recent toxicological study provides limited evidence for a possible biological mechanism (histopathology showing impaired spermatogenesis) for such an association.

7.4.2 Effects on Reproduction

Evidence suggests that exposure to air pollutants during pregnancy is associated with adverse birth outcomes, which has been attributed to the increased susceptibility of the fetus due to physiologic immaturity. Gametes (i.e., ova and sperm) may be even more susceptible, especially outside of the human body, as occurs with assisted reproduction. Smokers require twice the number of in vitro fertilization (IVF) attempts to conceive as

non-smokers (Feichtinger et al., 1997), suggesting that a preconception exposure can be harmful to pregnancy. A recent study used an established national-scale, log-normal kriging method to spatially estimate daily mean concentrations of criteria pollutants at addresses of women undergoing their first IVF cycle and at their IVF labs from 2000 to 2007 in the northeastern U.S. (Legro et al., 2010). Increasing O_3 concentration at the patient's address was significantly associated with an increased chance of live birth during ovulation induction (OR=1.13, [95% CI: 1.05, 1.22] per 10 ppb increase), but with decreased odds of live birth when exposed from embryo transfer to live birth (OR=0.79, [95% CI: 0.69, 0.90] per 10 ppb increase). After controlling for NO_2 in a copollutant model, however, O_3 was no longer significantly associated with IVF failure. The results of this study suggest that exposure to O_3 during ovulation was beneficial (perhaps due to early conditioning to O_3), whereas later exposure to O_3 (e.g., during gestation) was detrimental, and reduced the likelihood of a live birth.

In most toxicological studies, reproductive success appears to be unaffected by O_3 exposure. Nonetheless, one study has reported that 25% of the BALB/c mouse dams in the highest O_3 exposure group (1.2 ppm, GD9-18) did not complete a successful pregnancy, a significant reduction (Sharkhuu et al., 2011). Ozone administration (continuous 0.4, 0.8 or 1.2 ppm O_3) to CD-1 mouse dams during the majority of pregnancy (PD7-17, which excludes the pre-implantation period), led to no adverse effects on reproductive success (proportion of successful pregnancies, litter size, sex ratio, frequency of still birth, or neonatal mortality) (Bignami et al., 1994). There was a nearly statistically significant increase in pregnancy duration (0.8 and 1.2 ppm O_3). Initially, dam body weight (0.8 and 1.2 ppm), water consumption (0.4, 0.8 and 1.2 ppm O_3) and food consumption (0.4, 0.8 and 1.2 ppm) during pregnancy were decreased with O_3 exposure but these deficits dissipated a week or two after the initial exposure (Bignami et al., 1994). The anorexigenic effect of O_3 exposure on the pregnant dam appears to dissipate with time; the dams seem to adapt to the O_3 exposure. In males, data exist showing morphological evidence of altered spermatogenesis in O_3 exposed animals (Jedlinska-Krakowska et al., 2006). Some evidence suggests that O_3 may affect reproductive success when combined with other chemicals. Kavlock et al. (1979) showed that O_3 acted synergistically with sodium salicylate to increase the rate of pup resorptions after midgestational exposure (1.0 ppm O_3, GD9-12). At low doses of O_3 exposure, toxicological studies show reproductive effects to include a transient anorexigenic effect of O_3 on gestational weight gain, and a synergistic effect of O_3 on salicylate-induced pup resorptions; other fecundity, pregnancy and gestation related outcomes appear unaffected by O_3 exposure.

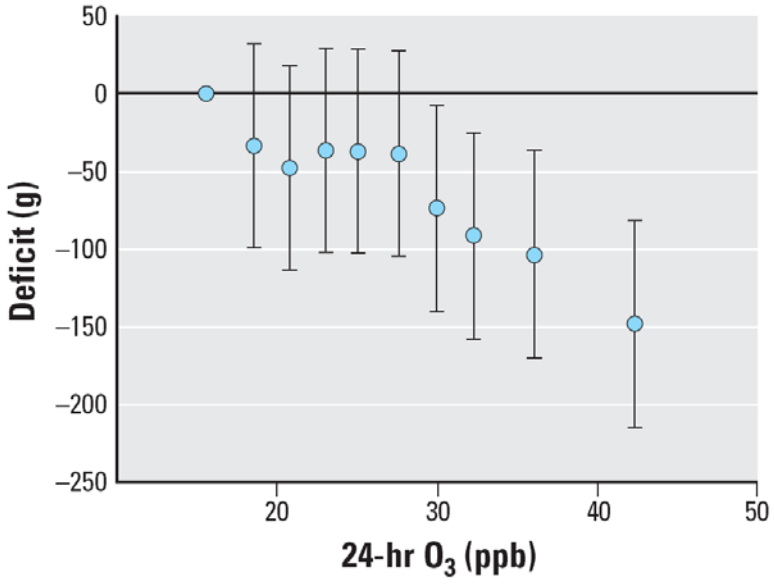
Collectively, there is very little epidemiologic evidence for the effect of O_3 on reproductive success, and the reproductive success in rats appears to be unaffected in toxicological studies of O_3 exposure.

7.4.3 Birth Weight

With birth weight routinely collected in vital statistics and being a powerful predictor of infant mortality, it is the most studied outcome within air pollution-birth outcome research. Air pollution researchers have analyzed birth weight as a continuous variable and/or as a dichotomized variable in the form of LBW (<2,500 g [5 lbs, 8 oz]).

Birth weight is primarily determined by gestational age and intrauterine growth, but also depends on maternal, placental and fetal factors as well as on environmental influences. In both developed and developing countries, LBW is the most important predictor for neonatal mortality and is a significant determinant of postneonatal mortality and morbidity. Studies report that infants who are smallest at birth have a higher incidence of diseases and disabilities, which continue into adulthood (Hack and Fanaroff, 1999).

The strongest evidence for an effect of O_3 on birth weight comes from the Children's Health Study conducted in southern California. In this study, Salam et al. (2005) report that maternal exposure to 24-h avg O_3 concentrations averaged over the entire pregnancy was associated with reduced birth weight (39.3 g decrease [95% CI: -55.8, -22.8] in birth weight per 10 ppb and 8-h avg (19.2-g decrease [95% CI: -27.7, -10.7] in birth weight per 10 ppb). This effect was stronger for concentrations averaged over the second and third trimesters. PM_{10}, NO_2 and CO concentrations averaged over the entire pregnancy were not statistically significantly associated with birth weight, although CO concentrations in the first trimester and PM_{10} concentrations in the third trimester were associated with a decrease in birth weight. Additionally, the authors observed a concentration-response relationship of birth weight with 24-h avg O_3 concentrations averaged over the entire pregnancy that was clearest above the 30-ppb level (see Figure 7-4). Relative to the lowest decile of 24-h avg O_3, estimates for the next 5 lowest deciles were approximately -40 g to -50 g, with no clear trend and with 95% confidence bounds that included zero. The highest four deciles of O_3 exposure showed an approximately linear decrease in birth weight, and all four 95% CIs excluded zero, and ranged from mean decreases of 74 grams to decreases of 148 grams.



Source: Salam et al. (2005)

Deficits are plotted against the decile-group-specific median O_3 exposure. Error bars represent 95% CIs. Indicator variables for each decile of O_3 exposure (except the least-exposed group) were included in a mixed model.

Figure 7-4 Birthweight deficit by decile of 24-h avg O_3 concentration averaged over the entire pregnancy compared with the decile group with the lowest O_3 exposure.

Several additional studies conducted in the U.S. and Canada also investigated the association between ambient O_3 concentrations and birth weight and report some weak evidence for an association. Morello-Frosch et al. (2010) estimated ambient O_3 concentrations throughout pregnancy and for each trimester in the neighborhoods of women who delivered term singleton births between 1996 and 2006 in California. A 10-ppb increase in O_3 averaged across the entire pregnancy was associated with a 5.7-g decrease (95% CI: -6.6, -4.9) in birth weight when exposures were calculated using monitors within 10 km of the maternal address at date of birth. When the distance from the monitor was restricted to 3 km, the decrease in birth weight associated with a 10-ppb increase in O_3 increased to 8.9 g (95% CI: -10.6, -7.1). These results persisted in copollutant models and in models that stratified by trimester of exposure, SES, and race. Darrow et al. (2011a) did not observe an association with birth weight and O_3 concentrations during two exposure periods of interest (i.e., the first month and last trimester), but did find an association with reduced birth weight when examining the cumulative air pollution concentration during the entire pregnancy period. Additionally, they observed effect modification by race and ethnicity, such that associations between birth weight and third-trimester O_3 concentrations were significantly stronger in

Hispanics and non-Hispanic African Americans than in non-Hispanic whites. Chen et al. (2002) used 8-h avg O_3 concentrations to create exposure variables based on average maternal exposure for each trimester. Ozone was not found to be related to birth weight in single-pollutant models, though the O_3 effect during the third trimester was borderline statistically significant in a copollutant model with PM_{10}.

Several studies found no association between ambient O_3 concentrations and birth weight. Wilhelm and Ritz (2005) extended previous analyses of term LBW (Ritz et al., 2000; Ritz and Yu, 1999) to include the period 1994-2000. The authors examined varying residential distances from monitoring stations to see if the distance affected risk estimation, exploring the possibility that effect attenuation may result from local pollutant heterogeneity inadequately captured by ambient monitors. As in their previous studies, the authors observed associations between elevated concentrations of CO and PM_{10} both early and late in pregnancy and risk of term LBW. After adjusting for CO and/or PM_{10} the authors did not observe associations between O_3 and term LBW in any of their models. Brauer et al. (2008) evaluated the impacts of air pollution (CO, NO_2, NO, O_3, SO_2, $PM_{2.5}$, PM_{10}) on birth weight for the period 1999-2002 using spatiotemporal residential exposure metrics by month of pregnancy in Vancouver, BC. Quantitative results were not presented for the association between O_3 and LBW, though the authors observed associations that were largely protective. Dugandzic et al. (2006) examined the association between LBW and ambient levels of air pollutants by trimester of exposure among a cohort of term singleton births from 1988-2000. Though there was some indication of an association with SO_2 and PM_{10}, there were no effects for O_3.

Similarly, studies conducted in Australia, Latin America, and Asia report limited evidence for an association between ambient O_3 and measures of birth weight. In Sydney, Australia, Mannes et al. (2005) found that O_3 concentrations in the second trimester of pregnancy had small adverse effects on birth weight (7.5-g decrease; [95 % CI: -13.8, 1.2] per 10 ppb), although this effect disappeared when the analysis was limited to births with a maternal address within 5 km of a monitoring station (87.7-g increase; [95% CI: 10.5, 164.9] per 10 ppb). Hansen et al. (2007) reported that trimester and monthly specific exposures to all pollutants were not statistically significantly associated with a reduction in birth weight in Brisbane, Australia. In Sao Paulo, Brazil, Gouveia et al. (2004) found that O_3 exhibited a small inverse relation with birth weight over the third trimester (6.0-g decrease; [95% CI: -30.8, 18.8] per 10 ppb). Lin et al. (2004b) reported a positive, though not statistically significant, exposure-response relationship for O_3 during the entire pregnancy in a Taiwanese study. In a study performed in Korea, Ha et al. (2001) reported no O_3 effect during the first trimester of pregnancy, but they found that during the third trimester of pregnancy O_3 was associated with LBW (RR=1.05 [95% CI: 1.02, 1.08] per 10 ppb).

Table 7-5 Brief summary of epidemiologic studies of birth weight

Study	Location Sample Size	Mean O_3 (ppb)	Exposure assessment	Effect Estimate[a] (95% CI)
Salam et al. (2005)	California, U.S. (n=3,901)	24-h avg: 27.3 8 h: 50.6	ZIP code level	Entire pregnancy: -39.3 g (-55.8, -22.8) T1: -6.1 g (-16.8, 4.8) T2: -20.0 g (-31.7, -8.4) T3: -20.7 g (-32.1, -9.3)
Morello-Frosch et al. (2010)	California, U.S. (n=3,545,177)	24-h avg: 23.5	Nearest Monitor (within 10, 5, 3 km)	Entire pregnancy: -5.7 g (-6.6, -4.9) T1: -2.1 g (-2.9, -1.4) T2: -2.3 g (-3.1, -1.5) T3: -1.3 g (-2.1, -0.6)
Darrow et al. (2011a)	Atlanta, GA (N=406,627)	8-h max: 44.8	Population-weighted spatial average	Entire pregnancy: -12.3 g (-17.8, -6.8) First 28 days: -0.5 g (-3.0, 2.1) T3: -0.9g (-4.5, 2.8)
Chen et al. (2002)	Northern Nevada, US (n=36,305)	8-h: 27.2	County level	Entire pregnancy: 20.9 g (6.3, 35.5) T1: 23.4 g (-35.6 , 82.4) T2: -19.4 g (-77.0, 38.2) T3: 7.7 g (-50.9, 66.3)
Wilhelm and Ritz (2005)	Los Angeles County, CA (n=136,134)	1-h: 21.1-22.2	Varying distances from monitor	T1: NR T3: NR 6 weeks before birth: NR
Brauer et al. (2008)	Vancouver, BC, Canada (n=70,249)	24-h avg: 14	Nearest Monitor (within 10 km) Inverse Distance Weighting (IDW)	Entire pregnancy: NR First 30 days of pregnancy: NR Last 30 days of pregnancy: NR T1: NR T3: NR
Dugandzic et al. (2006)	Nova Scotia, Canada (n=74,284)	24-h avg: 21	Nearest Monitor (within 25 km)	T1: 0.97 (0.81, 1.18)[d] T2: 1.06 (0.87, 1.27)[d] T3: 1.01 (0.83-1.24)[d]
Mannes et al. (2005)	Sydney, Australia (n=138,056)	1-h max: 31.6	City-wide avg and <5 km from monitor	T1: -0.9 g (-6.6, 4.8) T2: -7.5 g (-13.8, 1.2) T3: -4.5 g (-10.8, 1.8) Last 30 days: -1.1 g (-5.6, 3.4)
Hansen et al. (2007)	Brisbane, Australia (n=26,617)	8 h max: 26.7	City-wide avg	T1: 2.8 g (-10.5, 16.0) T2: 4.4 g (-11.4, 20.1) T3: 11.3 g (-4.4, 27.1)
Gouveia et al. (2004)	Sao Paulo, Brazil (n=179,460)	1-h max: 31.5	City-wide avg	T1: -3.2 g (-25.6, 19) T2: -0.2 g (-23.8, 23.4) T3: -6.0 g (-30.8, -18.8)
Lin et al. (2004b)	Kaohsiung and Taipei, Taiwan (n=92,288)	24-h avg: 15.86-47.78	Nearest monitor (within 3 km)	Entire pregnancy: 1.13 (0.92, 1.38)[c] T1: 1.02 (0.85, 1.22)[c] T2: 0.93 (0.78, 1.12)[c] T3: 1.05 (0.87, 1.26)[c]
Ha et al. (2001)	Seoul, Korea (n=276,763)	8-h avg: 22.4-23.3[b]	City-wide avg	T1: 0.87 (0.81, 0.94)[c] T3: 1.05 (1.02, 1.08)[c]

[a]Change in birthweight per 10 ppb change in O_3
[b]Median
[c]Odds ratios of LBW; Highest quartile of exposure compared to lowest quartile of exposure
[d]Relative risk of LBW per 10 ppb change in O_3
T1 = First Trimester, T2 = Second Trimester, T3 = Third Trimester
NR: No quantitative results reported

Table 7-5 provides a brief overview of the epidemiologic studies of birth weight. In summary, only the Children's Health Study conducted in southern California (Salam et al., 2005) provides strong evidence for an effect of ambient O_3 on birth weight. The study by Morello-Frosch et al. (2010), also conducted in California, provides support for the

results of the Children's Health Study. Additional studies conducted in the U.S., Canada, Australia, Latin America, and Asia provide limited and inconsistent evidence to support the effect reported in the Children's Health Study. The toxicological literature on the effect of O_3 on birth weight is sparse. In some studies, the reporting of birth weight may be avoided because birth weight can be confounded by decreased litter size resulting from an increased rate of pup resorption (aborted pups) in O_3 exposed dams. In one toxicological study by Haro and Paz (1993), no differences in litter size were observed and decreased birth weight in pups from dams who were exposed to 1ppm O_3 during pregnancy was reported. A second animal toxicology study recapitulated these finding with pregnant BALB/c mice that exposed to O_3 (1.2 ppm, GD9-18) producing pups with significantly decreased birth weights (Sharkhuu et al., 2011).

7.4.4 Preterm Birth

Preterm birth (PTB) is a syndrome (Romero et al., 2006) that is characterized by multiple etiologies. It is therefore unusual to be able to identify an exact cause for each PTB. In addition, PTB is not an adverse outcome in itself, but an important determinant of health status (i.e., neonatal morbidity and mortality). Although some overlap exists for common risk factors, different etiologic entities related to distinct risk factor profiles and leading to different neonatal and postneonatal complications are attributed to PTB and measures of fetal growth. Although both restricted fetal growth and PTB can result in LBW, prematurity does not have to result in LBW or growth restricted babies.

A major issue in studying environmental exposures and PTB is selecting the relevant exposure period, since the biological mechanisms leading to PTB and the critical periods of vulnerability are poorly understood (Bobak, 2000). Exposures proximate to the birth may be most relevant if exposure causes an acute effect. However, exposure occurring in early gestation might affect placentation, with results observable later in pregnancy, or cumulative exposure during pregnancy may be the most important determinant. The studies reviewed have dealt with this issue in different ways. Many have considered several exposure metrics based on different periods of exposure. Often the time periods used are the first month (or first trimester) of pregnancy and the last month (or 6 weeks) prior to delivery. Using a time interval prior to delivery introduces an additional problem since cases and controls are not in the same stage of development when they are compared. For example, a preterm infant delivered at 36 weeks is a 32-week fetus 4 weeks prior to birth, while an infant born at term (40 weeks) is a 36-week fetus 4 weeks prior to birth.

Recently, investigators have examined the association of PTB with both short-term (i.e., hours, days, or weeks) and long-term (i.e., months or years) exposure periods. Time-series studies have been used to examine the association between air pollution concentrations during the days immediately preceding birth. An advantage of these time-series studies is that this approach can remove the influence of covariates that vary across individuals over a short period of time. Retrospective cohort and case-control studies have been used to examine long-term exposure periods, often averaging air pollution concentrations over months or trimesters of pregnancy.

Reported studies fail to show consistency in pollutants and periods during pregnancy when an effect occurs. For example, while some studies find the strongest effects associated with exposures early in pregnancy, others report effects when the exposure is limited to the second or third trimester. However, the effect of air pollutant exposure during pregnancy on PTB has a biological basis. There is an expanding list of possible mechanisms that may explain the association between O_3 exposure and PTB (see Section 5. 4.2.4).

Many studies of PTB compare exposure in quartiles, using the lowest quartile as the reference (or control) group. No studies use a truly unexposed control group. If exposure in the lowest quartile confers risk, than it may be difficult to demonstrate additional risk associated with a higher quartile. Thus negative studies must be interpreted with caution.

Preterm birth occurs both naturally (*idiopathic preterm*), and as a result of medical intervention (*iatrogenic preterm*). Ritz et al. (2007; 2000) excluded all births by Cesarean section to limit their studies to idiopathic preterm. No other studies attempted to distinguish the type of PTB, although air pollution exposure maybe associated with only one type. This is a source of potential effect misclassification.

Generally, studies of air pollution-birth outcome conducted in North America and the United Kingdom have not identified an association between PTB and maternal exposure to O_3. Most recently, Darrow et al. (2009) used vital record data to construct a retrospective cohort of 476,489 births occurring between 1994 and 2004 in 5 central counties of metropolitan Atlanta. Using a time-series approach, the authors examined aggregated daily counts of PTB in relation to ambient levels of CO, NO_2, SO_2, O_3, PM_{10}, $PM_{2.5}$ and speciated PM measurements. This study investigated 3 gestational windows of exposure: the first month of gestation, the final week of gestation, and the final 6 weeks of gestation. The authors did not observe associations of PTB with O_3.

A number of U.S. studies were conducted in southern California, and report somewhat inconsistent results. Ritz et al. (2000) evaluated the effect of air pollution (CO, NO_2, O_3, PM_{10}) exposure during pregnancy on the occurrence of PTB in a cohort of 97,518

neonates born in southern California between 1989 and 1993. The authors use both short- and long-term exposure windows, averaging pollutant measures taken at the closest air-monitoring station over distinct periods, such as 1, 2, 4, 6, 8, 12, and 26 weeks before birth and the whole pregnancy period. Additionally, they calculated average exposures for the first and second months of pregnancy. The authors found no consistent effects for O_3 over any of the pregnancy periods in single or multi-pollutant models. Wilhelm and Ritz (2005) extended previous analyses of PTB (Ritz et al., 2000; Ritz and Yu, 1999) in California to include 1994-2000. The authors examined varying residential distances from monitoring stations to see if the distance affected risk estimation, because effect attenuation may result from local pollutant heterogeneity inadequately captured by ambient monitors. The authors analyzed the association between O_3 exposure during varying periods of pregnancy and PTB, finding a positive association between O_3 levels in both the first trimester of pregnancy (RR=1.23 [95% CI: 1.06, 1.42] per 10 ppb increase in 24-h avg O_3) and the first month of pregnancy (results for first trimester exposure were similar, but slightly smaller, quantitative results not presented) in models containing all pollutants. No association was observed between O_3 in the 6 weeks before birth and preterm delivery. Finally, Ritz et al. (2007) conducted a case-control survey nested within a birth cohort and assessed the extent to which residual confounding and exposure misclassification impacted air pollution effect estimates. The authors calculated mean exposure levels for three gestational periods: the entire pregnancy, the first trimester, and the last 6 weeks before delivery. Though positive associations were observed for CO and $PM_{2.5}$, no consistent patterns of increase in the odds of PTB for O_3 or NO_2 were observed.

One study conducted in Canada evaluated the impacts of air pollution (including CO, NO_2, NO, O_3, SO_2, $PM_{2.5}$, and PM_{10}) on PTBs (1999-2002) using spatiotemporal residential exposure metrics by month of pregnancy in Vancouver, BC (Brauer et al., 2008). The authors did not observe consistent associations with any of the pregnancy average exposure metrics except for $PM_{2.5}$ for PTB. The O_3 associations were largely protective, and no quantitative results were presented for O_3. Additionally, Lee et al. (2008c) used time-series techniques to investigate the short-term associations of O_3 and PTB in London, England. In addition to exposure on the day of birth, cumulative exposure up to 1 week before birth was investigated. The risk of PTB did not increase with exposure to the levels of ambient air pollution experienced by this population.

Conversely, studies conducted in Australia and China provide evidence for an association between ambient O_3 and PTB. Hansen et al. (2006) reported that exposure to O_3 during the first trimester was associated with an increased risk of PTB (OR=1.38, [95% CI: 1.14, 1.69] per 10 ppb increase). Although the test for trend was significant due to the strong effect in the highest quartile, there was not an obvious exposure-response pattern

across the quartiles of O_3 during the first trimester. The effect estimate was diminished and lost statistical significance when PM_{10} was included in the model (OR=1.23, [95% CI: 0.97, 1.59] per 10 ppb increase). Maternal exposure to O_3 during the 90 days prior to birth showed a weak, positive association with PTB (OR=1.09, [95% CI: 0.85, 1.39] per 10 ppb increase). Jalaludin et al. (2007) found that O_3 levels in the month and three months preceding birth had a statistically significant association with PTB. Ozone levels in the first trimester of pregnancy were associated with increased risks for PTBs (OR=1.15 [95% CI: 1.05, 1.24] per 10 ppb increase in 1-h max O_3 concentration), and remained a significant predictor of PTB in copollutant models (ORs between 1.07 and 1.10). ORs increased for first month of pregnancy when restricted to within 5 km of a monitoring station (OR=1.60, [95% CI: 1.27, 2.03]), but did not show a cumulative effect for first 3 months of pregnancy (OR=0.81, [95% CI: 0.67, 0.98]). Jiang et al. (2007) examined the acute effect of air pollution on PTB, including risk in relation to levels of pollutants for a single day exposure window with lags from 0 to 6 days before birth. An increase of 10 ppb of the 8-week avg of O_3 corresponded to 9.47 % (95% CI: 0.70, 18.7%) increase in PTBs. Increases in PTB were also observed for PM_{10}, SO_2, and NO_2. The authors did not observe any significant acute effect of outdoor air pollution on PTB among the 1-day acute time windows examined in the week before birth.

Little data is available from toxicological studies; one study reported a nearly statistically significant increase in pregnancy duration in mice when exposed to 0.8 or 1.2 ppm O_3. This phenomenon was most likely due to the anorexigenic effect of relatively high O_3 concentrations (Bignami et al., 1994).

Table 7-6 Brief summary of epidemiologic studies of PTB

Study	Location Sample Size	Mean O_3 (ppb)	Exposure assessment	Effect Estimate[a] (95% CI)
Darrow et al. (2009)	Atlanta, GA (n=476,489)	8-h max: 44.1	Population-weighted spatial averages Nearest Monitor (within 4 miles)	First month: 0.98 (0.97, 1.00) Last week: 0.99 (0.98, 1.00) Last 6 weeks: 1.00 (0.98, 1.02)
Ritz et al. (2000)	California, US (n=97,158)	8 h: 36.9	<2 mi of monitor	First month: NR Last 6 weeks: NR
Wilhelm and Ritz (2005)	Los Angeles, CA (n=106,483)	1 h: 21.1-22.2	Varying distances to monitor	First month: 1.23 (1.06, 1.42) T1: NR T2: 1.38 (1.14, 1.66) Last 6 weeks: NR
Ritz et al. (2007)	Los Angeles, CA (n=58,316)	24-h avg: 22.5	Nearest monitor to ZIP code	Entire pregnancy: NR T1: 0.93 (0.82, 1.06) Last 6 weeks: NR
Brauer et al. (2008)	Vancouver, BC, Canada (n=70,249)	24-h avg: 14	Nearest Monitor (within 10 km) Inverse Distance Weighting (IDW)	Entire pregnancy: NR First 30 days of pregnancy: NR Last 30 days of pregnancy: NR T1: NR T3: NR
Lee et al. (2008c)	London, UK	24-h avg: NR	1 monitor	Lag 0: 1.00 (1.00, 1.01)
Hansen et al. (2006)	Brisbane, Australia (n=28,200)	8-h max: 26.7	City-wide avg	T1: 1.39 (1.15, 1.70) T3: 1.09 (0.88, 1.39)
Jalaludin et al. (2007)	Sydney, Australia (n=123,840)	1-h max: 30.9	City-wide avg and <5 km from monitor	First month: 1.604 (1.268, 2.030)[b] T1: 0.807 (0.668, 0.976)[b] T3: 1.011 (0.910, 1.124)[b] Last month: 0.984 (0.906, 1.069)[b]
Jiang et al. (2007)	Shanghai, China (n=3,346 preterm births)	8-h avg: 32.7	City-wide avg	4 wks before birth: 1.06 (1.00, 1.12) 6 wks before birth: 1.06 (0.99, 1.13) 8 wks before birth: 1.09 (1.01, 1.19) L0: NR (results presented in figure) L1: NR (results presented in figure) L2: NR (results presented in figure) L3: NR (results presented in figure) L4: NR (results presented in figure) L5: NR (results presented in figure) L6: NR (results presented in figure)

[a]Relative risk of PTB per 10 ppb change in O3.

[b]Relative risk of PTB per 1 ppb change in O3.

T1 = First Trimester, T2 = Second Trimester, T3 = Third Trimester

L0 = Lag 0, L1= Lag 1, L2 = Lag 2, L3 = Lag 3, L4 = Lag 4, L5 = Lag 5, L6 = Lag 6

NR: No quantitative results reported

Table 7-6 provides a brief overview of the epidemiologic studies of PTB. In summary, the evidence is consistent when examining shorter-term, late-pregnancy exposure to O_3 and reports no association with PTB. However when long-term exposure to O_3 early in pregnancy is examined the results are inconsistent. Studies conducted in the U.S.,

Canada, and England find no association with O_3 and PTB, while studies conducted in Australia and China report an O_3 effect on PTB.

7.4.5 Fetal Growth

Low birth weight has often been used as an outcome measure because it is easily available and accurately recorded on birth certificates. However, LBW may result from either short gestation, or inadequate growth in utero. Most of the studies investigating air pollution exposure and LBW limited their analyses to term infants to focus on inadequate growth. A number of studies were identified that specifically addressed growth restriction in utero by identifying infants who failed to meet specific growth standards. Usually these infants had birth weight less than the 10th percentile for gestational age, using an external standard. Many of these studies have been previously discussed, since they also examined other reproductive outcomes (i.e., LBW or PTB).

Fetal growth is influenced by maternal, placental, and fetal factors. The biological mechanisms by which air pollutants may influence the developing fetus remain largely unknown. Several mechanisms have been proposed, and are the same as those hypothesized for birth weight (see Section 5. 4.2.4). Additionally, in animal toxicology studies, O_3 causes transient anorexia in exposed pregnant dams. This may be one of many possible contributors to O_3-dependent decreased fetal growth.

A limitation of environmental studies that use birth weight as a proxy measure of fetal growth is that patterns of fetal growth during pregnancy cannot be assessed. This is particularly important when investigating pollutant exposures during early pregnancy as birth weight is recorded many months after the exposure period. The insult of air pollution may have a transient effect on fetal growth, where growth is hindered at one point in time but catches up at a later point. For example, maternal smoking during pregnancy can alter the growth rate of individual body segments of the fetus at variable developmental stages, as the fetus experiences selective growth restriction and augmentation (Lampl and Jeanty, 2003).

The terms small-for-gestational-age (SGA), which is defined as a birth weight <10th percentile for gestational age (and often sex and/or race), and intrauterine growth retardation (IUGR) are often used interchangeably. However, this definition of SGA does have limitations. For example, using it for IUGR may overestimate the percentage of "growth-restricted" neonates as it is unlikely that 10% of neonates have growth restriction (Wollmann, 1998). On the other hand, when the 10th percentile is based on the distribution of live births at a population level, the percentage of SGA among PTB is most likely underestimated (Hutcheon and Platt, 2008). Nevertheless, SGA represents a

statistical description of a small neonate, whereas the term IUGR is reserved for those with clinical evidence of abnormal growth. Thus all IUGR neonates will be SGA, but not all SGA neonates with be IUGR (Wollmann, 1998). In the following section the terms SGA and IUGR are referred to as each cited study used the terms.

Over the past decade a number of studies examined various metrics of fetal growth restriction. Salam et al. (2005) assessed the effect of increasing O_3 concentrations on IUGR in a population of infants born in California from 1975-1987 as part of the Children's Health Study. The authors reported that maternal O_3 exposures averaged over the entire pregnancy and during the third trimester were associated with increased risk of IUGR. A 10-ppb difference in 24-h maternal O_3 exposure during the third trimester increased the risk of IUGR by 11% (95% CI: 0, 20%). Brauer et al. (2008) evaluated the impacts of air pollution (CO, NO_2, NO, O_3, SO_2, $PM_{2.5}$, PM_{10}) on SGA (1999-2002) using spatiotemporal residential exposure metrics by month of pregnancy in Vancouver, BC. The O_3 associations were largely protective (OR= 0.87, [95% CI: 0.81, 0.93] for a 10 ppb increase in inverse distance weighted SGA), and no additional quantitative results were presented for O_3. Liu et al. (2007b) examined the association between IUGR among singleton term live births and SO_2, NO_2, CO, O_3, and $PM_{2.5}$ in 3 Canadian cities for the period 1985-2000. No increase in the risk of IUGR in relation to exposure to O_3 averaged over each month and trimester of pregnancy was noted.

Three studies conducted in Australia provide evidence for an association between ambient O_3 and fetal growth restriction. Hansen et al. (2007) examined SGA among singleton, full-term births in Brisbane, Australia in relation to ambient air pollution (bsp, PM_{10}, NO_2, O_3) during pregnancy. They also examined head circumference and crown-heel length in a subsample of term neonates. Trimester specific exposures to all pollutants were not statistically significantly associated with a reduction in head circumference or an increased risk of SGA. When monthly-specific exposures were examined, the authors observed an increased risk of SGA associated with exposure to O_3 during month 4 (OR=1.11 [95% CI: 1.00, 1.24] per 10 ppb increase). In a subsequent study, Hansen et al. (2008) examined the possible associations between fetal ultrasonic measurements and ambient air pollution (PM_{10}, O_3, NO_2, SO_2) during early pregnancy. This study had two strengths: (1) fetal growth was assessed during pregnancy as opposed to at birth; and (2) there was little delay between exposures and fetal growth measurements, which reduces potential confounding and uses exposures that are concurrent with the observed growth pattern of the fetus. Fetal ultrasound biometric measurements were recorded for biparietal diameter (BPD), femur length, abdominal circumference, and head circumference. To further improve exposure assessment, the authors restricted the samples to include only scans from women for whom the centroid of their postcode was within 14 km of an air pollution monitoring site. Ozone during days 31-60 was associated with decreases in all

of the fetal growth measurements, and a 1.78 mm reduction in abdomen circumference per 10 ppb increase in O_3 concentration, though this effect did not persist in copollutant models. The change in ultrasound measurements associated with O_3 during days 31-60 of gestation indicated that increasing O_3 concentration decreased the magnitude of ultrasound measurements for women living within 2 km of the monitoring site. The relationship decreased toward the null as the distance from the monitoring sites increased. When assessing effect modification due to SES, there was some evidence of effect modification for most of the associations, with the effects of air pollution stronger in the highest SES quartile. In the third study, Mannes et al. (2005) estimated the effects of pollutant (PM_{10}, $PM_{2.5}$, NO_2, CO and O_3) exposure in the first, second and third trimesters of pregnancy and risk of SGA in Sydney, Australia. Citywide average air pollutant concentrations in the last month, third trimester, and first trimester of pregnancy had no effect on SGA. Concentrations of O_3 in the second trimester of pregnancy had small but adverse effects on SGA (OR=1.10 [95% CI: 1.00, 1.14] per 10 ppb increment). This effect disappeared when the analysis was limited to births with a maternal address within 5 km of a monitoring station (OR=1.00 [95% CI: 0.60, 1.79] per 10 ppb increment).

Very little information from toxicological studies is available to address effects on fetal growth. However, there is evidence to suggest that prenatal exposure to $O_{3\ can}$ affect postnatal growth. A few studies reported that mice or rats exposed developmentally (gestationally ± lactationally) to O_3 had deficits in body weight gain in the postpartum period (Bignami et al., 1994; Haro and Paz, 1993; Kavlock et al., 1980).

Table 7-7 provides a brief overview of the epidemiologic studies of fetal growth restriction. In summary, the evidence is inconsistent when examining exposure to O_3 and fetal growth restriction. Similar to PTB, studies conducted in Australia have reported an effect of O_3 on fetal growth, whereas studies conducted in other areas have not found such an effect. This may be due to the restriction of births to those within 2-14 km of a monitoring station, as was done in the Australian studies.

Table 7-7 Brief summary of epidemiologic studies of fetal growth

Study	Location (Sample Size)	Mean O_3 (ppb)	Exposure assessment	Effect Estimate[a] (95% CI)
Salam et al. (2005)	California, U.S. (n=3901)	24-h avg: 27.3 8 h: 50.6	ZIP code level	Entire pregnancy: 1.16 (1.00, 1.32) T1:1.00 (0.94, 1.11) T2: 1.06 (1.00, 1.12) T3: 1.11 (1.00, 1.17)
Brauer et al. (2008)	Vancouver, BC, Canada (n=70,249)	24-h avg: 14	Nearest Monitor (within 10 km) Inverse Distance Weighting (IDW)	Entire pregnancy: NR First 30 days of pregnancy: NR Last 30 days of pregnancy: NR T1: NR T3: NR
Liu et al. (2007b)	Calgary, Edmonton, and Montreal, Canada (n= 16,430)	24-h avg: 16.5 1-h max: 31.2	Census Subdivision avg	Entire pregnancy: NR (results presented in figure) T1: NR (results presented in figure) T2: NR (results presented in figure) T3: NR (results presented in figure)
Hansen et al. (2007)	Brisbane, Australia (n=26,617)	8-h max: 26.7	City-wide avg	T1: 1.01 (0.89, 1.15) T2: 1.00 (0.86, 1.17) T3: 0.83 (0.71, 0.97)
Hansen et al. (2008)	Brisbane, Australia (n=15,623)	8-h avg: 24.8	Within 2 km of monitor	M1: -0.32 (-1.56, 0.91)[b] M2: -0.58 (-1.97, 0.80)[b] M3: 0.26 (-1.07, 1.59)[b] M4: 0.11 (-0.98, 1.21)[b]
Mannes et al. (2005)	Sydney, Australia (n=138,056)	1-h max: 31.6	City-wide avg and <5 km from monitor	T1: 0.90 (0.48, 1.34) T2: 1.00 (0.60, 1.79) T3: 1.10 (0.66, 1.97) Last 30 days of pregnancy: 1.10 (0.74, 1.79)

[a]Relative risk of fetal growth restriction per 10 ppb change in O_3.

[b]Mean change in fetal ultrasonic measure of head circumference recorded between 13 and 26 weeks gestation for a 10-ppb increase in maternal exposure to O_3 during early pregnancy

T1 = First Trimester, T2 = Second Trimester, T3 = Third Trimester

M1 = Month 1, M2 = Month 2, M3 = Month 3, M4 = Month 4

NR: No quantitative results reported

7.4.6 Postnatal growth

Time-pregnant BALB/c mice were exposed to O_3 (0, 0.4, 0.8, or 1.2 ppm) GD9-18 with parturition at GD20-21 (Sharkhuu et al., 2011). As the offspring aged, postnatal litter body weight continued to be significantly decreased in the highest dose (1.2 ppm) O_3 group at PND3 and PND7. When the pups were weighed separately by sex at PND42, the males with the highest dose of O_3 exposure (1.2 ppm, GD9-18) had significant decrements in body weight (Sharkhuu et al., 2011).

7.4.7 Birth Defects

Despite the growing body of literature evaluating the association between ambient air pollution and various adverse birth outcomes, relatively few studies have investigated the effect of temporal variations in ambient air pollution on birth defects. Heart defects and oral clefts have been the focus of the majority of these recent studies, given the higher prevalence than other birth defects and associated mortality. Mechanistically, air pollutants could be involved in the etiology of birth defects via a number of key events (see Section 5. 4.2.4).

Several studies have been conducted examining the relationship between O_3 exposure during pregnancy and birth defects and reported a positive association with cardiac defects. The earliest of these studies was conducted in southern California (Ritz et al., 2002). This study evaluated the effect of air pollution on the occurrence of cardiac birth defects in neonates and fetuses delivered in southern California in 1987-1993. Maternal exposure estimates were based on data from the fixed site closest to the mother's ZIP code area. When using a case-control design where cases were matched to 10 randomly selected controls, results showed increased risks for aortic artery and valve defects (OR=1.56 [95% CI: 1.16, 2.09] per 10 ppb O_3), pulmonary artery and valve anomalies (OR=1.34 [95% CI: 0.96, 1.87] per 10 ppb O_3), and conotruncal defects (OR=1.36 [95% CI: 0.91, 2.03] per 10 ppb O_3) in a dose-response manner with second-month O_3 exposure. A study conducted in Texas (Gilboa et al., 2005) looked at a similar period of exposure but reported no association with most of the birth defects studied (O_3 concentration was studied using quartiles with the lowest representing <18 ppb and the highest representing ≥ 31 ppb). The authors found slightly elevated odds ratios for pulmonary artery and valve defects. They also detected an inverse association between O_3 exposure and isolated ventricular septal defects. Overall, this study provided some weak evidence that air pollution increases the risk of cardiac defects. Hansen et al. (2009) investigated the possible association between ambient air pollution and the risk of cardiac defects. When analyzing all births with exposure estimates for O_3 from the nearest monitor there was no indication for an association with cardiac defects. There was also no adverse association when restricting the analyses to only include births where the mother resided within 12 km of a monitoring station. However, among births within 6 km of a monitor, a 10 ppb increase in O_3 was associated with an increased risk of pulmonary artery and valve defects (OR=8.76 [95% CI: 1.80, 56.55]). As indicated by the very wide credible intervals, there were very few cases in the sensitivity analyses for births within 6 km of a monitor, and this effect could be a result of type I errors. Dadvand et al. (2011) investigated the association between maternal exposure to ambient air pollution and the occurrence of cardiac birth defects in England. Similar to Hansen et al. (2009), they found no associations with maternal exposure to O_3 except for when the analysis was

limited to those subjects residing within a 16 km distance of a monitoring station (OR for malformations of pulmonary and tricuspid valves=1.64 [95% CI: 1.04, 2.60] per 10 ppb increase in O_3).

Despite the association between O_3 and cardiac defects observed in the above studies, a recent study did not observe an increased risk of cardiac birth defects associated with ambient O_3 concentrations. The study, conducted in Atlanta, GA, examined O_3 exposure during the third through seventh week of pregnancy and reported no association with risk of cardiovascular malformations (mean long-term average of 8-h O_3 concentrations excluding November through February ranged by 5-year groups from 39.8 to 43.3 ppb) (Strickland et al., 2009).

Several of these studies have also examined the relationship between O_3 exposure during pregnancy and oral cleft defects. The study by Ritz et al. (Ritz et al., 2002) evaluated the effect of air pollution on the occurrence of orofacial birth defects and did not observe strong associations between ambient O_3 concentration and orofacial defects. They did report an OR of 1.13 (95% CI: 0.90, 1.40) per 10 ppb during the second trimester for cleft lip with or without cleft palate. Similarly, Gilboa et al. (Gilboa et al., 2005) reported and OR of 1.09 (95% CI: 0.70, 1.69) for oral cleft defects when the fourth quartile was contrasted with the first quartile of exposure during 3-8 weeks of pregnancy. Hansen et al. (2009) reported no indication for an association with cleft defects. Hwang and Jaakola (2008) conducted a population-based case-control study to investigate exposure to ambient air pollution and the risk of cleft lip with or without cleft palate in Taiwan. The risk of cleft lip with or without cleft palate was increased in relation to O_3 levels in the first gestational month (OR=1.17 [95% CI: 1.01, 1.36] per 10 ppb) and second gestational month (OR=1.22 [95% CI: 1.03, 1.46] per 10 ppb), but was not related to any of the other pollutants. In three-pollutant models, the effect estimates for O_3 exposure were stable for the four different combinations of pollutants and were all statistically significant. Marshall et al. (2010) compared estimated exposure to ambient pollutants during early pregnancy among mothers of children with oral cleft defects to that among mothers of controls. The authors observed no consistent elevated associations between any of the air pollutants examined and cleft malformations, though there was a weak association between cases of cleft palate only and increasing O_3 concentrations. This association increased when cases and controls were limited to those with residences within 10 km of the closest O_3 monitor (OR=2.2 [95% CI: 1.0, 4.9], comparing highest quartile [>33 ppb] to lowest quartile [<15 ppb]).

A limited number of toxicological studies have examined birth defects in animals exposed gestationally to O_3. Kavlock et al. (1979) exposed pregnant rats to O_3 for precise periods during organogenesis. No significant teratogenic effects were found in rats

exposed 8 hr/day to concentrations of O_3 varying from 0.44 to 1.97 ppm during early (days 6-9), mid (days 9-12), or late (days 17 to 20) gestation, or the entire period of organogenesis (days 6-15). Earlier research found eyelid malformation following gestational and postnatal exposure to 0.2 ppm O_3 (Veninga, 1967).

Table 7-8 provides a brief overview of the epidemiologic studies of birth defects. These studies have focused on cardiac and oral cleft defects, and the results from these studies are not entirely consistent. This inconsistency could be due to the absence of true associations between O_3 and risks of cardiovascular malformations and oral cleft defects; it could also be due to differences in populations, pollution levels, outcome definitions, or analytical approaches. The lack of consistency of associations between O_3 and cardiovascular malformations or oral cleft defects might be due to issues relating to statistical power or measurement error. A recent meta-analysis of air pollution and congenital anomalies concluded that there was no statistically significant increase in risk of congenital anomalies and O_3 (Vrijheid et al., 2011). These authors note that heterogeneity in the results of these studies may be due to inherent differences in study location, study design, and/or analytic methods, and comment that these studies have not employed some recent advances in exposure assessment used in other areas of air pollution research that may help refine or reduce this heterogeneity.

Table 7-8 Brief summary of epidemiologic studies of birth defects

Study	Outcomes Examined	Location (Sample Size)	Mean O_3 (ppb)	Exposure Assessment	Exposure Window
Ritz et al. (2002)	Cardiac and Cleft Defects	Southern California (n=3,549 cases; 10,649 controls)	24-h avg: NR	Nearest Monitor (within 10 mi)	Month 1,2,3 Trimester 2,3 3-mo period prior to conception
Gilboa et al. (2005)	Cardiac and Cleft Defects	7 Counties in TX (n=5,338 cases; 4,580 controls)	24-h avg: NR	Nearest Monitor	Weeks 3-8 of gestation
Hwang and Jaakola (2008)	Oral Cleft Defects	Taiwan (n=653 cases; 6,530 controls)	24-h avg: 27.31	Inverse Distance Weighting (IDW)	Months 1,2,3
Strickland et al. (2009)	Cardiac Defects	Atlanta, GA (n=3,338 cases)	8-h max: 39.8-43.3	Weighted City-wide avg	Weeks 3-7 of gestation
Hansen et al. (2009)	Cardiac and Cleft Defects	Brisbane, Australia (n=150,308 births)	8-h max: 25.8	Nearest Monitor	Weeks 3-8 of gestation
Marshall et al. (2010)	Oral Cleft Defects	New Jersey (n=717 cases; 12,925 controls)	24-h avg: 25	Nearest Monitor (within 40 km)	Weeks 5-10 of gestation
Dadvand et al. (2011)	Cardiac Defects	Northeast England (n=2,140 cases; 14,256 controls)	24-h avg: 18.8	Nearest Monitor	Weeks 3-8 of gestation`1

7.4.8 Developmental Respiratory Effects

The issue of prenatal exposure has assumed increasing importance since ambient air pollution exposures of pregnant women have been shown to lead to adverse pregnancy outcomes, as well as to respiratory morbidity and mortality in the first year of life. Growth and development of the respiratory system take place mainly during the prenatal and early postnatal periods. This early developmental phase is thought to be very important in determining long-term lung growth. Studies have recently examined this emerging issue. Several studies were included in Sections 7.2.1 and 7.2.3, and are included here because they reported both prenatal and post-natal exposure periods.

Mortimer et al. (2008a, b) examined the association of prenatal and lifetime exposures to air pollutants with pulmonary function and allergen sensitization in a subset of asthmatic children (ages 6-11) included in the Fresno Asthmatic Children's Environment Study (FACES). Monthly means of pollutant levels for the years 1989-2000 were created and averaged separately across several important developmental time-periods, including the entire pregnancy, each trimester, the first 3 years of life, the first 6 years of life, and the entire lifetime. The 8-h avg O_3 concentrations were approximately 50 ppb for each of the exposure metrics (estimated from figure). In the first analysis (Mortimer et al., 2008a), negative effects on pulmonary function were found for exposure to PM_{10}, NO_2, and CO during key neonatal and early life developmental periods. The authors did not find a negative effect of exposure to O_3 among this cohort. In the second analysis (Mortimer et al., 2008b), sensitization to at least one allergen was associated, in general, with higher levels of CO and PM_{10} during the entire pregnancy and second trimester and higher PM_{10} during the first 2 years of life. Lower exposure to O_3 during the entire pregnancy or second trimester was associated with an increased risk of allergen sensitization. Although the pollutant metrics across time periods are correlated, the strongest associations with the outcomes were observed for prenatal exposures. Though it may be difficult to disentangle the effect of prenatal and postnatal exposures, the models from this group of studies suggest that each time period of exposure may contribute independently to different dimensions of school-aged children's pulmonary function. For 4 of the 8 pulmonary-function measures (FVC, FEV_1, PEF, FEF_{25-75}), prenatal exposures were more influential on pulmonary function than early-lifetime metrics, while, in contrast, the ratio of measures (FEV_1/FVC and FEF_{25-75}/FVC) were most influenced by postnatal exposures. When lifetime metrics were considered alone, or in combination with the prenatal metrics, the lifetime measures were not associated with any of the outcomes, suggesting the timing of the exposure may be more important than the overall dose and prenatal exposures are not just markers for lifetime or current exposures.

Clark et al. (2010) investigated the effect of exposure to ambient air pollution in utero and during the first year of life on risk of subsequent asthma diagnosis (incident asthma diagnosis up to age 3-4) in a population-based nested case-control study. Air pollution exposure for each subject based on their residential address history was estimated using regulatory monitoring data, land use regression modeling, and proximity to stationary pollution sources. An average exposure was calculated for the duration of pregnancy (~15 ppb) and the first year of life (~14 ppb). In contrast to the Mortimer et al. studies (2008a, b), the effect estimates for first-year exposure were generally larger than for in utero exposures. However, similar to the Mortimer et al. studies, the observed associations with O_3 were largely protective. Because of the relatively high correlation between in utero and first-year exposures for many pollutants, it was difficult to discern the relative importance of the individual exposure periods.

Latzin et al. (2009) examined whether prenatal exposure to air pollution was associated with lung function changes in the newborn. Tidal breathing, lung volume, ventilation inhomogeneity and eNO were measured in 241 unsedated, sleeping neonates (age= 5 weeks). The median of the 24-h avg O_3 concentrations averaged across the post-natal period was ~44 ppb. Consistent with the previous studies, no association was found for prenatal exposure to O_3 and lung function.

The new toxicological literature since the 2006 O_3 AQCD, covering respiratory changes related to developmental O_3 exposure, reports ultrastructural changes in bronchiole development, alterations in placental and pup cytokines, and increased pup airway hyper-reactivity. These studies are detailed below. Older studies are discussed where new information is not available.

Fetal rat lung bronchiole development is triphasic, comprised of the glandular phase (measured at GD18), the canalicular phase (GD20), and the saccular phase (GD21). The ultrastructural lung development in fetuses of pregnant rats exposed to 1-ppm O_3 (12 h/day, out to either GD18, GD20 or GD21) was examined by electron microscopy during these three phases. In the glandular phase, bronchiolar columnar epithelial cells in fetuses of dams exposed to O_3 had cytoplasmic damage and swollen mitochondria. Bronchial epithelium at the canalicular phase in O_3 exposed pups had delayed maturation in differentiation, i.e., glycogen abundance in secretory cells had not diminished as it should with this phase of development. Congruent with this finding, delayed maturation of tracheal epithelium following early neonatal O_3 exposure (1 ppm, 4-5 h/day for first week of life) in lambs has been previously reported (Mariassy et al., 1990; Mariassy et al., 1989). Also at the canalicular phase, atypical cells were seen in the bronchiolar lumen of O_3 exposed rat fetuses. Finally, in the saccular phase, mitochondrial degradation was present in the non-ciliated bronchiolar cells of rats exposed in utero to

O_3. In conclusion, O_3 exposure of pregnant rats produced ultra-structural damage to near-term fetal bronchiolar epithelium (López et al., 2008).

Exposure of laboratory animals to multiple airborne pollutants can differentially affect pup physiology. One study showed that exposure of C57BL/6 mouse dams to 0.48 mg PM intratracheally twice weekly for 3 weeks during pregnancy augmented O_3-induced airway hyper-reactivity in juvenile offspring. Maternal PM exposure also significantly increased placental cytokines above vehicle-instilled controls. Pup postnatal O_3 exposure (1 ppm 3 h/day, every other day, thrice weekly for 4 weeks) induced significantly increased cytokine levels (IL-1β, TNF-α, KC, and IL-6) in whole lung versus postnatal air exposed groups; this was further exacerbated with gestational PM exposure (Auten et al., 2009).

A series of experiments using infant rhesus monkeys repeatedly exposed to 0.5 ppm O_3 starting at one-month of age have examined the effect of O_3 alone or in combination with an inhaled allergen on morphology and lung function (Plopper et al., 2007). Exposure to O_3 alone or allergen alone produced small but not statistically significant changes in baseline airway resistance and airway responsiveness, but the combined exposure to both O_3 + antigen produced statistically significant and greater than additive changes in both functional measurements. Additionally, cellular changes and significant structural changes in the respiratory tract have been observed in infant rhesus monkeys exposed to O_3 (Fanucchi et al., 2006). A more detailed description of these studies can be found in Section 7.2.3 (Pulmonary Structure and Function), with mechanistic information found in Section 5.4.2.4.

Lung immunological response in O_3 exposed pups was followed by analyzing BAL and lung tissue. Sprague Dawley (SD) pups were exposed to a single 3h exposure of air or O_3 (0.6 ppm) on PND 13 (Han et al., 2011). Bronchoalveolar lavage (BAL) was performed 10 hours after the end of O_3 exposure. BALF polymorphonuclear leukocytes (PMNs) and total BALF protein were significantly elevated in O_3 exposed pups. Lung tissue from O_3 exposed pups had significant elevations of manganese superoxide dismutase (SOD) protein and significant decrements of extra-cellular SOD protein.

Various immunological outcomes were followed in offspring after their pregnant dams (BALB/c mice) were exposed gestationally to O_3 (0, 0.4, 0.8, or 1.2 ppm, GD9-18) (Sharkhuu et al., 2011). Delayed type hypersensitivity (DTH) was initiated with initial BSA injection at 6 weeks of age and then challenge 7 days later. The normal edematous response of the exposed footpad (thickness after BSA injection) was recorded as an indicator of DTH. In female offspring, normal footpad swelling with BSA injection that was seen in air exposed animals was significantly attenuated with O_3 exposure (0.8 and 1.2 ppm O_3), implying immune suppression of O_3 exposure specifically in DTH.

Humoral immunity was measured with the sheep red blood cell (SRBC) response. Animals received primary immunization with SRBC and then blood was drawn for SRBC IgM measurement. A SRBC booster was given 2 weeks later with blood collected 5 days after booster for IgG measurement. Maternal O_3 exposure had no effect on humoral immunity in the offspring as measured by IgG and IgM titers after SRBC primary and booster immunizations (Sharkhuu et al., 2011).

Toxicity assessment and allergen sensitization was also assessed in these O_3 exposed offspring. At PND42, animals were euthanized for analysis of immune and inflammatory markers (immune proteins, inflammatory cells, T cell populations in the spleen). A subset of the animals was intra-nasally instilled or sensitized with ovalbumin on either PND2 and 3 or PND42 and 43. All animals were challenged with OVA on PND54, 55, and 56. One day after final OVA challenge, lung function, lung inflammation and immune response were determined. Offspring of O_3 exposed dams that were initially sensitized at PDN3 (early) or PND42 (late) were tested to determine the level of allergic sensitization or asthma-like inflammation after OVA challenge. Female offspring sensitized early in life developed significant eosinophilia (1.2 ppm O_3) and elevated serum OVA-specific IgE (1.2 ppm O_3), which is a marker of airway allergic inflammation. The females that were sensitized early also had significant decrements in BALF total cells, macrophages, and lymphocytes (1.2 ppm O_3). Offspring that were sensitized later (PND42) in life did not develop the aforementioned changes in BALF, but these animals did develop modest, albeit significant neutropenia (0.8 and 1.2 ppm O_3) (Sharkhuu et al., 2011).

BALF cytology in non-sensitized animals was followed. BALF of offspring born to dams exposed to O_3 was relatively unaffected (cytokines, inflammatory cell numbers/types) as were splenic T cell subpopulations. LDH was significantly elevated in BALF of females whose mothers were exposed to 1.2 ppm during pregnancy (Sharkhuu et al., 2011). In summary, the females born to mothers exposed to O_3 developed modest immunocompromise. Males were unaffected (Sharkhuu et al., 2011).

Overall, animal toxicological studies have reported ultrastructural changes in bronchiole development, alterations in placental and pup cytokines, and increased pup airway hyper-reactivity related to exposure to O_3 during the developmental period. Epidemiologic studies have found no association between prenatal exposure to O_3 and growth and development of the respiratory system. Fetal origins of disease have received a lot of attention recently, thus additional research to further explore the inconsistencies between these two lines of evidence is warranted.

7.4.9 Developmental Central Nervous System Effects

The following sections describe the results of toxicological studies of O_3 and developmental central nervous system effects. No epidemiologic studies of this association have been published.

7.4.9.1 Laterality

Two reports of laterality changes in mice developmentally exposed to O_3 have been reported in the literature. Mice developmentally exposed to 0.6 ppm O_3 (6 days before breeding to weaning at PND21) showed a turning preference (left turns) distinct from air exposed controls (clockwise turns) (Dell'Omo et al., 1995); in previous studies this behavior in mice has been found to correlate with specific structural asymmetries of the hippocampal mossy fiber projections (Schöpke et al., 1991). The 2006 O_3 AQCD evidence for the effect of O_3 on laterality or handedness demonstrated that rats exposed to O_3 during fetal and neonatal life showed limited, gender-specific changes in handedness after exposure to the intermediate dose of O_3 (only seen in female mice exposed to 0.6 ppm O_3, and not in males at 0.6 ppm or in either sex of 0.3 or 0.9 ppm O_3 with exposure from 6 days before breeding to PND26) (Petruzzi et al., 1999).

7.4.9.2 Brain Morphology and Neurochemical Changes

The nucleus tractus solitarius (NTS), a medullary area of respiratory control, of adult animals exposed prenatally to 0.5 ppm O_3 (12h/day, ED5-ED20) had significantly less tyrosine hydroxylase staining versus control (Boussouar et al., 2009). Tyrosine hydroxylase is the rate-limiting enzyme for dopamine synthesis and serves as a precursor for catecholamine synthesis; thus, decreased staining is used as a marker of dopaminergic or catecholaminergic cell or activity loss in these regions and thus functions in neuronal plasticity. After physical restraint stress, control animals respond at the histological level with Fos activation, a marker of neuronal activity, and tyrosine hydroxylase activation in the NTS, a response which is absent or attenuated in adult animals exposed prenatally to 0.5 ppm O_3 (Boussouar et al., 2009) when compared to control air exposed animals who also were restrained. The O_3-exposed offspring in this study were cross-fostered to control air exposed dams to avoid O_3-dependent dam related neonatal effects on offspring outcomes (i.e., dam behavioral or lactational contributions to pup outcomes) (Boussouar et al., 2009).

Developmental exposure to 0.3 or 0.6 ppm O_3 prior to mating pair formation through GD17 induced significant increased levels of BDNF in the striatum of adult (PND140) O_3 exposed offspring as compared to control air exposed animals; these O_3-exposed animals also had significantly decreased level of NGF in the hippocampus versus control (Santucci et al., 2006).

Changes in the pup cerebellum with prenatal 1 ppm O_3 exposure include altered morphology (Romero-Velazquez et al., 2002; Rivas-Manzano and Paz, 1999), decreased total area (Romero-Velazquez et al., 2002), decreased number of Purkinje cells (Romero-Velazquez et al., 2002), and altered monoamine neurotransmitter content with the catecholamine system affected and the indoleamine system unaffected by O_3 (Gonzalez-Pina et al., 2008).

7.4.9.3 Neurobehavioral Outcomes

O_3 administration to dams during pregnancy with or without early neonatal exposure has been shown to contribute to multiple neurobehavioral outcomes in offspring that are described in further detail below.

O_3 administration (0.4, 0.8 or 1.2 ppm O_3) during the majority of pregnancy (PD7-17) of CD-1 mice did not affect pup behavioral outcomes including early behavioral ultrasonic vocalizations and more permanent later measurements (PND60 or 61) including pup activity, habituation and exploration and d-amphetamine-induced hyperactivity (Bignami et al., 1994); these pups were all cross-fostered or reared on non- O_3 exposed dams.

Testing for aggressive behavior in mice continuously exposed to O_3 (0.3 or 0.6 ppm from 30 days prior to mating to GD17) revealed that mice had significantly increased defensive/ submissive behavior (increased freezing posturing on the first day only of a multiple-day exam) versus air exposed controls (Santucci et al., 2006). Similar to this and as reported in previous AQCDs, continuous exposure of adult animals to O_3 induced significant increases in fear behavior and decreased aggression as measured by significantly decreased freezing behavior (Petruzzi et al., 1995).

Developmentally exposed animals also had significantly decreased amount of time spent nose sniffing other mice (Santucci et al., 2006); this social behavior deficit, decreased sniffing time, was not found in an earlier study with similar exposures (Petruzzi et al., 1995), but sniffing of specific body areas was measured in Santucci et al. (2006) and total number of sniffs of the entire body was measured in Petruzzi et al. (1995). The two toxicology studies exploring social behavior (sniffing) employ different study designs and find opposite effects in animals exposed to O_3.

7.4.9.4 Sleep Aberrations after Developmental Ozone Exposure

The effect of gestational O_3 exposure (1 ppm O_3, 12h/day, during dark period) on sleep patterns in rat offspring was followed using 24 h polysomnographic recordings at 30, 60 and 90 days of age (Haro and Paz, 1993). Ozone-exposed pups manifested with inverted sleep-wake patterns or circadian rhythm phase-shift. Rat vigilance was characterized in wakefulness, slow wave sleep (SWS), and paradoxical sleep (PS) using previously characterized criteria. The O_3 exposed offspring spent longer time in the wakefulness state during the light period, more time in SWS during the period of darkness, and showed significant decrements in PS. Chronic O_3 inhalation significantly decreased the duration of PS during both the light and dark periods (Haro and Paz, 1993). These effects were consistent at all time periods measured (30, 60 and 90 days of age). These sleep effects reported after developmental exposures expand upon the existing literature on sleep aberrations in adult animals exposed to O_3 [rodents: (Paz and Huitron-Resendiz, 1996; Arito et al., 1992); and cats: (Paz and Bazan-Perkins, 1992)]. A role for inhibition of cyclooxygenase-2 and the interleukins and prostaglandins in the O_3-dependent sleep changes potentially exists with evidence from a publication on indomethacin pretreatment attenuating O_3-induced sleep aberrations in adult male animals (Rubio and Paz, 2003).

7.4.10 Early Life Mortality

Infants may be particularly susceptible to the adverse effects of air pollution. Within the first year of life, infants develop rapidly; therefore their susceptibility may change within weeks or months. During the neonatal and post-neonatal periods, the developing lung is highly susceptible to environmental toxicants. The lung is not well developed at birth, with 80% of alveoli being formed postnatally. An important question regarding the association between O_3 and infant mortality is the critical window of exposure during development for which infants are susceptible. Several age intervals have been explored: neonatal (<1 month); postneonatal (1 month to 1 year); and an overall interval for infants that includes both the neonatal and postneonatal periods (<1 year). Within these various age categories, multiple causes of deaths have been investigated, particularly total deaths and respiratory-related deaths. The studies reflect a variety of study designs, exposure periods, regions, and adjustment for confounders. As discussed below, a handful of studies have examined the effect of ambient air pollution on neonatal and postneonatal mortality, with the former the least studied. These studies varied somewhat with regard to the outcomes and exposure periods examined and study designs employed.

A major issue in studying environmental exposures and infant mortality is selecting the relevant exposure period, since the biological mechanisms leading to death and the

critical periods of exposure are poorly understood. Both short-term (days to weeks) and long-term (months to years) exposure studies are included in this section and are characterized accordingly in the text and tables. All studies of infant mortality are included in the Reproductive and Developmental Effects section, as opposed to the sections devoted to all- and cause-specific mortality, because infant development processes, much like fetal development processes, may be particularly susceptible to O_3-induced health effects. Exposures proximate to the death may be most relevant if exposure causes an acute effect. However, exposure occurring in early life might affect critical growth and development, with results observable later in the first year of life, or cumulative exposure during the first year of life may be the most important determinant. The studies reviewed below have dealt with this issue in different ways. Many have considered several exposure metrics based on different periods of exposure.

7.4.10.1 Stillbirth

Pereira et al. (1998) investigated the association among daily counts of intrauterine mortality (over 28 weeks of gestation) and air pollutant concentrations in Sao Paulo, Brazil from 1991 through 1992. The association was strong for NO_2, but lesser for SO_2 and CO. These associations exhibited a short lag time, less than 5 days. No significant association was detected between short-term O_3 exposure and intrauterine mortality.

7.4.10.2 Infant Mortality, Less than 1 Year

Ritz et al. (2006) linked birth and death certificates for infants who died between 1989 and 2000 to evaluate the influence of outdoor air pollution on infant death in the South Coast Air Basin of California. The authors examined short- and long-term exposure periods 2 weeks, 1 month, 2 months, and 6 months before each case subject's death and reported no association between ambient levels of O_3 and infant mortality. Similarly, Diaz et al. (2004) analyzed the effects of extreme temperatures and short-term exposure to air pollutants on daily mortality in children less than 1 year of age in Madrid, Spain, from 1986 to 1997 and observed no statistically significant association between mortality and O_3 concentrations. Hajat et al. (2007) analyzed time-series data of daily infant mortality counts in 10 major cities in the UK to quantify any associations with short-term changes in air pollution. When the results from the 10 cities were combined there was no relationship between O_3 and infant mortality, even after restricting the analysis to just the summer months.

Conversely, a time-series study of infant mortality conducted in the southwestern part of Mexico City in the years 1993-1995 found that infant mortality was associated with short-term exposure to NO_2 and O_3 3-5 days before death, but not as consistently as with PM. A 10-ppb increase in 24-h avg O_3 was associated with a 2.78% increase (95% CI: 0.29, 5.26%) in infant mortality (lag 3) (Loomis et al., 1999). This increase was attenuated, although still positive when evaluated in a two-pollutant model with $PM_{2.5}$. One-hour max concentrations of O_3 exceeded prevailing Mexican and international standards nearly every day.

7.4.10.3 Neonatal Mortality, Less than 1 Month

Several studies have evaluated ambient O_3 concentrations and neonatal mortality and observed no association. Ritz et al. (2006) linked birth and death certificates for infants who died between 1989 and 2000 to evaluate the influence of outdoor air pollution on infant death in the South Coast Air Basin of California. The authors examined short- and long-term exposure periods 2 weeks, 1 month, 2 months, and 6 months before each case subject's death and reported no association between ambient levels of O_3 and neonatal mortality. Hajat et al. (2007) analyzed time-series data of daily infant mortality counts in 10 major cities in the UK to quantify any associations with short-term changes in air pollution. When the results from the 10 cities were combined there was no relationship between O_3 and neonatal mortality, even after restricting the analysis to just the summer months. Lin et al. (2004a) assessed the impact of short-term changes in air pollutants on the number of daily neonatal deaths in Sao Paulo, Brazil. The authors observed no association between ambient levels of O_3 and neonatal mortality.

7.4.10.4 Postneonatal Mortality, 1 Month to 1 Year

A number of studies focused on the postneonatal period when examining the effects of O_3 on infant mortality. Ritz et al. (2006) linked birth and death certificates for infants who died between 1989 and 2000 to evaluate the influence of outdoor air pollution on infant death in the South Coast Air Basin of California. The authors examined short- and long-term exposure periods 2 weeks, 1 month, 2 months, and 6 months before each case subject's death and reported no association between ambient levels of O_3 and postneonatal mortality. Woodruff et al. (2008) evaluated the county-level relationship between cause-specific postneonatal infant mortality and long-term early-life exposure (first 2 months of life) to air pollutants across the U.S. Similarly, they found no association between O_3 exposure and deaths from respiratory causes. In the U.K., Hajat et al. (2007) analyzed time-series data of daily infant mortality counts in 10 major cities

to quantify any associations with short-term changes in air pollution. When the results from the 10 cities were combined there was no relationship between O_3 and postneonatal mortality, even after restricting the analysis to just the summer months. In Ciudad Juarez, Mexico, Romieu et al. (2004b) examined the daily number of deaths between 1997 and 2001, estimating the modifying effect of SES on the risk of postneonatal mortality. Ambient O_3 concentrations were not related to infant mortality overall, or in any of the SES groups. In a follow-up study, Carbajal-Arroyo (2011) evaluated the relationship of 1-h daily max O_3 levels with postneonatal infant mortality in the Mexico City Metropolitan Area between 1997 and 2005. Generally, short-term exposure to O_3 was not significantly related to infant mortality. However, upon estimating the modifying effect of SES on the risk of postneonatal mortality, the authors found that O_3 was statistically significantly related to respiratory mortality among those with low SES. In a separate analysis, the effect of PM_{10} was evaluated with O_3 level quartiles. PM_{10} alone was related to a significant increase in all-cause mortality. The magnitude of this effect remained the same when only the days when O_3 was in the lowest quartile were included in the analyses. However, when only the days when O_3 was in the highest quartile were included in the analyses, the magnitude of the PM_{10} effect increased dramatically (OR=1.06 [95% CI: 0.909, 1.241] for PM_{10} on days with O_3 in lowest quartile; OR=1.26 [95% CI: 1.08, 1.47] for PM_{10} on days with O_3 in the highest quartile. These results suggest that while O_3 alone may not have an effect on infant mortality, it may serve to potentiate the observed effect of PM_{10} on infant mortality.

Tsai et al. (2006) used a case-crossover analysis to examine the relationship between short-term exposure to air pollution and postneonatal mortality in Kaohsiung, Taiwan during the period 1994-2000. The risk of postneonatal deaths was 1.023 (95% CI: 0.564, 1.858) per 10-ppb increase in 24-h avg O_3. The confidence interval for this effect estimate is very wide, likely due to the small number of infants that died each day, making it difficult to interpret this result. Several other studies conducted in Asia did not find any association between O_3 concentrations and infant mortality in the postneonatal period. Ha et al. (2003) conducted a daily time-series study in Seoul, Korea to evaluate the effect of short-term changes in ambient 8-h O_3 concentrations on postneonatal mortality. Son et al. (2008) examined the relationship between air pollution and postneonatal mortality from all causes among firstborn infants in Seoul, Korea during 1999-2003. Yang et al. (2006) used a case-crossover analysis to examine the relationship between air pollution exposure and postneonatal mortality in Taipei, Taiwan for the period 1994-2000. The authors observed no associations between ambient levels of O_3 and postneonatal mortality.

7.4.10.5 Sudden Infant Death Syndrome

The strongest evidence for an association between ambient O_3 concentrations and SIDS comes from a study that evaluated the county-level relationship between SIDS and long-term early-life exposure (first 2 months of life) to air pollutants across the U.S.(Woodruff et al., 2008). The authors observed a 1.20 (95% CI: 1.09, 1.32) odds ratio for a 10-ppb increase in O_3 and deaths from SIDS. There was a monotonic increase in odds of SIDS for each quartile of O_3 exposure compared with the lowest quartile (highest quartile OR=1.51; [95% CI: 1.17, 1.96]). In a multi-pollutant model including PM_{10} or $PM_{2.5}$, CO and SO_2, the OR for SIDS and O_3 was not substantially lower than that found in the single-pollutant model. When examined by season, the relationship between SIDS deaths and O_3 was generally consistent across seasons with a slight increase for those babies born in the summer. When stratified by birth weight, the OR for LBW babies was 1.27 (95% CI: 0.95, 1.69) per 10-ppb increase in O_3 and the OR for normal weight babies was 1.16 (95% CI: 1.01, 1.32) per 10-ppb increase in O_3.

Conversely, two additional studies reported no association between ambient levels of O_3 and SIDS. Ritz et al. (2006) linked birth and death certificates for infants who died between 1989 and 2000 to evaluate the influence of outdoor air pollution on infant death in the South Coast Air Basin of California. The authors examined short- and long-term exposure periods 2 weeks, 1 month, 2 months, and 6 months before each case subject's death and reported no association between ambient levels of O_3 and SIDS. Dales et al. (2004) used time-series analyses to compare the daily mortality rates for SIDS and short-term air pollution concentrations in 12 Canadian cities during the period of 1984-1999. Increased daily rates of SIDS were associated with previous day increases in the levels of SO_2, NO_2, and CO, but not O_3 or $PM_{2.5}$.

Table 7-9 provides a brief overview of the epidemiologic studies of infant mortality. These studies have focused on short-term exposure windows (e.g., 1-3 days) and long-term exposure windows (e.g., up to 6 months). Collectively, they provide no evidence for an association between ambient O_3 concentrations and infant mortality.

Table 7-9 Brief summary of infant mortality studies

Study	Location	Mean O_3 (ppb)	Exposure Assessment	Effect Estimate[a] (95% CI):
Pereira et al. (1998)	Sao Paulo, Brazil	1-h max: 33.8	Citywide avg	L0-2: 1.00 (0.99, 1.01)
Diaz et al. (2004)	Madrid, Spain	24-h avg: 11.4	Citywide avg	NR
Loomis et al. (1999)	Mexico City, Mexico	24-h avg: 44.1 1-h max: 163.5	1 monitor	L0: 0.99 (0.97, 1.02) L1: 0.99 (0.96, 1.01) L2: 1.00 (0.98, 1.03) L3: 1.03 (1.00, 1.05) L4: 1.01 (0.98, 1.03) L5: 1.02 (0.99, 1.04) L0-2: 1.02 (0.99, 1.05)
Ritz et al. (2006)	Southern California	24-h avg: 21.9-22.1	Nearest Monitor	2 wk before death: 1.03 (0.93, 1.14) 1 mo before death: NR 2 mo before death: 0.93 (0.89, 0.97) 6 mo before death: NR
Hajat et al. (2007)	10 Cities in the UK	24-h avg: 20.5-42.6	Citywide avg	L0-2: 1.00 (0.96, 1.06)
Lin et al. (2004a)	Sao Paulo, Brazil	24-h avg: 38.06	Citywide avg	L0: 1.00 (0.99, 1.01)
Ha et al. (2003)	Seoul, South Korea	8-h avg: 21.2	Citywide avg	L0: 0.93 (0.90, 0.96)
Romieu et al. (2004b)	Ciudad Juarez, Mexico	8-h avg: 43.43-55.12	Citywide avg	L1: 0.96 (0.90, 1.03) L2: 0.97 (0.91, 1.04) L0-1 cum: 0.96 (0.89, 1.04) L0-2 cum: 0.94 (0.87, 1.02)
Carbajal-Arroyo et al. (2011)	Mexico City, Mexico	1-h max: 103.0	Citywide avg	L0: 1.00 (0.99, 1.00) L1: 0.99 (0.99, 0.99) L2: 0.99 (0.99, 1.00) L0-2: 0.99 (0.99, 1.00)
Son et al. (2008)	Seoul, South Korea	8-ha avg: 25.61	Citywide avg	L(NR): 0.984 (0.976, 0.992)[b]
Tsai et al. (2006)	Kaohsiung, Taiwan	24-h avg: 23.60	Citywide avg	L0-2 cum: 1.02 (0.56, 1.86)
Woodruff et al. (2008)	Nationwide, US	24-h avg: 26.6	County wide avg	First 2 mo of life: 1.04 (0.98, 1.10)
Yang et al. (2006)	Taipei, Taiwan	24-h avg: 18.14	Citywide avg	L0-2 cum:1.00 (0.62, 1.61)
Dales et al. (2004)	12 Canadian cities	24-h: 31.77	Citywide avg	L0: NR L1: NR L2: NR L3: NR L4: NR L5: NR Multiday lags of 2-6 days: NR

[a]Relative risk of infant mortality per 10 ppb change in O_3

[b]No increment provided

L0 = Lag 0, L1= Lag 1, L2 = Lag 2, L3 = Lag 3, L4 = Lag 4, L5 = Lag 5, L6 = Lag 6

NR: No quantitative results reported

Table 7-10 Summary of Key Reproductive and Developmental Toxicological Studies

Study	Model	O_3 (ppm)	Exposure Duration	Effects
Sharkhuu et al. (2011)	Pregnant mice; BALB/c; F; GD9-18; effects in offspring	0.4, 0.8, or 1.2	Continuously for 10 consecutive days	Dams: Decreased number of dams reaching parturition. Offspring: 1-Decreased birth weights. 2-Decreased rate of postnatal growth (body weight). 3-Impaired delayed type hypersensitivity.4-No effect on humoral immunity. 5-Significantly affected allergic airway inflammation markers (eosinophilia, IgE) in female offspring sensitized early in life. 6-BALF LDH significantly elevated in female offspring.
Bignami et al. (1994)	Pregnant CD-1 dams (PD7-17)	0.4, 0.8 or 1.2	Continuous	Reproductive success was not affected by O_3 exposure (PD7-17, proportion of successful pregnancies, litter size, ex ratio, frequency of still birth, or neonatal mortality). Ozone acted as a transient anorexigen in pregnant dams.
Haro and Paz (1993)	Rat dams, Exposure over the entirety of pregnancy;	1.0	12h/day during dark cycle	Decreased birth weight and postnatal body weight of offspring out to PND 90. Ozone-exposed pups manifested with inverted sleep-wake patterns or circadian rhythm phase-shift.
López et al. (2008)	Rats; Pregnant dams; GD1-GD18, GD20, or GD21.	1.0	(12 h/day, out to either GD18, GD20 or GD21)	O_3 induced delayed maturation of near term rodent bronchioles, with ultra-structural damage to bronchiolar epithelium.
Auten et al. (2009)	C57BL/6 mouse pups	1.0	3 h/day, every other day, thrice weekly for 4 weeks	Postnatal O_3 exposure significantly increased lung inflammatory cytokine levels; this was further exacerbated with gestational PM exposure.
Plopper et al. (2007)	Infant rhesus monkeys	0.5	Postnatal, PND30-6month of age, 5 months of cyclic exposure, 5 days O_3 followed by 9 days of filtered air, 8h/day.	Non-significant increases airway resistance and airway responsiveness with O_3 or inhaled allergen alone. Allergen + O_3 produced additive changes in both measures.
Fanucchi et al. (2006)	Infant male Rhesus monkeys, post-natal exposure	0.5	5 months of episodic exposure, age 1 month-age 6 months, 5 days O_3 followed by 9 days of filtered air, 8h/day.	Cellular changes and significant structural changes in the distal respiratory tract in infant rhesus monkeys exposed to O_3 postnatally.
Dell'Omo et al. (1995)	CD-1 Mouse dams and pups	0.6	6 days before breeding to weaning at PND21	Laterality changes in offspring: Ozone exposed pups showed a turning preference (left turns) distinct from air exposed controls (clockwise turns) as adults.
Santucci et al. (2006)	CD-1 Mouse dams	0.3 or 0.6	Dam exposure prior to mating through GD17.	Developmental O_3 caused increased defensive/submissive behavior in offspring. O_3 exposed offspring also had significant elevations of striatal BDNF and hippocampal NGF v. air exposed controls.
Han et al. (2011)	Rat; Sprague Dawley, M & F; PND13	0.6	3 h, BALF examined 10h after O_3 exposure	BALF polymorphonuclear leukocytes and total BALF protein were significantly elevated in O_3 exposed pups. Lung tissue from O_3 exposed pups had significant elevations of manganese superoxide dismutase (SOD) protein and significant decrements of extra-cellular SOD protein.
Campos-Bedolla et al. (2002)	Pregnant Rats; Sprague Dawley (GD5, 10 or 18)	3.0	1h on one day of gestation, uteri collected 16-18 h later	Ozone inhalation modifies the contractile response of the pregnant uterus. The O_3 exposed pregnant uteri had significant increases in the maximum response to acetyl choline stimulation at GD5 and 10; they also had a significant increase in maximal response to oxytocin at GD 5.
Kavlock et al. (1980)	CD-1 mice; (pregnancy day 7-17)	0.4, 0.8 and 1.2	Continuous, pregnancy day 7-17	O_3 induced decrements in postnatal body weight gain. When O_3 was co-administered with sodium salicylate, O_3 synergistically increased the rate of pup resorption (1.0 ppm GD9-12).
Jedlinska-Krakowska et al. (2006)	5 month old male Wistar Hannover rats	3.0	0.5 ppm, 5h/day for 50 days	Histopathological evidence of impaired spermatogenesis (round spermatids/ 21 spermatocytes, giant spermatid cells, and focal epithelial desquamation with denudation to the 22 basement membrane). Vitamin E exposure concomitant with O_3 protected against pathological changes but Vitamin C did not.

7.4.11 Summary and Causal Determination

The 2006 O_3 AQCD concluded that the limited number of studies that investigated O_3 demonstrated no associations between O_3 and birth outcomes, with the possible exception of birth defects. The current review included an expanded body of evidence on the associations between O_3 and reproductive and developmental effects. Recent epidemiologic and toxicological studies provide evidence for an effect of prenatal exposure to O_3 on pulmonary structure and function, including lung function changes in the newborn, incident asthma, ultrastructural changes in bronchiole development, alterations in placental and pup cytokines, and increased pup airway hyper-reactivity. Also, there is limited toxicological evidence for an effect of prenatal and early life exposure on central nervous system effects, including laterality, brain morphology, neurobehavioral abnormalities, and sleep aberration. Recent epidemiologic studies have begun to explore the effects of O_3 on sperm quality, and provide limited evidence for decrements in sperm concentration, while there is limited toxicological evidence for testicular degeneration associated with O_3.

While the collective evidence for many of the birth outcomes examined is generally inconsistent (including birth defects), there are several well-designed, well-conducted studies that indicate an association between O_3 and adverse outcomes. For example, as part of the southern California Children's Health Study, Salam et al. (2005) observed a concentration-response relationship of decreasing birth weight with increasing O_3 concentrations averaged over the entire pregnancy that was clearest above the 30-ppb level (see Figure 7-4). Simiarly,Hansen et al. (2008) utilized fetal ultrasonic measurements and found a change in ultrasound measurements associated with O_3 during days 31-60 of gestation indicated that increasing O_3 concentration decreased an ultrasound measurement for women living within 2 km of the monitoring site.

There is no evidence that prenatal or early life O_3 concentrations are associated with infant mortality. Collectively, there is limited though positive toxicological evidence for O_3-induced developmental effects, including effects on pulmonary structure and function and central nervous system effects. Limited epidemiologic evidence for an effect on prenatal O_3 exposure on respiratory development provides coherence with the effects observed in toxicological studies. There is also limited epidemiologic evidence for an association with O_3 concentration and decreased sperm concentration. A recent toxicological study provides limited evidence for a possible biological mechanism (histopathology showing impaired spermatogenesis) for such an association. Additionally, though the evidence for an association between O_3 concentrations and adverse birth outcomes is generally inconsistent, there are several influential studies that indicate an association with reduced birth weight and restricted fetal growth. Taking into

consideration the positive evidence for developmental and reproductive outcomes from toxicological and epidemiological studies, and the few influential birth outcome studies, the evidence is **suggestive of a causal relationship between long-term exposures to O_3 and reproductive and developmental effects.**

7.5 Central Nervous System Effects

7.5.1 Effects on the Brain and Behavior

The 2006 O_3 AQCD included toxicological evidence that acute exposures to O_3 are associated with alterations in neurotransmitters, motor activity, short and long term memory, and sleep patterns. Additionally, histological signs of neurodegeneration have been observed. Reports of headache, dizziness, and irritation of the nose with O_3 exposure are common complaints in humans, and some behavioral changes in animals may be related to these symptoms rather than indicative of neurotoxicity. Research in the area of O_3-induced neurotoxicity has notably increased over the past few years, and new studies examining the effects of long-term exposure have demonstrated progressive damage in various regions of the brains of rodents in conjunction with altered behavior. Evidence from epidemiologic studies has been more limited. A recently published epidemiologic study examined the association between O_3 exposure and neurobehavioral effects. Chen et al. (2009) utilized data from the NHANES III cohort to study the relationship between O_3 levels (mean annual O_3 concentration 26.5 ppb) and neurobehavioral effects among adults aged 20-59 years. The authors observed an association between annual exposure to O_3 and tests measuring coding ability (symbol-digit substitution test) and attention/short-term memory (serial-digit learning test). Each 10-ppb increase in annual O_3 levels corresponded to an aging-related cognitive performance decline of 3.5 yr for coding ability and 5.3 years for attention/short-term memory. These associations persisted in both crude and adjusted models. There was no association between O_3 levels and reaction time tests. The authors concluded that overall, there is an association between long-term O_3 exposure and reduced performance on neurobehavioral tests.

A number of new toxicological studies demonstrate various perturbations in neurologic function or histology with long-term exposure to O_3, including changes similar to those observed in neurodegenerative disorders such as Parkinson's and Alzheimer's disease pathologies in relevant regions of the brain (Table 7-11). The central nervous system is very sensitive to oxidative stress, due in part to its high content of polyunsaturated fatty acids, high rate of oxygen consumption, and low antioxidant enzyme capacity. Oxidative

stress has been identified as one of the pathophysiological mechanisms underlying neurodegenerative disease (Simonian and Coyle, 1996), and it is believed to play a role in altering hippocampal function, which causes cognitive deficits with aging (Vanguilder and Freeman, 2011). A particularly common finding in studies of O_3-exposed rats is lipid peroxidation in the brain, especially in the hippocampus, which is important for higher cognitive function including contextual memory acquisition. Performance in passive avoidance learning tests is impaired when the hippocampus is injured. For example, in a subchronic study, exposure of rats to 0.25 ppm O_3 (4 h/day) for 15-90 days caused a complex array of responses, including a time-dependent increase in lipid peroxidation products and immunohistochemical changes in the hippocampus that were correlated with decrements in passive avoidance behavioral tests (Rivas-Arancibia et al., 2010). Changes included increased numbers of activated microglia, a sign of inflammation, and progressive neurodegeneration. Notably, continued exposure tends to bring about progressive, cumulative damage, as shown by this study (Rivas-Arancibia et al., 2010) and others (Santiago-López et al., 2010; Guevara-Guzmán et al., 2009; Angoa-Pérez et al., 2006). The effects of O_3 on passive avoidance test performance were particularly evident at 90 days for both short- and long-term memory. The greatest extent of cell loss was also observed at this time point, whereas lipid peroxidation did not increase much beyond 60 days of exposure.

The substantia nigra is another region of the brain affected by O_3, and seems particularly sensitive to oxidative stress because the metabolism of dopamine, central to its function, is an oxidative process perturbed by redox imbalance. Oxidative stress has been implicated in the premature death of substantia nigra dopamine neurons in Parkinson's disease. Progressive damage has been found in the substantia nigra of male rats after 15, 30, and 60 days of exposure to 0.25 ppm O_3 for 4 h/day. Santiago-López and colleagues (2010) observed a reduction dopaminergic neurons within the substantia nigra over time, with a complete loss of normal morphology in the remaining cells and virtually no dopamine immunoreactivity at 60 days. This was accompanied by an increase in p53 levels and nuclear translocation, a process associated with programmed cell death. Similarly, Angoa-Pérez et al. (2006) have shown progressive lipoperoxidation in the substantia nigra and a decrease in nigral neurons in ovariectomized female rats exposed to 0.25 ppm O_3, 4h/day, for 7 - 60 days. Lipid peroxidation effectively doubled between the 30 and 60 day time points. Total nigral cell number was also diminished to the greatest extent at 60 days, and cell loss was particularly evident in the tyrosine hydroxylase positive cell population (90%), indicating a selective loss of dopamine neurons or a loss of dopamine pathway functionality.

The olfactory bulb also undergoes oxidative damage in O_3-exposed animals, in some cases altering olfactory-dependent behavior. Lipid peroxidation was observed in the

olfactory bulbs of ovariectomized female rats exposed to 0.25 ppm O_3 (4 h/day) for 30 or 60 days (Guevara-Guzmán et al., 2009). O_3 also induced decrements in a selective olfactory recognition memory test, which were significantly greater at 60 days compared to 30 days, and the authors note that early deficits in odor perception and memory are components of human neurodegenerative diseases. The decrements in olfactory memory did not appear to be due to damaged olfactory perception based on other tests early on, but by 60 days deficits in olfactory perception had emerged.

Memory deficits and associated morphological changes can be attenuated by administration of α-tocopherol (Guerrero et al., 1999), taurine (Rivas-Arancibia et al., 2000), and estradiol (Guevara-Guzmán et al., 2009; Angoa-Pérez et al., 2006), all of which have antioxidant properties. In the study by Angoa-Pérez et al. (2006) described above, estradiol seemed particularly effective at protecting against lipid peroxidation and nigral cell loss at 60 days compared to shorter exposure durations. The same was true for amelioration of decrements in olfactory recognition memory (Guevara-Guzmán et al., 2009), although protection against lipid peroxidation was similar for the 30 and 60 day exposures.

Table 7-11 Central nervous system effects of long-term O_3 exposure in rats

Study	Model	O_3 (ppm)	Exposure Duration	Effects
Angoa-Pérez et al. (2006)	Rat; Wistar; F; Weight: 300 g; Ovariectomized	0.25	7 to 60 days, 4 h/day, 5 days/wk	Long-term estradiol treatment protected against O_3-induced oxidative damage to nigral dopamine neurons, lipid peroxidation, and loss of tyrosine hydrolase-immunopositive cells.
Guevara-Guzmán et al. (2009)	Rat; Wistar; F; Weight: 264 g; Ovariectomized	0.25	30 and 60 days, 4h/day	Long-term estradiol treatment protected against O_3-induced oxidative stress and decreases in α and β estrogen receptors and dopamine β-hydroxlyase in olfactory bulb, and deficits in olfactory social recognition memory and chocolate recognition.
Rivas-Arancibia et al. (2010)	Rat; Wistar; M; Weight: 250-300 g	0.25	15 to 90 days, 4h/day	Ozone produced significant increases in lipid peroxidation in the hippocampus, and altered the number of p53 positive immunoreactive cells, activated and phagocytic microglia, GFAP immunoreactive cells, double cortine cells, and short- and long-term memory-retention latency
Santiago-López et al. (2010)	Rat; Wistar; M; Weight: 250-300 g	0.25	15, 30, and 60 days, 4 h/day	Progressive loss of dopamine reactivity in the substantia nigra, along with morphological changes. Increased p53 levels and nuclear translocation.
Santucci et al. (2006)	Mice; CD-1; M; 18 weeks old	0.3; 0.6	Females continuously exposed from 30 days prior to breeding until GD17	Upon behavioral challenge with another male, there was a significant increase in defensive and freezing postures and decrease in the frequency of nose-sniffing. These behavioral changes were accompanied by a significant increase in BDNF in the striatum and a decrease of NGF in the hippocampus.

CNS effects have also been demonstrated in adult mice whose only exposure to O_3 occurred while *in utero, a period particularly critical for brain development*. Santucci et al. (2006) investigated behavioral effects and gene expression after in utero exposure of mice to 0.3 or 0.6 ppm O_3. Exposure began 30 days prior to mating and continued throughout gestation. Testing of adult animals demonstrated increased defensive/submissive behavior and reduced social investigation were observed in both the 0.3 and 0.6 ppm O_3 groups. Changes in gene expression of brain-derived neurotrophic factor (BDNF, increased in striatum) and nerve growth factor (NGF, decreased in hippocampus) accompanied these behavioral changes. BDNF and NGF are involved in neuronal organization and the growth, maintenance, and survival of neurons during early development and in adulthood. This study and two others using short-term exposures demonstrate that CNS effects can occur as a result of *in utero* exposure to O_3, and although the mode of action of these effects is not known, it has been suggested that circulating lipid peroxidation products may play a role (Boussouar et al., 2009). Importantly, these CNS effects occurred in rodent models after *in utero* only exposure to (semi-) relevant concentrations of O_3.

7.5.2 Summary and Causal Determination

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

7.6 Carcinogenic and Genotoxic Potential of Ozone

7.6.1 Introduction

The radiomimetic and clastogenic qualities of O_3, combined with its ability to stimulate proliferation of cells in the respiratory tract, have suggested that O_3 could act as a carcinogen. However, toxicological studies of tumorigenesis in the rodent lung have yielded mixed and often confusing results, and the epidemiologic evidence is equally conflicted. The 2006 O_3 AQCD concluded that, "the weight of evidence from recent animal toxicological studies and a very limited number of epidemiologic studies do not support ambient O_3 as a pulmonary carcinogen" [2](U.S. EPA, 2006b).

Multiple epidemiologic studies reported in the 2006 O_3 AQCD examined the association between O_3 exposure and cancer. The largest of these studies, by Pope et al. (2002), included 500,000 adults from the American Cancer Society's (ACS) Cancer Prevention II study. In this study, no association was observed between O_3 and lung cancer mortality. The Adventist Health Study of Smog (AHSMOG) also examined the association between O_3 and lung cancer mortality (Abbey et al., 1999). There was a positive association between O_3 levels and lung cancer mortality among men. No association was reported for women. Another study using the AHSMOG cohort assessed the risk of incident lung cancer (Beeson et al., 1998). Among males, an association with incidence of lung cancer was observed with increasing O_3 concentrations. When stratified by smoking status, the association persisted among never smokers but was null for former smokers. No association was detected for females. The Six Cities Study examined various air pollutants and mortality but did not specifically explore the association between O_3 concentrations and lung cancer mortality due to low variability in O_3 levels across the cities (Dockery et al., 1993). An ecologic study performed in Sao Paulo City, Brazil examined the correlations between O_3 levels in four of the city districts and incident cancer of the larynx and lung reported in 1997 (Pereira et al., 2005). A correlation between the average number of days O_3 levels exceeded air quality standards from 1981 to 1990 and cancer incidence was present for larynx cancer but not for lung cancer.

Early toxicological research demonstrated lung adenoma[3] acceleration in mice with daily exposure to 1 ppm over 15 months (Stokinger, 1962). Later work demonstrated a significant increase in lung tumor numbers in one strain of mouse (A/J) but not another

[2] The toxicological evidence is presented in detail in Table 6-18 on p. 6-116 of the 1996 O_3 AQCD and Table AX5-13 on p. AX5-43 of the 2006 O_3 AQCD.

[3] NOTE: Although adenomas are benign, over time they may progress to become malignant, at which point they are called adenocarcinomas. Adenocarcinoma is the predominant lung cancer subtype in most countries, and is the only lung cancer found in nonsmokers. From page 8-33 of the 1970 O_3 AQCD: "No true lung cancers have been reported, however, from experimental exposures to either O3 alone or any other combination or ingredient of photochemical oxidants."

after exposure to 0.3-0.8 ppm O_3 (Last et al., 1987; Hassett et al., 1985). The A/J mouse strain is known to have a high incidence of spontaneous adenomas, and further studies using this strain found a statistically significant increase in lung tumor incidence after a 9-month exposure to 0.5 ppm and incidence and multiplicity after a 5 month exposure to 0.12 ppm with a 4-month recovery period (Witschi et al., 1999). However, these findings were discounted by the study authors due to the lack of a clear dose response, and results from the Hassett et al. 1985 and Last et al. 1987 studies were retrospectively deemed spurious based on what appeared to be unusually low spontaneous tumor incidences in the control groups (Witschi, 1991). A study of carcinogenicity of O_3 by the National Toxicology Program (NTP, 1994) reported increased incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in female $B6C3F_1$ mice exposed over 2 years to 1.0 ppm O_3, but not 0.12 or .5 ppm. No effect was detected in male mice. For a lifetime exposure to 0.5 or 1.0 ppm O_3, an increase in the number of female mice with adenomas (but not carcinomas or total neoplasms) was found. The number of total neoplasms was also unaffected in male mice, but there was a marginally increased incidence of carcinoma in males exposed to 0.5 and 1.0 ppm. Thus there was equivocal evidence of carcinogenic activity in male mice and some evidence of carcinogenic activity of O_3 in females. Some semblance of a dose-response relationship was also evident in this study. Experimental details of the NTP study are available in Table 6-19 on p. 6-121 of the 1996 O_3 AQCD.

In Fischer-344/N rats (50 of each sex per group), neither a 2-year nor lifetime exposure to O_3 ranging from 0.12 to 1.0 ppm was found to be carcinogenic (Boorman et al., 1994). However, a marginally significant carcinogenic effect of 0.2 ppm O_3 was reported in a study of male Sprague-Dawley rats exposed for 6 months (n = 50) (Monchaux et al., 1996). These two studies also examined co-carcinogenicity of O_3 with NNK[4] (Boorman et al., 1994) or a relatively high dose of radon (Monchaux et al., 1996), finding no enhancement of NNK related tumors and a slight non-significant increase in tumor incidence after combined exposure with radon, respectively. Another study exploring co-carcinogenicity was conducted in hamsters. Not only was there no enhancement of chemically induced tumors in the peripheral lung or nasal cavity, but results suggested that O_3 could potentially delay or inhibit tumor development (Witschi et al., 1993). Thus there is no concrete evidence that O_3 can act as a co-carcinogen.

Immune surveillance is an important defense against cancer, and it should be noted that natural killer (NK) cells, which destroy tumor cells in the lung, appear to be inhibited by higher doses of O_3 and either unaffected or stimulated at lower doses (Section 6.2.5.4,

[4] 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone

Infection and Adaptive Immunity). This aspect of tumorigenesis adds yet another layer of complexity which may be reflected by conflicting results across studies.

The following sections will examine epidemiologic studies of cancer incidence and mortality and toxicological studies that have been published since the 2006 O_3 AQCD. An epidemiologic study has been published with cancer as the outcome; most epidemiologic studies examine markers of exposure or susceptibility.

7.6.2 Lung Cancer Incidence and Mortality

A recent re-analysis of the full ACS CPSII cohort by the Health Effects Institute is the only epidemiologic study that has explored the association between O_3 and cancer mortality since the last O_3 AQCD. Krewski et al. (2009) conducted an extended follow-up of the cohort (1982-2000). Mean O_3 levels [obtained from the Aerometric Information Retrieval System (AIRS) for 1980] were 22.91 ppb for the full year and 30.15 ppb for the summer months (April-September). No association was reported between lung cancer mortality and O_3 (HR=1.00 [95% CI: 0.96-1.04] per 10 ppb $O_{3)}$. Additionally, no association was observed when O_3 was restricted to the summer months. There was also no association present in a sub-analysis of the cohort examining the relationship between O_3 and lung cancer mortality in the Los Angeles area.

Since the 2006 O_3 AQCD, two toxicological studies have examined potential carcinogenicity of O_3 (Kim and Cho, 2009a, b). Looking across both studies, which used the same mouse strain as the National Toxicology Program study described above (NTP, 1994), 0.5 ppm O_3 alone or in conjunction with chemical tumor inducers did not enhance lung tumor incidence in males or females. However, a 10% incidence of oviductal carcinoma was observed in mice exposed to 0.5 ppm O_3 for 16 weeks. The implications of this observation are unclear, particularly in light of the lack of statistical information reported. Additionally, there is no mention of oviductal carcinoma after 32 weeks of exposure, and no oviductal carcinoma was observed after one year of exposure. The NTP study did not report any increase in tumors at extrapulmonary sites.

7.6.3 DNA Damage

The potential for genotoxic effects relating to O_3 exposure was predicted from the radiomimetic properties of O_3. The decomposition of O_3 in water produces OH and HO_2 radicals, the same species that are generally considered to be the biologically active products of ionizing radiation. Ozone has been observed to cause degradation of DNA in a number of different models and bacterial strains. The toxic effects of O_3 have been

generally assumed to be confined to the tissues directly in contact with the gas, such as the respiratory epithelium. Due to the highly reactive nature of O_3, little systemic absorption is predicted. Zelac et al. (1971a, b), however, reported a significant increase in chromosome aberrations in peripheral blood lymphocytes from Chinese hamsters exposed to 0.2 ppm for 5 hours. Other *in vivo* exposure studies found increased DNA strand breaks in respiratory cells from guinea pigs (Ferng et al., 1997) and mice (Bornholdt et al., 2002) but only with exposure to higher doses of O_3 (1 ppm for 72 hours and 1 or 2 ppm for 90 minutes, respectively). In other studies there were no observations of chromosomal aberrations in germ cells, but mutagenic effects have been seen in offspring of mice exposed to 0.2 ppm during gestation (blepharophimosis or dysplasia of the eyelids). The overall evidence for mutagenic activity from *in vitro* studies is positive, and in the National Toxicology Program report described above, O_3 was found to be mutagenic in *Salmonella*, with and without S9 metabolic activation. No new toxicological studies of DNA damage have become available since the 2006 O_3 AQCD.

A number of epidemiologic studies looked at the association between O_3 and DNA and cellular level damages. These changes may be relevant to mechanisms leading to cancers development and serve as early indicators of elevated risk of mutagenicity.

Two studies performed in California examined cytogenetic damage in relation to O_3 exposures. Huen et al. (2006) examined cytogenetic damage among African American children and their mothers in Oakland, CA. Increased O_3 (mean monthly 8-h O_3 concentrations ranged from about 30 ppb in April to 14 ppb in November) was associated with increased cytogenetic damage (micronuclei frequency among lymphocytes and buccal cells) even after adjustment for household/personal smoking status and distance-weighted traffic density. Chen et al. (2006a) recruited college students at the University or California, Berkeley who reported never smoking and compared their levels of cytogenetic damage (micronuclei frequency from buccal cells) in the spring and fall. Cytogenetic damage was greater in the fall, which the authors attributed to the increase in O_3 over the summer. However, O_3 levels over 2, 7, 10, 14, or 30 days (concentrations not given) before collection of buccal cells did not correlate with cytogenetic damage. Estimated lifetime O_3 exposure was also not correlated with cytogenetic damage. Additionally, the authors exposed a subset of the students (n=15) to 200 ppb O_3 for 4 hours while the students exercised intermittently. Ozone was found to be associated with an increase in cytogenetic damage in degenerated cells but not in normal cells 9-10 days after exposure. Increased cytogenetic damage was also noted in peripheral blood lymphocytes collected 18 hours after exposure.

A study performed in Mexico recruited 55 male workers working indoors (n=27) or outdoors (n=28) in Mexico City or Puebla, Mexico in order to study the relationship

between O_3 and DNA damage (detected from peripheral blood samples using the Comet assay) (Tovalin et al., 2006). The median estimated daily O_3 concentrations were estimated to be 28.5 ppb for outdoor workers and 5.1 ppb for indoor workers in Mexico City and 36.1 ppb for outdoor workers and 19.5 ppb for indoor workers in Puebla. Overall, a positive correlation between O_3 levels and DNA damage was observed. However, when examining the relationship by city and workplace, only DNA damage in outdoor workers in Mexico City remained correlated with O_3 levels.

Three studies examining the relationship between O_3 and DNA-level damage have been performed in Europe. The largest of these was the GenAir case-control study, which was nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study, and included individuals recruited between 1993 and 1998 from ten European countries. Only non-smokers (must not have smoked for at least 10 years prior to enrollment) were enrolled in the study. The researchers examined DNA adduct levels (DNA bonded to cancer-causing chemicals) and their relationship with O_3 concentrations (concentrations not given) (Peluso M Hainaut et al., 2005). A positive association was seen between DNA adduct levels and O_3 concentrations from 1990-1994 but not O_3 levels from 1995-1999. In adjusted analyses with DNA adduct levels dichotomized as high and low (detectable versus non-detectable), the OR was 1.97 (95% CI: 1.08, 3.58) when comparing the upper tertile of O_3 concentration to the lower two tertiles. Two other European studies were conducted in Florence, Italy. The most recent of these enrolled individuals from the EPIC study into a separate study between March and September of 1999 (Palli et al., 2009). The purpose of the study was to examine oxidative DNA damage (determined by Comet assay using blood lymphocytes) in association with varying periods of O_3 exposure. The researchers observed that longer periods of high O_3 exposure (concentrations not given) were more strongly correlated with oxidative DNA damage than shorter exposures (i.e., the rho [p-value] was 0.26 [0.03] for 0-10 days and 0.35 [0.002] for 0-90 days). This correlation was stronger among men compared to women. The correlations for all time periods had p-values <0.05 for ex- and never-smokers. For current smokers, the correlation was only observed among time periods ≤ 25 days. When adjusted for age, gender, smoking history, traffic pollution exposure, period of blood draw, and area of residence, the association between O_3 levels and oxidative DNA damage was positive for O_3 levels 0-60 days, 0-75 days, and 0-90 days prior to blood draw. Positive, statistically significant associations were not observed among shorter time periods. The other study performed in Florence recruited healthy volunteers who reported being non-smokers or light smokers (Giovannelli et al., 2006). The estimated O_3 levels during the study ranged from approximately 4-40 ppb for 3-day avgs, 5-35 ppb for 7-day avgs, and 7.5-32.5 ppb for 30-day avgs. Ozone concentrations were correlated with DNA strand breaks (measured from blood lymphocytes) over longer exposure periods (p-value: 0.002 at 30 days, p-value: 0.04 at 7 days; p-value: 0.17 at

3 days). This association was robust to control for temperature, solar radiation, gender, and age. No association was seen between O_3 concentrations and measures of oxidative DNA damage at 3, 7, or 30 days.

7.6.4 Summary and Causal Determination

The 2006 O_3 AQCD reported that evidence did not support ambient O_3 as a pulmonary carcinogen. Since the 2006 O_3 AQCD, very few epidemiologic and toxicological studies have been published that examine O_3 as a carcinogen, but collectively, study results indicate that O_3 may contribute to DNA damage. Overall, the evidence is **inadequate to determine if a causal relationship exists between ambient O_3 exposures and cancer.**

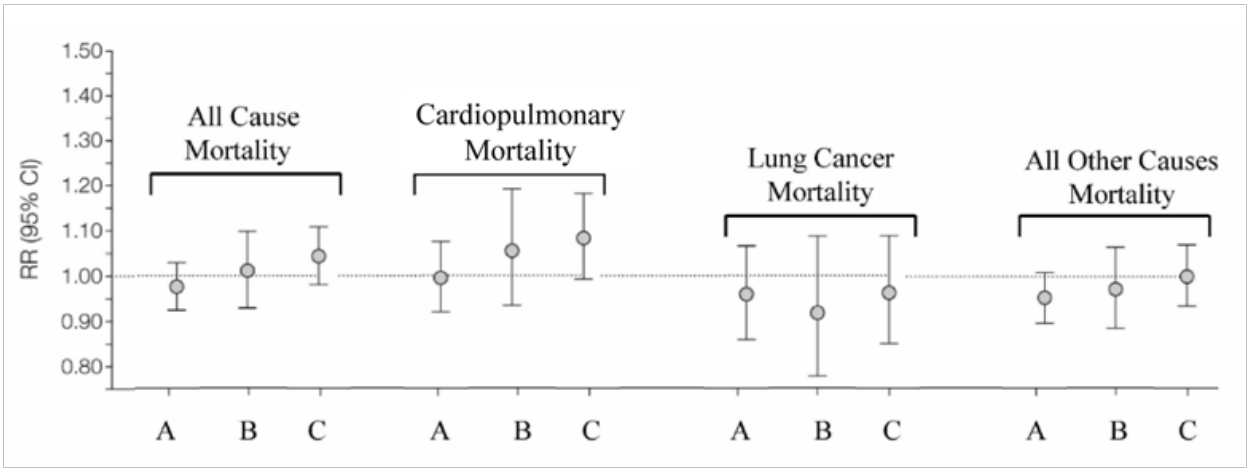
7.7 Mortality

A limited number of epidemiologic studies have assessed the relationship between long-term exposure to O_3 and mortality in adults. The 2006 O_3 AQCD concluded that an insufficient amount of evidence existed "to suggest a causal relationship between chronic O_3 exposure and increased risk for mortality in humans" (U.S. EPA, 2006b). In addition to the infant mortality studies discussed in Section 7.4.9, additional studies have been conducted among adults since the last review; an ecologic study that finds no association between mortality and O_3, several reanalyses of the ACS cohort, one of which specifically points to a relationship between long-term O_3 exposure and an increased risk of respiratory mortality, and a study of four cohorts of persons with potentially predisposing conditions. These studies supplement the evidence from long-term cohort studies characterized in previous reviews of O_3, and are summarized here briefly.

In the Harvard Six Cities Study (Dockery et al., 1993), adjusted mortality rate ratios were examined in relation to long-term mean O_3 concentrations in six cities: Topeka, KS; St. Louis, MO; Portage, WI; Harriman, TN; Steubenville, OH; and Watertown, MA. Mean O_3 concentrations from 1977 to 1985 ranged from 19.7 ppb in Watertown to 28.0 ppb in Portage. Long-term mean O_3 concentrations were not found to be associated with mortality in the six cities. However, the authors noted that "The small differences in O_3 levels among the (six) cities limited the power of the study to detect associations between mortality and O_3 levels." In addition, while total and cardio-pulmonary mortality were considered in this study, respiratory mortality was not specifically considered.

In a subsequent large prospective cohort study of approximately 500,000 U.S. adults, Pope et al. (2002) examined the effects of long-term exposure to air pollutants on

mortality (American Cancer Society, Cancer Prevention Study II). All-cause, cardiopulmonary, lung cancer and other mortality risk estimates for long-term O_3 exposure are shown in Figure 7-5. While consistently positive associations were not observed between O_3 and mortality (effect estimates labeled A in Figure 7-5) , the mortality risk estimates were larger in magnitude when analyses considered more accurate exposure metrics, increasing when the entire period was considered (effect estimates labeled B in Figure 7-5) and becoming marginally significant when the exposure estimate was restricted to the summer months (July to September; effect estimates labeled C in Figure 7-5), especially when considering cardiopulmonary deaths. In contrast, consistent positive and significant effects of $PM_{2.5}$ were observed for both lung cancer and cardio-pulmonary mortality.



	Years of Data Collection	Number of Metropolitan Areas	Number of Participants (in thousands)	1-h Max O_3 Mean (SD)
A	1980-1981	134	559	47.9 (11.0)
B	1982-1998	119	525	45.5 (7.3)
C	1982-1998 (July – Sept)	134	557	59.7 (12.8)

Source: Reprinted with permission of American Medical Association, Pope et al. (2002).

Figure 7-5 Adjusted ozone-mortality relative risk estimates (95% CI) by time period of analysis per subject-weighted mean O_3 concentration in the Cancer Prevention Study II by the American Cancer Society.

A study by Abbey et al. (1999) examined the effects of long-term air pollution exposure, including O_3, on all-cause (n = 1,575), cardiopulmonary (n = 1,029), nonmalignant respiratory (n = 410), and lung cancer (n = 30) mortality in the long-term prospective Adventist Health Study of Smog (AHSMOG) of 6,338 nonsmoking, non-Hispanic white individuals living in California. A particular strength of this study was the extensive

effort devoted to assessing long-term air pollution exposures, including interpolation to residential and work locations from monitoring sites over time and space. No associations with long-term O_3 exposure were observed for all cause, cardiopulmonary, and nonmalignant respiratory mortality. In a follow-up, Chen et al. (2005) utilized data from the AHSMOG study and reported no evidence of associations between long-term O_3 exposure (mean O_3 concentration 26.2 ppb) and fatal coronary heart disease. Thus, no association of chronic O_3 exposure with mortality outcomes has been detected in this study.

Lipfert et al. (2003, 2000) reported positive effects on all-cause mortality for peak O_3 exposures (95th percentile levels) in the U.S. Veterans Cohort study of approximately 50,000 middle-aged men recruited with a diagnosis of hypertension. The actual analysis involved smaller subcohorts based on exposure and mortality follow-up periods. Four separate exposure periods were associated with three mortality follow-up periods. For concurrent exposure periods, peak O_3 was positively associated with all-cause mortality, with a 9.4% (95% CI: 0.4, 18.4) excess risk per mean 95th percentile O_3 less estimated background level (not stated). "Peak" refers, in this case, to the 95th percentile of the hourly measurements, averaged by year and county. In a further analysis, Lipfert et al. (2003) reported the strongest positive association for concurrent exposure to peak O_3 for the subset of subjects with low diastolic blood pressure during the 1982 to 1988 period. Two more recent studies of this cohort focused specifically on traffic density (Lipfert et al., 2006a; 2006b). Lipfert (2006b) concluded that: "Traffic density is seen to be a significant and robust predictor of survival in this cohort, more so than ambient air quality, with the possible exception of O_3," reporting a significant O_3 effect even with traffic density included in the model: RR=1.080 per 40 ppb peak O_3 (95% CI: 1.019, 1.146). However, in Lipfert (2006a), which considers only the EPA Speciation Trends Network (STN) sites, O_3 drops to non-significant predictor of total mortality for this cohort. The authors acknowledge that: "Peak O_3 has been important in analyses of this cohort for previous periods, but in the STN data set, this variable has limited range and somewhat lower values and its small coefficient of variation results in a relatively large standard error." The restriction to subjects near STN sites likely reduced the power of this analysis, though the size of the remaining subjects considered was not reported in this paper. In addition, these various Veterans Cohort studies considered only total mortality, and did not consider mortality on a by-cause basis.

An ecological study in Brisbane, Australia used a geospatial approach to analyze the association of long-term exposure to gaseous air pollution with cardio-respiratory mortality, in the period 1996-2004 (Wang et al., 2009c). A generalized estimating equations model was employed to investigate the impact of NO_2, O_3 and SO_2, but PM was not addressed. The results indicated that long-term exposure to O_3 was not

associated with cardio-respiratory mortality, but the fact that this study considered only one city, and that the range of O_3 exposure across that city (23.7-35.6 ppb) was low and slight in variation in comparison to the range of other pollutants across the city, limited study power. In addition, confounding factors (e.g., smoking) could not be addressed at the individual level in this ecological study. Respiratory mortality was not evaluated separately.

A recent study by Zanobetti and Schwartz (In Press) examined whether year-to-year variations in 8-h mean daily O_3 concentrations for the summer (May-September) around their city-specific long-term trend were associated with year-to-year variations in mortality around its long-term trend. This association was examined among Medicare participants with potentially predisposing conditions, including COPD, diabetes, CHF, and MI, defined as patients discharged alive after an emergency admission for one of these four conditions. The analyses was repeated in 105 cities using available data from 1985 through 2006, and the results were combined using methods previously employed by these authors (Zanobetti et al., 2008; Zanobetti and Schwartz, 2007). This study design eliminated potential confounding by factors that vary across city, which is a common concern in most air pollution cohort studies, and also avoided both confounding by cross-sectional factors that vary by city and the short-term factors that confound daily time-series studies, but are not present in annual analyses. The average 8-h mean daily summer O_3 concentrations ranged from 15.6 ppb (Honolulu, HI) to 71.4 ppb (Bakersfield, CA) for the 105 cities. The authors observed associations between yearly fluctuations in summer O_3 concentrations and mortality in each of the four cohorts; the hazard ratios (per 10 ppb increment) were 1.12 (95% CI: 1.06, 1.17) for the CHF cohort, 1.19 (95% CI 1.12, 1.25) for the MI cohort, 1.14 (95% CI: 1.10, 1.21) for the diabetes cohort, and 1.14 (95% CI: 1.08, 1.19) for the COPD cohort. A key advantage to this study is that fluctuations from summer to summer in O_3 concentrations around long-term level and trend in a specific city are unlikely to be correlated with most other predicators of mortality risk, except for temperature, which was controlled for in the regression. Key limitations of the study were the inability to control for $PM_{2.5}$, since it was not reliably measured in these cities until 1999, and the inability to separate specific causes of death (e.g., respiratory, cardiovascular), since Medicare does not provide the underlying cause of death.

In the most recent follow-up analyses of the ACS cohort (Jerrett et al., 2009; Smith et al., 2009a), the effects of long-term exposure to O_3 were evaluated alone, as well as in copollutant models with $PM_{2.5}$ and components of $PM_{2.5}$. Jerrett et al. (2009) utilized the ACS cohort with data from 1977 through 2000 (mean O_3 concentration ranged from 33.3 to 104.0 ppb) and subdivided cardiopulmonary deaths into respiratory and cardiovascular, separately, as opposed to combined into one category, as was done by Pope et al. (2002).

Increases in exposure to O_3 were associated with an elevated risk of death from cardiopulmonary, cardiovascular, ischemic heart disease, and respiratory causes. Inclusion of $PM_{2.5}$ concentrations measured in 1999-2000 as a copollutant attenuated the association with O_3 for all end points except death from respiratory causes, for which a significant association persisted (Table 7-12). The association between increased O_3 concentrations and increased risk of death from respiratory causes was insensitive to the use of a random-effects survival model allowing for spatial clustering within the metropolitan area and state of residence, and adjustment for several ecologic variables considered individually. Subgroup analyses showed that temperature and region of country, but not sex, age at enrollment, body-mass index, education, or $PM_{2.5}$ concentration, modified the effects of O_3 on the risk of death from respiratory causes (i.e., risks were higher at higher temperature, and in the Southeast, Southwest, and Upper Midwest). Ozone threshold analyses indicated that the threshold model was not a better fit to the data ($p > 0.05$) than a linear representation of the overall O_3-mortality association. Overall, this new analysis indicates that long-term exposure to $PM_{2.5}$ increases risk of cardiac death, while long-term exposure to O_3 is specifically associated with an increased risk of respiratory death, and suggests that combining cardiovascular and respiratory causes of mortality into one category for analysis may obscure any effect that O_3 may have on respiratory-related causes of mortality.

Table 7-12 Relative risk (and 95% CI) of death attributable to a 10-ppb change in the ambient O_3 concentration*

Cause of Death	O_3 (96 MSAs)	O_3 (86 MSAs)	O_3 +$PM_{2.5}$ (86 MSAs)
Any Cause	1.001 (0.996, 1.007)	1.001 (0.996, 1.007)	0.989 (0.981, 0.996)
Cardiopulmonary	1.014 (1.007, 1.022)	1.016 (1.008, 1.024)	0.992 (0.982, 1.003)
Respiratory	1.029 (1.010, 1.048)	1.027 (1.007, 1.046)	1.040 (1.013, 1.067)
Cardiovascular	1.011 (1.003, 1.023)	1.014 (1.005, 1.023)	0.983 (0.971, 0.994)
Ischemic Heart Disease	1.015 (1.003, 1.026)	1.017 (1.006, 1.029)	0.973 (0.958, 0.988)

* Ozone concentrations were measured from April to September during the years from 1977 to 2000, with follow-up from 1982 to 2000; changes in the concentration of PM2.5 of 10 µg per cubic meter were recorded for members of the cohort in 1999 and 2000.

Source: Reprinted with permission of Massachusetts Medical Society (Jerrett et al., 2009)

In a similar analysis, Smith et al. (2009a) used data from 66 MSAs in the ACS cohort to examine the association of O_3 concentrations during the warm season and all-cause and cardiopulmonary mortality. Mortality effects were estimated in single pollutant and copollutant models, adjusting for two $PM_{2.5}$ constituents, sulfate and EC. When all-cause mortality was investigated, there was a 0.8% (95% CI: -0.31, 1.9) increase associated with a 10 ppb increase in O_3 concentration. This association was diminished when sulfate or EC were included in the model. There was a 2.48% (95% CI: 0.74, 4.3) increase in cardiopulmonary mortality associated with a 10 ppb increase in O_3 concentration. The

cardiopulmonary association was robust to adjustment for sulfate, and diminished, though still positive, after adjustment for EC (1.63% increase; 95% CI: -0.41, 3.7). Smith et al. (2009a) did not specifically separate out cardiovascular and respiratory causes of death from the cardiopulmonary category, as was done by Jerrett et al. (2009).

7.7.1 Summary and Causal Determination

The 2006 O_3 AQCD concluded that an insufficient amount of evidence existed "to suggest a causal relationship between chronic O_3 exposure and increased risk for mortality in humans" (U.S. EPA, 2006b). Several additional studies have been conducted since the last review, including an ecologic study that finds no association between mortality and O_3 (Wang et al., 2009c), a study of four cohorts of Medicare enrollees with potentially predisposing conditions that observes associations between O_3 and mortality among each of the cohorts (Zanobetti and Schwartz, In Press), and reanalyses of the ACS cohort that provide weak evidence for an association with cardiopulmonary mortality (Smith et al., 2009a) and specifically point to a relationship between long-term O_3 exposure and an increased risk of respiratory mortality (Jerrett et al., 2009). The findings from the Jerrett et al. (2009) study are consistent and coherent with the evidence from epidemiologic, controlled human exposure, and animal toxicological studies for the effects of short- and long-term exposure to O_3 on respiratory effects. Additionally, the evidence for short- and long-term respiratory morbidity provides biological plausibility for mortality due to respiratory disease. Collectively, **the evidence is suggestive of a causal relationship between long-term O_3 exposures and mortality.**

7.8 Overall Summary

The evidence reviewed in this chapter describes the recent findings regarding the health effects of long-term exposure to ambient O_3 concentrations. Table 7-13 provides an overview of the causal determinations for each of the health categories evaluated.

Table 7-13 Summary of causal determinations for long-term exposures to ozone

Health Category	Causal Determination
Respiratory Effects	Likely to be a causal relationship
Cardiovascular Effects	Suggestive of a causal relationship
Reproductive and Developmental Effects	Suggestive of a causal relationship
Central Nervous System Effects	Suggestive of a causal relationship
Carcinogenicity and Genotoxicity	Inadequate to infer a causal relationship
Mortality	Suggestive of a causal relationship

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8 POPULATIONS POTENTIALLY AT INCREASED RISK FOR OZONE-RELATED HEALTH EFFECTS

Interindividual variation in human responses to air pollution exposure suggests that some groups are at increased risk for detrimental effects in response to ambient exposure to an air pollutant. The NAAQS are intended to provide an adequate margin of safety for both the population as a whole and those individuals potentially at increased risk for health effects in response to ambient air pollution (Preface to this ISA). To facilitate the identification of populations at greater risk for O_3-related health effects, studies have evaluated factors that may contribute to the susceptibility and/or vulnerability of an individual to O_3. The definitions of susceptibility and vulnerability have been found to vary across studies, but in most instances "susceptibility" refers to biological or intrinsic factors (e.g., lifestage, sex) while "vulnerability" refers to nonbiological or extrinsic factors (e.g., socioeconomic status [SES]) (U.S. EPA, 2010c, 2009d). Additionally, in some cases, the terms "at-risk" and "sensitive" populations have been used to encompass these concepts more generally. Previous ISAs and reviews (Sacks et al., 2011; U.S. EPA, 2010c, 2009d) have used an all encompassing definition for "susceptible population" to focus on identifying the populations at greater risk for O_3-induced heath effects and circumvent the need to distinguish between susceptible and vulnerable factors. In this chapter, "at-risk" groups are defined as those with characteristics that increase the risk of O_3-related health effects in a population. These characteristics include various factors, such as genetic background, race, sex, lifestage, diet, preexisting disease, SES, and characteristics that may modify exposure to O_3 (e.g., time spent outdoors).

Individuals, and ultimately populations, could experience increased risk for O_3-induced health effects due to:

- Intrinsically increased risk: This describes individuals at greater risk due to a biological mechanism;
- Extrinsically increased risk: This describes individuals at greater risk due to an external, non-biological factor; and
- Increased dose: This describes individuals that have a greater dose at a given concentration due to breathing patterns or other factors

In addition, some individuals might be placed at risk of experiencing a greater exposure by being exposed at higher concentrations. For example, individuals in lower SES groups might be exposed to higher O_3 concentrations due to less availability/use of home air conditioners (i.e., more open windows on high O_3 days).

Examples of potential factors intrinsically related to increased risk through biological mechanisms are genetic background and sex, while extrinsic factors, such as SES, may also increase the risk of O_3-related health effects. However, some factors that may lead to increased risk of O_3-related health effects have both intrinsic and extrinsic components. For example, SES may affect access to medical care, which could then affect the presence of preexisting diseases and conditions often considered to be intrinsic factors. Additionally, children tend to spend more time outdoors than adults, which increases their dose of O_3, but they also have intrinsic differences compared to adults based on lung growth and development.

The emphasis of this chapter is on identifying and understanding the characteristics that potentially increase the risk of O_3-related health effects, regardless of whether the increased risk at a given concentration is due to intrinsic factors, extrinsic factors, or increased dose. The following sections examine factors that may modify the association between O_3 and health effects, but does not categorize them as intrinsic factors, extrinsic factors, or increased dose, due to the convoluted and often connected pathways between factors. However, the different role of intrinsic risk, extrinsic risk, and increased dose are discussed as appropriate throughout the chapter.

Epidemiologic studies often conduct stratified analyses to identify the presence or absence of effect measure modification to indicate whether O_3 differentially affects certain populations. This allows researchers to examine the effects of O_3 exposure within each group under study. A thorough evaluation of potential effect measure modifiers may help identify populations that are more at-risk to health effects associated with O_3 exposure. Toxicological and controlled human exposure studies can provide support and biological plausibility for factors that may lead to increased risk for O_3-related health effects through the study of animal models of disease or individuals with underlying disease or genetic polymorphisms that allow for comparisons between subgroups. The results from these studies, combined with those results obtained through stratified analyses in epidemiologic studies, comprise the overall weight of evidence for the increased risk of specific populations to O_3-related health effects.

This chapter discusses the epidemiologic, controlled human exposure, and toxicological studies evaluated in Chapters 5, 6, and 7 that provide information on potential at-risk populations. The epidemiologic studies included in this chapter consist of only those studies that presented stratified results (e.g., males versus females or <65 years of age versus $\geq$ 65 years of age). This approach allowed for a comparison between populations exposed to similar O_3 concentrations and within the same study design. Numerous studies that focus on only one potentially at-risk population are described in previous chapters, but these studies are not discussed in detail in this chapter because of the lack of

an adequate comparison group within the study. Controlled human exposure studies that consisted of individuals with an underlying disease or genetic polymorphism, or studies that categorized the study population by age, race, etc., and toxicological studies that used animal models of disease were also evaluated for coherence and biological plausibility.

Factors examined that may lead to increased risk of O_3-related health effects based on the overall evidence integrated across disciplines are described in greater detail in the following sections.

8.1 Preexisting Disease/Conditions

Individuals with certain preexisting diseases are likely to constitute an at-risk population. Previous O_3 AQCDs concluded that some people with preexisting pulmonary disease, especially asthma, are among those at increased risk from O_3 exposure. Extensive toxicological evidence was available indicating that altered physiological, morphological and biochemical states typical of respiratory diseases, such as asthma, COPD, and chronic bronchitis, may render people sensitive to additional oxidative burden induced by O_3 exposure. In addition, a number of epidemiologic studies found that some individuals with respiratory diseases are at increased risk of O_3-related effects. Little evidence, however, was available on the potential for increased risk for people with other preexisting conditions, such as cardiovascular diseases.

Recent studies that examined whether preexisting diseases and conditions lead to increased risk of O_3-induced health effects were identified and are summarized below. Table 8-1 displays the prevalence rates of some of these conditions categorized by age and region among adults in the U.S. population; data for children, when available, are presented within sections. Substantial proportions of the U.S. population are affected by these conditions and therefore may represent a potentially large at-risk population. While these diseases and conditions are intrinsic to individuals, the pathways to their development may have intrinsic or extrinsic origins.

Table 8-1 Prevalence of respiratory diseases, cardiovascular diseases, and diabetes among adults by age and region in the U.S.

		Adults							
	N (in thousands)	Age				Region			
Chronic Disease/Condition		18-44	45-64	65-74	75+	Northeast	Midwest	South	West
Respiratory Diseases									
Asthma[a]	28,260	13.5	12.0	12.0	10.0	12.8	13.4	11.2	13.9
COPD									
Chronic Bronchitis	9,832	3.2	5.5	5.9	5.3	3.4	4.8	5.2	2.9
Emphysema	3,789	0.2	2.0	5.7	5.0	1.2	1.9	1.9	1.3
Cardiovascular Diseases									
All Heart Disease	26,628	4.6	12.3	26.7	39.2	11.3	12.7	12.2	9.9
Coronary Heart Disease	14,428	1.1	6.7	16.9	26.7	5.7	6.5	7.3	4.9
Hypertension	56,159	8.7	32.5	54.4	61.1	22.9	24.1	27.1	20.6
Diabetes	18,651	2.3	12.1	20.4	17.3	4.5	7.6	9.0	7.7

[a]Asthma prevalence is reported for "ever had asthma"

Source: Statistics for adults: Pleis et al. (2009)

8.1.1 Influenza/Infections

Recent studies have indicated that underlying infections may increase the risk of individuals to O_3-related health effects, although there are only a limited number of studies. A study of hospitalizations in Hong Kong reported that increased levels of influenza intensity resulted in increased excess risk of respiratory disease hospitalizations related to O_3 exposure (Wong et al., 2009). In addition, a study of lung function in asthmatic children reported decreases in lung function with increased short-term O_3 exposure for those with upper respiratory infections but not for those without infections (Lewis et al., 2005). Toxicological studies provide biological plausibility for the increase in O_3-induced health effects observed in epidemiologic studies that examined infections. Toxicological studies demonstrated that 0.08 ppm O_3 increased streptococcus-induced mortality, regardless of whether O_3 exposure precedes or follows infection (Miller et al., 1978; Coffin and Gardner, 1972; Coffin et al., 1967). Ozone exposure likely impairs host defenses, which may increase mortality due to an infectious agent. However, there is little toxicological evidence that infection or influenza itself renders an individual at greater risk of an O_3-induced health effect.

8.1.2 Asthma

Previous O_3 AQCDs identified individuals with asthma as a population at risk for O_3-related health effects. Within the U.S., approximately 12% of adults have reported ever

having asthma (Pleis et al., 2009). The prevalence of asthma is approximately 7.2%. 16.2%, and 16.6% among U.S. children aged 0-4, 5-11, and 12-17, respectively (Bloom et al., 2008).

Multiple epidemiologic studies included within this ISA have evaluated the potential for increased risk of O_3-related health effects among individuals with asthma. A study of lifeguards in Texas reported decreased lung function with short-term O_3 exposure among both individuals with and without asthma, however, the decrease was greater among those with asthma (Thaller et al., 2008). A Mexican study of children ages 6-14 detected an association between short-term O_3 and wheeze, cough, and bronchodilator use among asthmatics but not non-asthmatics, although this may have been the result of a small non-asthmatic population (Escamilla-Nuñez et al., 2008). A study of the modification of the effect of greater O_3 associated decreases in short-term O_3 exposure on lung function by airway hyperresponsiveness (AHR) (a condition common among asthmatics) reported greater O_3-associated decreases in lung function in elderly individuals with AHR, especially among those who were obese (Alexeeff et al., 2007). However, no evidence for increased risk was found in a study performed among children in Mexico City that examined the effect of short-term O_3 exposure on respiratory health (Barraza-Villarreal et al., 2008). In this study, a positive association was reported for airway inflammation among asthmatic children, but the observed association was similar in magnitude to that of non-asthmatics. Similarly, a study of children in California reported an association between O_3 concentration and exhaled nitric oxide fraction (FeNO) that persisted both among children with and without asthma as well as those with and without respiratory allergy (Berhane et al., 2011). Finally, some studies have reported null results for both individuals with and without asthma. Khatri et al. (2009) found no association between short-term O_3 exposure and altered lung function for either asthmatic or non-asthmatic adults, but did note a decrease in lung function among individuals with allergies.

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

Controlled human exposure studies that have examined the effects of O_3 on both individuals with asthma and healthy controls are limited. Based on studies reviewed in the 1996 and 2006 O_3 AQCDs, subjects with asthma appeared to be more sensitive to acute effects of O_3 in terms of FEV_1 and inflammatory responses than healthy non-asthmatic subjects. For instance, Horstman et al. (1995) observed that mild-to-moderate asthmatics, on average, experienced double the O_3-induced FEV_1 decrement of healthy subjects (19% versus 10%, respectively, $p = 0.04$). Moreover, a statistically significant positive correlation between FEV_1 responses to O_3 exposure and baseline lung function was observed in individuals with asthma, i.e., responses increased with severity of disease. Minimal evidence exists suggesting that individuals with asthma have smaller O_3-induced FEV_1 decrements than healthy subjects (3% versus 8%, respectively) (Mudway et al., 2001). However, the asthmatics in that study also tended to be older than the healthy subjects, which could partially explain their lesser response since FEV_1 responses to O_3 exposure diminish with age. Individuals with asthma also had significantly more neutrophils in the BALF (18 hours postexposure) than similarly exposed healthy individuals (Peden et al., 1997; Scannell et al., 1996; Basha et al., 1994). Furthermore, one newer study examined the effects of O_3 on both individuals with atopic asthma and healthy controls (Hernandez et al., 2010). Greater numbers of neutrophils, higher levels of cytokines and hyaluronan, and greater expression of macrophage cell-surface markers were observed in induced sputum of atopic asthmatics compared with healthy controls. Differences in O_3-induced epithelial cytokine expression were noted in bronchial biopsy samples from asthmatics and healthy controls (Bosson et al., 2003). Cell-surface marker and cytokine expression results, and the presence of hyaluronan, are consistent with O_3 having greater effects on innate and adaptive immunity in these asthmatic individuals (see Section 5.4.2.2). In addition, older studies have demonstrated that O_3 exposure leads to increased bronchial reactivity to inhaled allergens in mild allergic asthmatics (Kehrl et al., 1999; Jorres et al., 1996) and to the influx of eosinophils in individuals with pre-existing allergic disease (Vagaggini et al., 2002; Peden et al., 1995). Taken together, these results point to several mechanistic pathways which could account for the enhanced sensitivity to O_3 in subjects with asthma (see Section 5.4.2.2).

Toxicological studies provide biological plausibility for greater effects of O_3 among those with asthma or AHR. In animal toxicological studies, an asthmatic phenotype is modeled by allergic sensitization of the respiratory tract. Many of the studies that provide evidence that O_3 exposure is an inducer of AHR and remodeling utilize these types of animal models. For example, a series of experiments in infant rhesus monkeys have shown these effects, but only in monkeys sensitized to house dust mite allergen (Fanucchi et al., 2006; Joad et al., 2006; Schelegle et al., 2003). Similarly, Funabashi et al. (2004) demonstrated adverse changes in pulmonary function in mice exposed to O_3, and Wagner

et al. (2007) demonstrated enhanced inflammatory responses in rats exposed to O_3, but only in animals sensitized to allergen. In general, it is the combined effects of O_3 and allergic sensitization which result in measurable effects on pulmonary function. In a bleomycin induced pulmonary fibrosis model, exposure to 250 ppb O_3 for 5 days increased pulmonary inflammation and fibrosis, along with the frequency of bronchopneumonia in rats. Thus, short-term exposure to O_3 may enhance damage in a previously injured lung (Oyarzún et al., 2005).

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

8.1.3 Chronic Obstructive Pulmonary Disease (COPD)

Although not extensively examined in the literature, initial evidence suggests that preexisting COPD may modify the association between short-term O_3 exposure and cardiovascular-related health effects. In the U.S. over 4% of adults report having chronic bronchitis and almost 2% report having emphysema, both of which are classified as COPD (Pleis et al., 2009).

In a recent study, Peel et al. (2007) found that individuals with COPD were at increased risk of cardiovascular ED visits in response to short-term O_3 exposure compared to healthy individuals in Atlanta, GA. The authors reported that short-term O_3 exposure was associated with higher odds of an ED visit for peripheral and cerebrovascular disease among individuals with COPD compared to individuals without COPD. However, preexisting COPD did not increase the odds of hospitalization for all CVD outcomes (i.e. IHD, dysrhythmia, or congestive heart failure). In an additional study performed in Taiwan, both individuals with and without COPD had higher odds of congestive heart failure associated with O_3 exposure on warm days (Lee et al., 2008a). An additional study also found no association between O_3 exposure and lung function regardless of whether the study participant had COPD or other health issues (asthma or IHD) (Lagorio et al., 2006).

Recent epidemiologic evidence indicates that persons with COPD may have increased O_3-related cardiovascular effects, but little information is available for other O_3-related health effects among individuals with COPD.

8.1.4 Cardiovascular Disease

Cardiovascular disease (CVD) has become increasingly prevalent in the U.S., with about 12% of adults reporting a diagnosis of heart disease (Table 8-1). A high prevalence of other cardiovascular-related conditions has also been observed, such as hypertension which is prevalent among approximately 24% of adults. In the 2006 O_3 AQCD, little evidence was available regarding preexisting CVD as a susceptibility factor. Recent epidemiologic studies have examined cardiovascular-related diseases as modifiers of the O_3-outcome associations; however, no recent evidence is available from controlled human exposure studies or toxicological studies.

Peel et al. (2007) compared the associations between short-term O_3 exposure and cardiovascular ED visits in Atlanta, GA among multiple comorbid conditions. The authors found no evidence of increased risk of cardiovascular ED visits in individuals previously diagnosed with dysrhythmia, congestive heart failure, or hypertension compared to healthy individuals. Similarly, a study in France examined the association between O_3 concentrations and ischemic cerebrovascular events (ICVE) and myocardial infarction (MI) and the influence of multiple vascular risk factors on any observed associations (Henrotin et al., 2010). The association between O_3 exposure and ICVE was elevated for individuals with multiple risk factors, specifically individuals with diabetes or hypertension. For the association between O_3 and MI, increased odds were apparent only for those with hypercholesterolaemia. In a study conducted in Taiwan, a positive

association was observed for O_3 on warm days and congestive heart failure hospital admissions (HAs), but the association did not differ between individuals with/without hypertension or with/without dysrhythmia (Lee et al., 2008a). Another study in Taiwan reported that the association between O_3 levels and ED visits for arrhythmias were greater on warm days among those with congestive heart failure compared to those without congestive heart failure; however, the estimate and 95% CIs for those without congestive heart failure is completely contained within the 95% CI of those with congestive heart failure (Chiu and Yang, 2009).

Although not studied extensively, a study has examined the increased risk of O_3-related changes in blood markers for individuals with CVD. There was a greater association between O_3 exposure and some, but not all, blood inflammatory markers among individuals with a history of CVD. Liao et al. (2005) found that fibrinogen was positively associated with short-term O_3 exposure but this association was present only among individuals with a history of CVD. No association was observed among those without a history of CVD. However, for another biomarker (vWF), CVD status did not modify the positive association with short-term O_3 exposure (Liao et al., 2005).

Mortality studies provide some evidence for a potential increase in O_3-induced mortality in individuals with preexisting atrial fibrillation and atherosclerosis. In a study of 48 U.S. cities, increased risk of mortality with short-term O_3 exposure was observed only among individuals with secondary atrial fibrillation (Medina-Ramón and Schwartz, 2008). No association was observed for short-term O_3 exposure and mortality in a study of individuals with diabetes with or without CVD prior to death; however, there was some evidence of increased risk of mortality during the warm season if individuals had diabetes and atherosclerosis compared to only having diabetes (Goldberg et al., 2006).

Finally, although not extensively examined, a study explored whether a preexisting CVD increased the risk of an O_3-induced respiratory effect. Lagorio et al. (2006) examined the effect of O_3 exposure on lung function among participants with a variety of preexisting diseases, including IHD. No association was observed regardless of whether the participant had IHD.

Overall, most short-term exposure studies did not report increased O_3-related health effects for individuals with preexisting CVD, with the possible exception of O_3 exposure and mortality. Future research among those with CVD compared to those without will increase the understanding of potential increased risk of O_3-related health effects among this group.

8.1.5 Diabetes

Recent literature has not extensively examined whether individuals with diabetes (about 8% of U.S. adults) are potentially at increased risk of O_3-related health effects. In a study of short-term O_3 exposure and cardiovascular ED visits in Atlanta, GA, no association was observed for individuals with or without diabetes (Peel et al., 2007). A similar study conducted in Taiwan reported a positive association between O_3 exposure on warm days and HAs for congestive heart failure; however, no modification of the association by diabetes was observed (Lee et al., 2008a). Finally, in a study of O_3 exposure and ED visits for arrhythmia in Taiwan, there was no evidence of effect measure modification by diabetes on warm or cool days (Chiu and Yang, 2009).

8.1.6 Hyperthyroidism

Hyperthyroidism has been identified in toxicological studies as a potential factor that may lead to increased risk of O_3-related health effects but has not yet been explored in epidemiologic or controlled human exposure studies. Lung damage and inflammation due to oxidative stress may be modulated by thyroid hormones. Compared to controls, hyperthyroid rats exhibited elevated levels of BAL neutrophils and albumin after a 4-hour exposure to O_3, indicating O_3-induced inflammation and damage. Hyperthyroidism did not affect production of reactive oxygen or nitrogen species, but BAL phospholipids were increased, indicating greater activation of Type II cells and surfactant protein production compared to normal rats (Huffman et al., 2006). Thus, this study provides some underlying evidence which suggests that individuals with hyperthyroidism may represent an at-risk population.

8.2 Lifestage

The 1996 and 2006 O_3 AQCDs identified children, especially those with asthma, and older adults as at-risk populations. These previous AQCDs reported clinical evidence that children have greater spirometric responses to O_3 than middle-aged and older adults (U.S. EPA, 1996a). Similar results were observed for symptomatic responses and O_3 exposure. Among older adults, most studies reported in the 2006 O_3 AQCD reported greater effects of short-term O_3 exposure and mortality compared to other age groups. New evidence, summarized below, further supports these findings.

8.2.1 Children

The 2000 Census reported that 28.6% of the U.S. population was under 20 years of age, with 14.1% under the age of 10 (SSDAN CensusScope, 2010a). Children are considered to be more at risk for O_3-related health effects compared to adults because they spend more time outside and are more highly active, especially during the summer when O_3 concentrations are the highest (U.S. EPA, 2006b). Moreover, children's respiratory systems are undergoing lung growth until about 18-20 years of age and are therefore thought to be intrinsically more at risk for O_3-induced damage (U.S. EPA, 2006b).

The 1996 O_3 AQCD, reported clinical evidence that children, adolescents, and young adults (<18 years of age) appear, on average, to have nearly equivalent spirometric responses to O_3 exposure, but have greater responses than middle-aged and older adults (U.S. EPA, 1996a). Sycalmptomatic responses (e.g., cough, shortness of breath, pain on deep inspiration) to O_3 exposure, however, appear to increase with age until early adulthood and then gradually decrease with increasing age (U.S. EPA, 1996a). For subjects aged 18-36 years, McDonnell et al. (1999) reported that symptom responses from O_3 exposure also decrease with increasing age. Complete lung growth and development is not achieved until 18-20 years of age in women and the early 20s for men; pulmonary function is at its maximum during this time as well. Additionally, PBPK modeling reported regional extraction of O_3 to be higher in infants compared to adults. This is thought to be due to the smaller nasal and pulmonary regions' surface area in children under the age of 5 years compared to the total airway surface area observed in adults (Sarangapani et al., 2003).

Recent epidemiologic studies have been performed examining different age groups and their susceptibility to O_3-related respiratory HAs and emergency department (ED) visits. A study in Cyprus of short-term O_3 concentrations and respiratory HA detected possible effect measure modification by age with a larger association among individuals < 15 years of age compared with those > 15 years of age. However, this difference was only apparent with a 2-day lag (Middleton et al., 2008). Similarly, a Canadian study of asthma-ED visits reported the strongest O_3-related associations among 5- to 14-year olds compared to the other age groups (ages examined 0-75+) (Villeneuve et al., 2007). Greater O_3-associated change in asthma-related ED visits were also reported among children (<15 years) as compared to adults (15 to 64 years) in a study from Finland (Halonen et al., 2009). A study of New York City HAs demonstrated an increase in the association between O_3 exposure and asthma-related HAs for 6- to 18-year olds compared to those < 6 years old and those > 18 years old (Silverman and Ito, 2010). When examining long-term O_3 exposure and asthma HA among children, associations were determined to be larger among children 1 to 2 years old compared to children 2 to 6

years old (Lin et al., 2008b). A few studies reported positive associations among both children and adults and no modification of the effect by age. A study performed in Hong Kong examined O_3 exposure and asthma-related HAs for ages 0 to14, 15 to 65, and >65 (Ko et al., 2007). The researchers reported that the association was greater among the 0 to 14 and 14 to 65 age groups compared to the >65 age group. Another study looking at asthma-related ED visits and O_3 exposure in Maine reported positive associations for all age groups (ages 2 to 65) (Paulu and Smith, 2008). Effects of O_3 exposure on asthma hospitalizations among both children and adults (<18 and ≥18 years old) were demonstrated in a study in Washington, but only children (<18 years of age) had statistically significant results at lag day 0, which the authors wrote, "suggests that children are more immediately responsive to adverse effects of O_3 exposure" (Mar and Koenig, 2009).

The evidence observed in epidemiologic studies is supported by recent toxicological studies which observed O_3-induced health effects in immature animals. Early life exposures of multiple species of laboratory animals, including infant monkeys, resulted in changes in conducting airways at the cellular, functional, ultra-structural, and morphological levels. Carey et al. (2007) conducted a study of O_3 exposure in infant rhesus macaques, whose nasal airways closely resemble that of humans. Monkeys were exposed either acutely for 5 days to 0.5 ppm O_3, or episodically for 5 biweekly cycles alternating 5 days of 0.5 ppm O_3 with 9 days of filtered air, designed to mimic human exposure (70 days total). All monkeys acutely exposed to O_3 had moderate to marked necrotizing rhinitis, with focal regions of epithelial exfoliation, numerous infiltrating neutrophils, and some eosinophils. The distribution, character, and severity of lesions in episodically exposed monkeys were similar to that of acutely exposed animals. Neither group exhibited mucous cell metaplasia proximal to the lesions, a protective adaptation observed in adult monkeys exposed continuously to 0.3 ppm O_3 in another study (Harkema et al., 1987a). Functional (increased airway resistance and responsiveness with antigen + O_3 co-exposure) and cellular changes in conducting airways (increased numbers of inflammatory eosinophils) also manifested among the infant monkeys (Plopper et al., 2007). In addition, the lung structure of the conducting airways was significantly stunted or altered versus control animals and this aberrant development was persistent 6 months postexposure (Fanucchi et al., 2006).

Similarly, rat fetuses exposed to O_3 in utero had significant ultrastructural changes in bronchiolar epithelium when examined near the end of gestation (López et al., 2008). In addition, exposure of mice to mixtures of air pollutants early in development affected pup lung cytokine levels (TNF, IL-1, KC, IL-6, and MCP-1) (Auten et al., 2009). In utero exposure of animals to PM augmented O_3-induced airway hyper-reactivity in these pups as juveniles.

Age may affect the inflammatory response to O_3 exposure. In comparing neonatal mice to adult mice, increased bronchoalveolar lavage (BAL) neutrophils were observed in four strains of neonates 24 hours after exposure to 0.8 ppm O_3 for 5 hours (Vancza et al., 2009). Three of these strains also exhibited increased BAL protein, although the two endpoints were not necessarily consistently correlated in a given strain. In some strains, however, adults were more sensitive, indicating a strain-age interaction. Toxicological studies reported that the difference in effects among younger lifestage may be due to age-related changes in endogenous antioxidants and sensitivity to oxidative stress. A recent study demonstrated that 0.25 ppm O_3 exposure differentially alters expression of metalloproteinases in the skin of young (8 weeks old) and aged (18 months old) mice, indicating age-related susceptibility to oxidative stress (Fortino et al., 2007). Valacchi et al. (2007) found that aged mice had more vitamin E in their plasma but less in their lungs compared to young mice, which may affect their pulmonary antioxidant defenses. Servais et al. (2005) found higher levels of oxidative damage indicators in immature (3 weeks old) and aged (20 months old) rats compared to adult rats, which were relatively resistant to an intermittent 7-day exposure to 0.5 ppm O_3. Immature rats exhibited a higher ventilation rate, which may have increased exposure. Additionally, a series of toxicological studies reported an association between O_3 exposure and bradycardia that was present among young mice but not among older mice (Hamade et al., 2010; Tankersley et al., 2010; Hamade and Tankersley, 2009; Hamade et al., 2008). Regression analysis revealed a significant interaction between age and strain on heart rate, which implies that aging may affect heart rate differently between mouse strains (Tankersley et al., 2010). The authors proposed that the genetic differences between the mice strains could be altering the formation of ROS, which tends to increase with age, thus modulating the changes in cardiopulmonary physiology after O_3 exposure.

The previous and current human clinical and toxicological studies reported evidence of increased risk from O_3 exposure for younger ages, which provides coherence and biological plausibility to the epidemiologic studies on children. Recent studies of respiratory HAs and ED visits observed inconsistent findings for associations among children and young adults, although generally studies reported positive associations among both children and adults or just among children. For other outcomes, there were also inconsistent findings regarding increased risk of O_3-related health effects. The interpretation of these studies is limited by the lack of consistency in comparison age groups and outcomes examined.

8.2.2 Older Adults

Older adults may be at greater risk of health effects associated with O_3 exposure through a variety of intrinsic pathways. The gradual decline in physiological processes that occur with aging may lead to increased risk of O_3-related health effects (U.S. EPA, 2006a). Older adults may also differ in amounts of exposure because diminished symptomatic responses may allow the elderly to withstand increased continued O_3 exposure. In addition, older adults, in general, have a higher prevalence of preexisting diseases compared to younger age groups and this may also lead to increased susceptibility to O_3-related health effects (see Table 8-1 that gives preexisting rates by age).With the number of older Americans increasing in upcoming years (estimated to increase from 12.4% of the U.S. population to 19.7% between 2000 to 2030, which is approximately 35 million and 71.5 million individuals, respectively) this group represents a large population potentially at risk of O_3-related health effects (SSDAN CensusScope, 2010a; U.S. Census Bureau, 2010).

Multiple epidemiologic studies of O_3 exposure and HAs were stratified by age groups. A positive association was reported between O_3 levels and respiratory HAs for adults ≥65 years old but not for those adults aged 15 to 64 years (Halonen et al., 2009). In the same study, no association was observed between O_3 concentration and respiratory mortality among those ≥65 years old or those 15 to 64 years old; however, an inverse association between O_3 concentration and cardiovascular mortality was present among individuals ≥ 65 years old but not among individuals < 65 years old. This inverse association among those ≥65 years old persisted when examining HAs for coronary heart disease. A study of CVD-related hospital visits in Bangkok, Thailand reported an increase in percent change for hospital visits with previous day and cumulative 2-day O_3 levels among those ≥ 65 years old, whereas no association was present for individuals less than 65 years of age (Buadong et al., 2009). No association was observed for current day or cumulative 3-day averages in any age group. A study examining O_3 and HAs for CVD-related health effects reported no association for individuals aged 15 to 64 or individuals aged ≥ 65 years, although one lag-time did show an inverse effect for coronary heart disease among elderly that was not present among 15- to 64-year olds (Halonen et al., 2009). No modification by age (40 to 64 year olds versus >64 year olds) was observed in a study from Brazil examining O_3 levels and COPD ED visits (Arbex et al., 2009).

The majority of recent studies reported greater effects of short-term O_3 exposure and mortality among older adults, which is consistent with the findings of the 2006 O_3 AQCD. A study conducted in 48 cities across the U.S. reported larger effects among adults ≥65 years old compared to those < 65 years (Medina-Ramón and Schwartz, 2008). Further investigation of this study population revealed no association between O_3

exposure and mortality until age 50 and a reduced effect after age 80 (Zanobetti and Schwartz, 2008a). A study of 7 urban centers in Chile reported similar results, with greater effects in adults ≥65 years old, however the effects were smaller among those ≥85 years old compared to those in the 75 to 84 years old age range (Cakmak et al., 2007). More recently, a study conducted in the same area reported similar associations between O_3 exposure and mortality in adults aged < 64 years old and 65 to 74 years old, but the risk was increased among older age groups (Cakmak et al., 2011). A study performed in China reported greater effects in populations ≥45 years old (compared to 5 to 44 year olds), with statistically significant effects present only among those ≥65 years old (Kan et al., 2008). An Italian study reported higher risk of all-cause mortality associated with increased O_3 concentrations among individuals ≥85 year old as compared to those 35 to 84 years old. Those 65 to 74 and 75 to 84 years old did not show a greater increase in risk compared to those aged 35 to 64 years (Stafoggia et al., 2010). The Air Pollution and Health: A European and North American Approach (APHENA) project examined the association between O_3 exposure and mortality for those <75 and ≥ 75 years of age. In Canada, the associations for all-cause and cardiovascular mortality were greater among those ≥75 years old in the summer-only and all-year analyses. Age groups were not compared in the analysis for respiratory mortality in Canada. In the U.S., the association for all-cause mortality was slightly greater for those <75 years of age compared to those ≥75 years old in summer-only analyses. No consistent pattern was observed for CVD mortality. In Europe, slightly larger associations for all-cause mortality were observed in those <75 years old in all-year and summer-only analyses. Larger associations were reported among those <75years for CVD mortality in all-year analyses, but the reverse was true for summer-only analyses (Katsouyanni et al., 2009).

Biological plausibility for increased risk among older adults is provided by clinical and toxicological studies. Respiratory symptom responses to O_3 exposure appears to increase with age until early adulthood and then gradually decrease with increasing age (U.S. EPA, 1996a), which may put them at increased risk by withstanding continued O_3 exposure. Regarding cardiac outcomes, biological plausibility is provided by a toxicological study. O_3 exposure resulted in an increase in left ventricular chamber dimensions at end diastole (LVEDD) in young and old mice, whereas decreases in left ventricular posterior wall thickness at end systole (PWTES) were only observed among older mice (Tankersley et al., 2010). Other toxicological studies also indicate increased susceptibility in older animals for some endpoints. The hippocampus, one of the main regions affected by age-related neurodegenerative diseases, may be more sensitive to oxidative damage in aged rats. In a study of young (47 days) and aged (900 days) rats exposed to 1 ppm O_3 for 4 hours, O_3-induced lipid peroxidation occurred to a greater extent in the striatum of young rats, whereas it was highest in the hippocampus in aged rats (Rivas-Arancibia et al., 2000). In young mice, healing of skin wounds is not

significantly affected by O_3 exposure (Lim et al., 2006). However, exposure to 0.5 ppm O_3 for 6 h/day significantly delays wound closure in aged mice.

Although some outcomes reported mixed findings regarding an increase in risk for older adults, recent studies of O_3 exposure and mortality reported associations present for older adults. This is consistent with the results reported in the 2006 O_3 AQCD.

8.3 Sex

The distribution of males and females in the U.S. is similar. In 2000, 49.1% of the U.S. population was male and 50.9% were female. The distribution did vary by age with a greater prevalence of females ≥65 years old compared to males (SSDAN CensusScope, 2010a). The 2006 O_3 AQCD did not report evidence of differences between the sexes in health responses to O_3 exposure. Recent epidemiologic studies have evaluated the effects of short-term and long-term exposure to O_3 on multiple health endpoints stratified by sex and overall, the results are inconsistent.

A study in Maine that examined short-term O_3 concentrations and asthma ED visits detected greater effects among males ages 2 to14 years and among females ages 15 to 34 years compared to males and females in the same age groups (no difference was detected for males and females aged 35 to 64) (Paulu and Smith, 2008). A Canadian study reported no associations between short-term O_3 and respiratory infection HAs for either boys or girls under the age of 15 (Lin et al., 2005), whereas another Canadian study reported a slightly higher but non-statistically significant increase in respiratory HA for males (mean ages 47.6 to 69.0 years) (Cakmak et al., 2006b). A recent study from Hong Kong examining individuals of all ages reported no effect measure modification by sex for overall respiratory disease HAs, but did detect a greater excess risk of HAs for COPD among females compared to males (Wong et al., 2009). Similarly a study in Brazil found higher effect estimates for COPD ED visits among females compared to males (Arbex et al., 2009). Higher levels of respiratory HA with greater O_3 concentrations was also observed for females in a study of individuals living in Cyprus (Middleton et al., 2008). A study of lung function unrelated to HA and ED visits was conducted among lifeguards in Texas and reported decreased lung function with increased O_3 exposure among females but not males (Thaller et al., 2008). This study included individuals aged 16 to 27 years, and the majority of participants were male. A New York study found no effect measure modification of the association between long-term O_3 exposure and asthma HA among males and females between 1 and 6 years old (Lin et al., 2008b).

In addition to examining the potential modification of O_3 associations with respiratory outcomes by sex, studies also examined cardiovascular-related outcomes specifically

HAs and ED visits. All of these studies reported no effect modification by sex with some studies reporting null associations for both males and females (Wong et al., 2009; Middleton et al., 2008; Villeneuve et al., 2006a) and one study reporting a positive associations for both sexes (Cakmak et al., 2006a). A French study examining the associations between O_3 concentrations and risk of ischemic strokes (not limited to ED visits or HAs) reported no association for either males or females with lags of 0, 2, or 3 days (Henrotin et al., 2007). A positive association was reported for males with a lag of 1 day, but this association was null for females. The authors noted that men in the study had much higher rates of current and former smoking than women (67.4% versus 9.3%).

A biomarker study investigating the effects of O_3 concentrations on high-sensitivity C-reactive protein (hs-CRP), fibrinogen, and white blood cell (WBC) count, reported observations for various lag times ranging from 0 to 7 days (Steinvil et al., 2008). Most of the associations were null for males and females although one association between O_3 and fibrinogen was positive for males and null for females (lag day 4); however, this positive association was null or negative when other pollutants were included in the model. Only one study examining correlations between O_3 levels and oxidative DNA damage examined results stratified by sex. In this study Palli et al. (2009) reported stronger correlations for males than females, both during short-term exposure (less than 30 days) and long-term exposure (0-90 days). However, the authors commented that this difference could have been partially explained by different distributions of exposure to traffic pollution at work.

A few studies have examined the association between short-term O_3 concentrations and mortality stratified by sex and in contrast with studies of other endpoints, were more consistent in reporting elevated risks among females. These studies, conducted in the U.S. (Medina-Ramón and Schwartz, 2008), Italy (Stafoggia et al., 2010), and Asia (Kan et al., 2008), reported larger effect estimates in females compared to males. In the U.S. study, the elevated risk of mortality among females was greater specifically among those ≥60 years old (Medina-Ramón and Schwartz, 2008). However, a recent study in Chile reported similar associations between O_3 exposure and mortality among both men and women (Cakmak et al., 2011). One long-term O_3 exposure study of respiratory mortality stratified their results by sex and reported relative risks of 1.01 (95 % CI: 0.99, 1.04) for males and 1.04 (95% CIs 1.03, 1.07) for females (Jerrett et al., 2009).

Experimental research provided a further understanding of the underlying mechanisms that may explain a possible differential risk in O_3-related health effects among males and females. Several studies have suggested that physiological differences between sexes may predispose females to a greater susceptibility to O_3. In females, lower plasma and nasal lavage fluid (NLF) levels of uric acid (most prevalent antioxidant), the initial

defense mechanism of O_3 neutralization, may be a contributing factor (Housley et al., 1996). Consequently, reduced absorption of O_3 in the upper airways of females may promote its deeper penetration. Dosimetric measurements have shown that the absorption distribution of O_3 is independent of sex when absorption is normalized to anatomical dead space (Bush et al., 1996). Thus, a differential removal of O_3 by uric acid seems to be minimal. In general, the physiologic response of young healthy females to O_3 exposure appears comparable to the response of young males (Hazucha et al., 2003). A few studies have examined changes in O_3 responses during various menstrual cycle phases. Lung function response to O_3 was enhanced during the follicular phase of the menstrual cycle compared to the luteal phase in a small study of women (Fox et al., 1993). However, Seal et al. (1996) later reported no effect of menstrual cycle phase in their analysis of responses from 150 women, but conceded that the methods used by Fox et al. (1993) more precisely defined the menstrual cycle phase. Another study also reported no difference in responses among females during the follicular and luteal phases of their cycle (Weinmann et al., 1995a). Additionally, in this study the responses in women were comparable to those reported for men in the study. In a toxicological study, small differences in effects by sex were seen in adult mice with respect to pulmonary inflammation and injury after a 5-h exposure to 0.8 ppm O_3, and although adult females were generally more susceptible, these differences were strain-dependent, with some strains exhibiting greater susceptibility in males (Vancza et al., 2009). The most obvious sex difference was apparent in lactating females, which incurred the greatest lung injury or inflammation among several of the strains.

Overall, results have varied, with recent evidence for increased risk for O_3-related health effects present for females in some studies and males in other studies. Most studies examining the associations O_3 and mortality report females to be at greater risk than males. Little evidence is available regarding a difference between the sexes for other outcomes. Inconsistent findings were reported on whether effect measure modification exists by sex for respiratory and cardiovascular HAs and ED visits.

8.4 Genetics

Multiple studies that examined the effect of short- and long-term O_3 exposure on respiratory function have focused on whether various gene profiles modify the effect of O_3 on various health effects. A study of wheeze in infants reported larger associations between short-term O_3 exposure and wheeze and difficulty breathing in infants whose mothers have asthma compared to infants of mothers without asthma, illustrating the potential for genetics to play a role in O_3-related health effects (Triche et al., 2006).

Multiple genes, including glutathione S-transferase Mu 1 (GSTM1) and tumor necrosis factor-α (TNF-α) were evaluated in the 2006 O_3 AQCD and found to have a "potential role… in the innate susceptibility to O_3." Studies performed since the 2006 O_3 AQCD have continued to examine the roles of GSTM1 and TNF-α on O_3-related health effects and have also examined other gene variants that may increase the risk of O_3-related health effects. Due to small sample sizes, many controlled human exposure studies are limited in their ability to test genes with low frequency and therefore, some genes important for O_3-related health effects may not have been examined.

Epidemiologic studies that examined the effects of short-term exposure to O_3 on lung function included analyses of potential gene-environment interactions. Romieu et al. (2006) reported an association between O_3 and respiratory symptoms that were larger among children with GSTM1 null or glutathione S-transferase P 1 (GSTP1) Val/Val genotypes. However, results suggested that O_3-associated decreases in lung function may be greater among children with GSTP1 Ile/Ile or Ile/Val compared to GSTP1 Val/Val. Alexeef et al. (2008) reported greater decreases in lung function among GSTP1 Val/Val adults than those with other genotypes. In addition, they detected greater decreases in lung function for adults with long GT dinucleotide repeats in heme-oxygenase-1 (HMOX1) promoters.

Several controlled human exposure studies have reported that genetic polymorphism of antioxidant enzymes may modulate pulmonary function and inflammatory response to O_3 challenge. It appears that healthy carriers of NAD(P)H quinone oxidoreductase 1 (NQO1) wild type (wt) in combination with GSTM1 null genotype had greater decreases in lung function parameters with exposure to O_3 (Bergamaschi et al., 2001). Adults with GSTM1 null only genotype did not show the same response to O_3. In contrast, asthmatic children with GSTM1 null genotype (Romieu et al., 2004a) were reported to have greater decreases in lung function in relation to O_3 exposure. In a similar study, Vagaggini et al. (2010) exposed mild-to-moderate asthmatics to O_3 during moderate exercise. In subjects with NQO1 wt and GSTM1 null, there was no evidence of changes in lung function or inflammatory responses to O_3. Kim et al. (2011) also recently conducted a study among young adults, about half of whom were GSTM1-null and half of whom were GSTM1-sufficient. They detected no difference in the FEV_1 responses to O_3 exposure by GSTM1 genotype.

In a study of healthy volunteers with GSTM1 sufficient (n=19; 24 ± 3) and GSTM1 null (n=16; 25 ± 5) genotypes exposed to 400 ppb O_3 for 2 hours with exercise, Alexis et al. (2009) found genotype effects on inflammatory responses but not lung function responses to O_3. At 4 hours post O_3 exposure, individuals with either GSTM1 genotype had significant increases in sputum neutrophils with a tendency for a greater increase in

GSTM1 sufficient than GSTM1 nulls. At 24 hours postexposure, neutrophils had returned to baseline levels in the GSTM1 sufficient individuals. In the GSTM1 null subjects, neutrophil levels increased from 4 to 24 hours and were significantly greater than both baseline levels and levels at 24 hours in the GSTM1 sufficient individuals. In addition, O_3 exposure increased the expression of the surface marker CD14 in airway neutrophils of GSTM1 null subjects compared with GSTM1 sufficient subjects. CD14 and TLR4 are co-receptors for endotoxin, and signaling through this innate immune pathway has been shown to be important for a number of biological responses to O_3 exposure in toxicological studies (Garantziotis et al., 2010; Hollingsworth et al., 2010; Hollingsworth et al., 2004; Kleeberger et al., 2000). Alexis et al. (2009) also demonstrated decreased numbers of airway macrophages at 4 and 24 hours following O_3 exposure in GSTM1 sufficient subjects. Airway macrophages in GSTM1 null subjects were greater in number and found to have greater oxidative burst and phagocytic capability than those of GSTM1 sufficient subjects. Airway macrophages and dendritic cells from GSTM1 null subjects exposed to O_3 expressed higher levels of the surface marker HLA-DR, again suggesting activation of the innate immune system. Since there was no FA control in the Alexis et al. (2009) study, effects of the exposure other than O_3 cannot be ruled out. In general, the findings between these studies are inconsistent and additional, better-controlled studies are needed to clarify the influence of genetic polymorphisms on O_3 responsiveness in humans.

Several epidemiologic studies of long-term O_3 exposure examined interactions with different gene variants, including GSTP1, HMOX1, and TNF-α using data from the Children's Health Study. A study among children reported a three-way interaction effect between Ile105 homozygotes of GSTP1, O_3 exposure, and playing more than two team sports, and new onset of asthma (Islam et al., 2009). Additionally, Islam et al. found that non-Hispanic white children with less than 23 repeats in the HMOX1 gene had decreased risk of new-onset asthma (Islam et al., 2008). ARG1 and ARG2 (encoded by arginases) modification were examined for the association between genotypes and new-onset asthma (Salam et al., 2009). Reduced asthma risk was observed among atopic children living in high O_3 concentration areas and having the ARG1 haplotypes. There was no difference in risk for children with ARG2 haplotypes. A decreased risk of bronchitic symptoms was observed among asthmatic children in low O_3 concentration areas with TNF-α variant G-308A (TNF-308GG genotype), a variant that may alter gene expression. There was no decrease in risk for children with this TNF-α variant and living in areas with high O_3 concentrations. Additionally, this modification for high and low levels of O_3 was not present among non-asthmatic children (Lee et al., 2009b). Wenten et al. (2009) observed increased risk of respiratory-related school absences among children with variants of catalase (CAT) and myeloperoxidase (MPO) genes, especially when the children were living in high O_3 concentration areas.

In general, toxicological studies have reported differences in cardiac and respiratory effects after O_3 exposure among different mouse strains, which alludes to differential risk among individuals due to genetic variability (Tankersley et al., 2010; Chuang et al., 2009; Hamade and Tankersley, 2009; Hamade et al., 2008). Thus strains of mice which are prone to or resistant to O_3-induced effects have been used to systematically identify candidate genes that may increase risk of O_3-related health effects. Genome wide linkage analyses have identified quantitative trait loci for O_3-induced lung inflammation and hyperpermeability on chromosome 17 (Kleeberger et al., 1997) and chromosome 4 (Kleeberger et al., 2000), respectively, using recombinant inbred strains of mice. More specifically, these studies found that Tnf (protein product is the inflammatory cytokine TNF-α) and Tlr4 (protein product is TLR4, involved in endotoxin responses) were candidate susceptibility genes (Kleeberger et al., 2000; Kleeberger et al., 1997). The TNF receptors 1 and 2 have also been found to play a role in injury, inflammation, and airway hyperreactivity in studies of O_3-exposed knockout mice (Cho et al., 2001). In addition to Tlr4, other innate immune pattern recognition signaling pathway genes, including Tlr2 and Myd88, appear to be important in responses to O_3, as demonstrated by Williams et al. (2007b). A role for the inflammatory cytokine IL-6 has been demonstrated in gene-deficient mice with respect to inflammation and injury, but not AHR (Johnston et al., 2005b; Yu et al., 2002). Mice deficient in IL-10, an anti-inflammatory cytokine, demonstrated increased pulmonary inflammation in response to O_3 exposure (Backus et al., 2010). Thus genes related to innate immune signaling and pro- and anti-inflammatory genes are important for O_3-induced responses.

Altered O_3 responses between mouse strains could be due to genetic variability in nuclear factor erythroid 2-related factor 2 (Nrf-2), suggesting a role for genetic differences in altering the formation of ROS (Hamade et al., 2010; Cho and Kleeberger, 2007). Additionally, some studies have reported O_3-related effects to vary by Inf-1 and Inf-2 quantitative trait loci (Tankersley and Kleeberger, 1994) and a gene coding for Clara cell secretory protein (CCSP) (Broeckaert et al., 2003; Wattiez et al., 2003). Other investigations in inbred mouse strains found that differences in expression of certain proteins, such as CCSP (Broeckaert et al., 2003) and MARCO (Dahl et al., 2007), are responsible for phenotypic characteristics, such as epithelial permeability and scavenging of oxidized lipids, respectively, which confer sensitivity to O_3.

Nitric oxide (NO), derived from activated macrophages, is produced upon exposure to O_3 and is thought to participate in lung damage. Mice deficient in the gene for inducible nitric oxide synthase (NOS2/NOSII/iNOS) are partially protected against lung injury (Kleeberger et al., 2001), and it appears that O_3-induced iNOS expression is tied to the TLR4 pathway described above. Similarly, iNOS deficient mice do not produce reactive nitrogen intermediates after O_3 exposure, in contrast to their wild-type counterparts, and

also produce less PGE2 comparatively (Fakhrzadeh et al., 2002). These gene-deficient mice were protected from O_3-induced lung injury and inflammation. In contrast, another study using a similar exposure concentration but longer duration of exposure found that iNOS deficient mice were more susceptible to O_3-induced lung damage (Kenyon et al., 2002). Therefore it is unclear whether inducible nitric oxide synthase plays a protective role or mediates damage.

Voynow et al. (2009) have shown that NQO1 deficient mice, like their human counterparts, are resistant to O_3-induced AHR and inflammation. NQO1 catalyzes the reduction of quinones to hydroquinones, and is capable of both protective detoxification reactions and redox cycling reactions resulting in the generation of reactive oxygen species. Reduced production of inflammatory mediators and cells and blunted AHR were observed in NQO1 null mice after exposure to 1 ppm O_3 for 3 hours. These results correlated with those from in vitro experiments in which human bronchial epithelial cells treated with an NQO1 inhibitor exhibited reduced inflammatory responses to exposure to 0.4 ppm O_3 for 5 hours. This study may provide biological plausibility for the increased biomarkers of oxidative stress and increased pulmonary function decrements observed in O_3-exposed individuals bearing both the wild-type NQO1 gene and the null GSTM1 gene (Corradi et al., 2002; Bergamaschi et al., 2001).

The role of TNF-α signaling in O_3-induced responses has been previously established through depletion experiments, but a more recent toxicological study investigated the effects of combined O_3 and PM exposure in transgenic TNF overexpressing mice. Kumarathasan et al. (2005) found that subtle effects of these pollutants were difficult to identify in the midst of the severe pathological changes caused by constitutive TNF-α overexpression. However, there was evidence that TNF transgenic mice were more susceptible to O_3/PM-induced oxidative stress, and they exhibited elevation of a serum creatine kinase after pollutant exposure, which may suggest potential systemic or cardiac related effects. Differential susceptibility to O_3 among inbred strains of animals does not seem to be dose dependent since absorption of ^{18}O in various strains of mice did not correlate with resistance or sensitivity (Vancza et al., 2009).

Defects in DNA repair mechanisms may also confer increased risk of O_3-related health effects. Cockayne syndrome, a rare autosomal recessive disorder in humans, is characterized by UV sensitivity abnormalities, neurological abnormalities, and premature aging. The same genetic defect in mice ($Csb^{-/-}$) makes them sensitive to oxidative stressors, including O_3. Kooter et al. (2007) demonstrated that $Csb^{-/-}$ mice produced significantly more TNF-α after exposure to 0.8 ppm O_3 than their wild-type counterparts. However, there were no significant differences in other markers of inflammation or lung

injury between the two strains of mice. Further discussion of candidate genes in the context of their respective signaling pathways can be found in Chapter 5.

Overall, multiple genes, such as GSTM1, GSTP1, HMOX-1, NQO1, and TNF-α, appear to potentially be involved in populations being more at-risk than others to the effects of O_3 exposure on health. Future studies of these and other genes in human populations will be important for determining the role of each genotype and its effect on risk. For NQO1 and TNF-α, biological plausibility is provided by toxicological studies. Additionally, studies of rodents have identified a number of other genes that may affect O_3-related health outcomes, but testing of these genes has not been performed in humans due to power limitations.

8.5 Diet

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

Epidemiologic studies have examined effect measure modification by diet and found evidence that certain dietary components are related to the effect O_3 has on respiratory outcomes. The most recent study examined fruit/vegetable intake and Mediterranean diet (Romieu et al., 2009). Increases in these food patterns, which have been noted for their high vitamins C and E and omega-3 fatty acid content, protected against O_3-related decreases in lung function among children living in Mexico City. Another study examined supplementation of the diets of asthmatic children in Mexico with vitamins C and E (Sienra-Monge et al., 2004). Associations were detected between short-term O_3 exposure and nasal airway inflammation among children in the placebo group but not in those receiving the supplementation. The authors concluded that "vitamin C and E supplementation above the minimum dietary requirement in asthmatic children with a low intake of vitamin E might provide some protection against the nasal acute inflammatory response to ozone."

The epidemiologic evidence is supported by controlled human exposure studies, which have shown that the first line of defense against oxidative stress is antioxidants-rich extracellular lining fluid (ELF) which scavenge free radicals and limit lipid peroxidation. Exposure to O_3 depletes the antioxidant level in nasal ELF probably due to scrubbing of O_3 (Mudway et al., 1999a); however, the concentration and the activity of antioxidant

enzymes either in ELF or plasma do not appear to be related to O_3 responsiveness (Samet et al., 2001; Avissar et al., 2000; Blomberg et al., 1999). Carefully controlled studies of dietary antioxidant supplementation have demonstrated some protective effects of α-tocopherol (a form of vitamin E) and ascorbate (vitamin C) on spirometric measures of lung function after O_3 exposure but not on the intensity of subjective symptoms and inflammatory response including cell recruitment, activation and a release of mediators (Samet et al., 2001; Trenga et al., 2001). Dietary antioxidants have also afforded partial protection to asthmatics by attenuating postexposure bronchial hyperresponsiveness (Trenga et al., 2001).

Toxicological studies provide evidence of biological plausibility to the epidemiologic and controlled human exposure studies. Wagner et al. (2009; 2007) have shown reductions in O_3-exacerbated nasal allergy responses in rats with γ-tocopherol treatment (a form of vitamin E). O_3-induced inflammation and mucus production were also inhibited by γ-tocopherol. Inconsistent results were observed in toxicological studies of vitamin C deficiency and O_3-induced responses. Guinea pigs deficient in vitamin C displayed only minimal injury and inflammation after exposure to O_3 (Kodavanti et al., 1995). A recent study in mice demonstrated a protective effect of β-carotene in the skin, where it limited the production of proinflammatory markers and indicators of oxidative stress induced by O_3 exposure (Valacchi et al., 2009). Deficiency of vitamin A, which has a role in regulating the maintenance and repair of the epithelial layer, particularly in the lung, appears to enhance the risk of O_3-induced lung injury (Paquette et al., 1996). Differentially susceptible strains that were fed a vitamin A sufficient diet were observed to have different tissue concentrations of the vitamin, potentially contributing to their respective differences in O_3-related outcomes. In addition to the studies of antioxidants, one toxicological study examined protein deficiency. Protein deficiency alters the levels of enzymes and chemicals in the brain involved with redox status; exposure to 0.75 ppm O_3 has been shown to differentially affect Na^+/K^+ ATPase, glutathione, and lipid peroxidation, depending on the nutritional status of the animal, but the significance of these changes is unclear (Calderon Guzman et al., 2006). There may be a protective effect of overall dietary restriction with respect to lung injury, possibly related to increased vitamin C in the lung surface fluid (Kari et al., 1997).

Epidemiologic studies find that individuals with diets deficient in vitamins E and C are at risk for O_3 -related health effects. This is supported by controlled human exposure and toxicological studies.

8.6 Body Mass Index and Physical Conditioning

Obesity, defined as a BMI of 30 kg/m^2 or greater, is an issue of increasing importance in the U.S., with self-reported rates of 26.7% in 2009, up from 19.8% in 2000 (Sherry et al., 2010). A few studies have been performed examining the association between BMI and O_3-related changes in lung function. An epidemiologic study reported decreased lung function with increased short-term O_3 exposure for both obese and non-obese subjects; however, the magnitude of the reduction in lung function was greater for those subjects who were obese (Alexeeff et al., 2007). Further decrements in lung function were noted for obese individuals with AHR. Controlled human exposure studies have also detected differential effects of O_3 exposure on lung function for individuals with varying BMIs. In a retrospective analysis of data from 541 healthy, nonsmoking, white males between the ages of 18-35 years from 15 studies conducted at the U.S. EPA Human Studies Facility in Chapel Hill, North Carolina, McDonnell et al. (2010) found that increased body mass index (BMI) was found to be associated with enhanced FEV_1 responses. The BMI effect was of the same order of magnitude but in the opposite direction of the age effect whereby FEV_1 responses diminish with increasing age. In a similar analysis, Bennett et al. (2007) found enhanced FEV_1 decrements following O_3 exposure with increasing BMI in a group of healthy, nonsmoking, women (BMI range 15.7 to 33.4), but not among healthy, nonsmoking men (BMI range 19.1 to 32.9). In the women, greater O_3-induced FEV_1 decrements were seen in individuals that were overweight/obese (BMI >25) compared normal weight (BMI from 18.5 to 25), and in normal weight compared to underweight (BMI <18.5). Even disregarding the five underweight women, a greater O_3 response in the overweight/obese category (BMI >25) was observed compared with the normal weight group (BMI from 18.5 to 24.9).

Studies in genetically and dietarily obese mice have shown enhanced pulmonary inflammation and injury with acute O_3exposure, but responses to longer exposures at a lower concentration appear to differ. A recent study found that obese mice are actually resistant to O_3-induced pulmonary injury and inflammation and reduced lung compliance following exposure to 0.3 ppm O_3 for 72 hours, regardless of whether obesity was genetic- or diet-induced (Shore et al., 2009).

In addition to studies of obesity, physical conditioning affects BMI and may also affect the risk of O_3-related health effects. The *2008 Summary of Health Statistics for U.S. Adults* from the CDC reported the prevalence of regular leisure-time physical activity as slightly above 30% for adults ≥18 years of age in the U.S. (Pleis et al., 2009). Forty-nine percent of individuals ≥65 years old reported no leisure-time physical activity. A study of effect measure modification by exercise habits ten years prior to death observed excess risk of mortality with increasing O_3 concentrations among individuals that never

exercised compared to individuals that exercised at least once a month for both adults ≥30 years of age and adults ≥65 years of age (Wong et al., 2007). No recent studies examining modification of O_3-related health effects by current physical activity were identified.

Multiple epidemiologic and human clinical studies have reported increased O_3-related respiratory health effects among obese individuals. Future research of the effect modification of the relationship between O_3 and other health-related outcomes besides respiratory health effects by BMI and studies examining the role of physical conditioning will advance understanding of obesity as a factor potentially increasing an individual's risk.

8.7 Socioeconomic Status

SES is often represented by personal or neighborhood SES, educational attainment, health insurance status, and other such factors. SES is indicative of such things as access to healthcare, quality of housing, and pollution gradient. Based on the 2000 Census data, 12.4% of Americans live in poverty (poverty threshold for family of four was $17,463) (SSDAN CensusScope, 2010c).

Multiple epidemiologic studies have reported individuals of low SES to have increased risk for the effects of short-term O_3 exposure on respiratory HAs and ED visits. A study performed in Korea examined the association between O_3 concentrations and asthma HA and reported larger effect estimates in areas of moderate and low SES compared with areas of high SES (SES was based on average regional insurance rates) (Lee et al., 2006). A Canadian study reported inverse effects of O_3 on respiratory HA and ED visits regardless of SES, measured by average census tract household income (Burra et al., 2009). In addition, a study conducted across 10 cities in Canada found the largest association between O_3 exposure and respiratory HA was among those with an educational level less than grade 9, but no consistent trend in the effect was seen across quartiles of income (Cakmak et al., 2006b). In New York State, larger associations between long-term O_3 exposure and asthma HA were observed among children of mothers who did not graduate from high school, whose births were covered by Medicaid/self-paid, or who were living in poor neighborhoods compared to children whose mothers graduated from high school, whose births were covered by other insurance, or who were not living in poor neighborhoods, respectively (Lin et al., 2008b).

The examination of the potential effects of SES on O_3-related cardiovascular health effects is relatively limited. A study conducted in Canada reported the association between short-term O_3 and ED visits for cardiac disease by quartiles of

neighborhood-level education and income. No effect measure modification was apparent for either measure of SES (Cakmak et al., 2006a).

Several studies were conducted that examined the modification of the relationship between short-term O_3 concentrations and mortality by SES. A U.S. multicity study reported that communities with a higher proportion of the population unemployed had higher mortality effect estimates (Bell and Dominici, 2008). A study in seven urban centers in Chile reported on modification of the association between O_3 exposure and mortality using multiple SES markers (Cakmak et al., 2011). Increased risk was observed among the categories of low SES for all measures (personal educational attainment, personal occupation, community income level). Additionally, the APHENA study, which examined the association between O_3 and mortality by percentage unemployed, reported a higher percent change in mortality with increased percent unemployed but this varied across the regions included in the study (U.S., Canada, Europe) (Katsouyanni et al., 2009). A Chinese study reported that the greatest effects between O_3 concentrations and mortality at lag day 0 were among individuals living in areas of high social deprivation (i.e. low SES), but this association was not consistent across lag days (at other lag times, the middle social deprivation index category had the greatest association) (Wong et al., 2008). However, another study in Asia comparing low to high educational attainment populations reported no evidence of greater mortality effects (total, CVD, or respiratory) (Kan et al., 2008). Additionally, a study in Italy reported no difference in risk of mortality among census-block level derived income levels (Stafoggia et al., 2010). A study of infant mortality in Mexico reported no association between O_3 concentrations and infant mortality among any of the three levels of SES determined using a socioeconomic index based on residential areas (Romieu et al., 2004b). Another study in Mexico reported a positive association between O_3 levels at lag 0 and respiratory-related infant mortality in only the low SES group (determined based on education, income, and household conditions across residential areas), but no association was observed in any of the SES groups with other lags (Carbajal-Arroyo et al., 2011).

Studies of O_3 concentrations and reproductive outcomes have also examined associations by SES levels. A study in California reported greater decreases in birth weight associated with full pregnancy O_3 concentration for those with neighborhood poverty levels of at least 7% compared with those in neighborhoods with less than 7% poverty (Morello-Frosch et al., 2010). However, no dose response was apparent and those with neighborhood poverty levels of 7-21% had greater decreases observed for the association than those living in areas with poverty rates of at least 22%. An Australian study reported an inverse association between O_3 exposure during days 31-60 of gestation and abdominal circumference during gestation (Hansen et al., 2008). The interaction with SES (area-level measured socioeconomic disadvantage) was examined and although the

inverse association remained statistically significant in only the highest SES quartile, there were large confidence interval overlaps among estimates for each quartile so no difference in the association for the quartiles was apparent.

Evidence from a controlled human exposure study that examined O_3 effects on lung function does not provide support for greater O_3-related health effects in individuals of lower SES. In a follow-up study (Seal et al., 1993) on modification by race, Seal et al. (1996) reported that, of three SES categories, individuals in the middle SES category showed greater concentration-dependent decline in percent-predicted FEV_1 (4-5% at 400 ppb O_3) than in low and high SES groups. The authors did not have an "immediately clear" explanation for this finding and controlled human exposure studies are typically not designed to answer questions about SES.

Overall, most studies of individuals have reported that individuals with low SES and those living in neighborhoods with low SES are more at risk for O_3-related health effects, resulting in higher odds of respiratory HAs and ED visits. Inconsistent results have been observed in the few studies examining effect modification of associations between O_3 exposure and mortality and reproductive outcomes.

8.8 Race/Ethnicity

Based on the 2000 Census, 69.1% of the U.S. population comprises non-Hispanic whites. Approximately 12.1% of people reported their race/ethnicity as non-Hispanic black and 12.6% reported being Hispanic (SSDAN CensusScope, 2010b).

Two studies examined the associations between short-term O_3 concentrations and mortality and reported higher effect estimates among blacks (Medina-Ramón and Schwartz, 2008) and among communities with larger proportions of blacks (Bell and Dominici, 2008). Another study examined long-term exposure to O_3 concentrations and asthma HAs among children in New York State. These authors reported no statistically significant difference in the odds of asthma HA for blacks compared to other races but did detect higher odds for Hispanics compared to non-Hispanics (Lin et al., 2008b).

Additionally, recent epidemiologic studies have stratified by race when examining the association between O_3 concentration and birth outcomes. A study conducted in Atlanta, GA reported decreases in birth weight with increased third trimester O_3 concentrations among Hispanics but not among non-Hispanic whites (Darrow et al., 2011a). An inverse association was also present for non-Hispanic blacks but was not statistically significant. A California study reported that the greatest decrease in birth weight associated with full pregnancy O_3 concentration was among non-Hispanic whites (Morello-Frosch et al.,

2010). The inverse association was also apparent, although not as strong, for non-Hispanic blacks. Increased birth weight was associated with higher O_3 exposure among Hispanics and among non-Hispanic Asians and Pacific Islanders but neither of these results were statistically significant.

Similar to the epidemiologic studies, a controlled human exposure study suggested differences in lung function responses by race (Seal et al., 1993). The independent effects of sex-race group and O_3 concentration on lung function were positive, but the interaction between sex-race group and O_3 concentration was not statistically significant. The findings indicated some overall difference between the sex-race groups that was independent of O_3 concentration (the concentration-response curves for the four sex-race groups are parallel). In a multiple comparison procedure on data collapsed across all O_3 concentrations for each sex-race group, both black men and black women had larger decrements in FEV_1 than did white men. The authors noted that the O_3 dose per unit of lung tissue would be greater in blacks and females than whites and males, respectively. That this difference in tissue dose might have affected responses to O_3 cannot be ruled out. The college students recruited for the Seal et al. (1993) study were probably from better educated and more SES advantaged families, thus reducing potential for these variables to be confounding factors. Que et al. also examined pulmonary responses to O_3 exposure in blacks of African American ancestry and in whites. On average, the black males experienced the greatest decrements in FEV_1 following O_3 exposure. This decrease was larger than the decrement observed among black females, white males, and white females.

Overall, the results of recent studies suggest that there may be race-related increase in risk of O_3-related health effects for some outcomes, although the overall understanding of potential effect measure modification by race is limited by the small number of studies. Additionally, these results may be confounded by other factors, such as SES.

8.9 Smoking

Previous O_3 AQCDs have concluded that smoking does not increase the risk of O_3-related health effects; in fact, in controlled human exposure studies, smokers have been found to be at less risk of O_3-related health effects than non-smokers. Data from recent interviews conducted as part of the 2008 National Health Interview Survey (NHIS) (Pleis et al., 2009) have shown the rate of smoking among adults ≥18 years old to be approximately 20% in the U.S. Approximately 21% of individuals surveyed were identified as former smokers.

Baccarelli et al. (2007) performed a study of O_3 concentrations and plasma homocysteine levels (a risk factor for vascular disease). They found no interaction of smoking (smokers versus non-smokers) for the associations between O_3 concentrations and plasma homocysteine levels. Another study examined the association between O_3 and resting heart rate and also reported no interaction with smoking status (current smokers versus current non-smokers) (Ruidavets et al., 2005a).

A study examining correlations between O_3 levels and oxidative DNA damage examined results stratified by current versus never and former smokers (Palli et al., 2009). Ozone was positively associated with DNA damage for short-term and long-term exposures among never/former smokers. For current smokers, short-term O_3 concentrations were inversely associated with DNA damage; however, the number of current smokers in the study was small (n=12).

The findings of Palli et al. (2009) were consistent with those from controlled human exposure studies that have confirmed that smokers are less responsive to O_3 exposure than non-smokers. Spirometric and plethysmographic pulmonary function decline, nonspecific AHR, and inflammatory responses of smokers to O_3 exposure were all weaker than those reported for non-smokers. Similarly, the time course of development and recovery from these effects, as well as their reproducibility, was not different from non-smokers. Chronic airway inflammation with desensitization of bronchial nerve endings and an increased production of mucus may plausibly explain the pseudo-protective effect of smoking (Frampton et al., 1997b; Torres et al., 1997).

These findings for smoking are consistent with previous AQCD conclusions. An epidemiologic study of O_3-associated DNA damage reported smokers to be less at risk for O_3-related health effects. However, both epidemiologic studies of short-term exposure and CVD outcomes found no effect measure modification by smoking.

8.10 Heightened Exposure

Studies included in the 2006 O_3 AQCD reported that individuals who participate in outdoor activities or work to be a population at increased risk based on consistently reported associations between O_3 exposure and respiratory health outcomes in these groups (U.S. EPA, 2006b). Outdoor workers are exposed to ambient O_3 concentrations outside for a greater period of time than individuals who spend their days indoors. Additionally, an increase in dose to the lower airways is possible during exercise due to both increases in the amount of air breathed (i.e., minute ventilation) and a shift from nasal to oronasal breathing (Sawyer et al., 2007; Nodelman and Ultman, 1999; Hu et al., 1994). For further discussion of the association between FEV_1 responses to O_3 exposure

and minute ventilation, refer to Section 6.2.3.1 of the 2006 O_3 AQCD. A recent study has explored the potential effect measure modification of O_3 exposure and DNA damage by indoor/outdoor workplace (Tovalin et al., 2006). In a study of indoor and outdoor workers in Mexico, individuals who worked outdoors in Mexico City had a slight association between O_3 exposure and DNA damage (measured by comet tail length assay), whereas no association was observed for indoor workers in Mexico City. Workers in another Mexican city, Puebla, demonstrated no association between O_3 levels and DNA damage, regardless of whether they worked indoors or outdoors.

Air conditioning use is an important component of O_3 exposure, as use of central air conditioning will limit exposure to O_3 by blocking the penetration of O_3 into the indoor environment (further information can be found in Section 4.4 of this ISA). Air conditioning use is a difficult effect measure modifier to examine in epidemiologic studies. Air conditioning use is often measured based on regional prevalence and may not reflect individual-level use. More generally, air conditioning prevalence is associated with temperature of a region; those areas with higher temperatures have a greater prevalence of households with air conditioning. Despite these limitations, a few studies have examined effect measure modification by prevalence of air conditioning use in an area. Studies examining multiple cities across the U.S. have assessed whether associations between O_3 concentrations and HA and mortality varied among areas with high and low prevalence of air conditioning. Medina-Ramon et al. (2006) conducted a study during the warm season and observed a greater association between O_3 levels and pneumonia HA among areas with a lower proportion of households having central air conditioning compared to areas with a larger proportion of households with air conditioning. The same trend of increased association for areas with a lower prevalence of central air conditioning was noted in a study of O_3 concentrations and mortality (Bell and Dominici, 2008). Conversely, Medina-Ramón and Schwartz (2008) found that among individuals with atrial fibrillation, a lower risk of mortality was observed for areas with a lower prevalence of central air conditioning.

Previous work has shown that increased dose of O_3 concentrations from outdoor work leads to increased risk of O_3-related health effects among individuals who participate in outdoor activities or work, although there is no evidence of modification by outdoor activity in this recent study. Lower prevalence of air conditioning also appears to affect risk of O_3–related health effects, but this is not true of all studies. Overall, increased exposure to outdoor air does appear to confer additional risk and individuals with greater exposure to outdoor air may experience more O_3–related health effects.

8.11 Healthy Responders

Within the general population, there is evidence for variability in responses to O_3 exposure, with some healthy individuals demonstrating greater O_3-related health effects compared to other healthy individuals in controlled human exposure studies. These individuals do not fit in any of the at-risk populations discussed in this chapter; however, studies have found that they have greater responses to O_3 exposure than would be expected, indicating a unique population that needs to be considered.

Controlled human exposure studies have demonstrated a large degree of intersubject variability in lung function decrements, symptomatic responses, pulmonary inflammation, AHR, and altered epithelial permeability in healthy adults exposed to O_3 (Que et al.; Holz et al., 2005; McDonnell, 1996). The magnitude of increases in pulmonary inflammation, AHR, and epithelial permeability, in response to O_3 exposure, do not appear to be correlated, nor are these responses correlated with changes in lung function (Que et al.; Balmes et al., 1997; Balmes et al., 1996; Aris et al., 1995). However, these responses to O_3 exposure in healthy individuals tend to be reproducible within a given individual over a period of several months indicating differences in the intrinsic responsiveness of individuals (Holz et al., 2005; Hazucha et al., 2003; Holz et al., 1999; McDonnell et al., 1985a). It should be noted that even when group mean responses are small and seem physiologically insignificant, some intrinsically more responsive individuals experience distinctly larger effects under the same exposure conditions. For example, small group mean changes (e.g., <5%) in FEV_1 have been observed in healthy young adults at levels as low as 120 ppb O_3 for 1 to 3 hour exposure periods. However, some individuals within a study may experience FEV_1 decrements in excess of 15% under these conditions, even with group mean decrements of less than 5%. Therefore, within the general population, a proportion of otherwise healthy individuals, who do not have characteristics discussed above that increase risk, may be at increased risk of O_3-induced health effects.

8.12 Summary

In this section, epidemiologic, controlled human exposure, and toxicological studies have been evaluated that contribute information on potential at-risk populations. Overall, this review provides evidence that various factors may lead to increased risk of O_3-related health effects.

The populations identified in this section that are most at risk for O_3-related health effects are individuals with influenza/infection, individuals with asthma, and younger and older

age groups. There were a small number of studies on influenza/infection but both reported influenza/infection to modify the association between O_3 exposure and respiratory effects, with individuals having influenza or an infection being at increased risk. Asthma as a factor affecting risk was supported by controlled human exposure and toxicological studies, as well as some evidence from epidemiologic studies. Most studies comparing age groups reported greater effects of short-term O_3 exposure on mortality among older adults, although studies of other health outcomes had inconsistent findings regarding whether older adults were at increased risk. Generally, studies of age groups also reported positive associations for respiratory HAs and ED visits among children. Biological plausibility for this increased risk is supported by toxicological and clinical research. Diet and obesity are also both likely factors affecting risk. Multiple epidemiologic, controlled human exposure, and toxicological studies reported that diets deficient in vitamins E and C are associated with risk of O_3-related health effects. Similarly, studies of effect measure modification by BMI observed greater O_3-related respiratory decrements for individuals who were obese.

Other potential factors [preexisting conditions (such as COPD and CVD), sex, and multiple genes (such as *GSTM1, GSTP1, HMOX-1, NQO1,* and *TNF-α)*] provided some evidence of increased risk, but further evidence is needed. In addition, examination of modification of the associations between O_3 exposure and health effects by SES and race were available in a limited number of studies, and demonstrated possible increased odds of health effects related to O_3 exposure among those with low SES and black race.

Individuals with increased outdoor exposure were examined in a recent study of outdoor workers, in which no effect modification was observed, and studies of air conditioning prevalence, which demonstrated inconsistent findings. However, previous evidence along with biological plausibility from toxicological and controlled human studies has shown individuals exposed to more outdoor air to be at increased risk of O_3-related health effects. Studies of physical conditioning and smoking were conducted but little evidence was available to determine whether increased risk of O_3-related health effects is present for these factors. The only studies examining effect measure modification by diabetes examined O_3 exposure and cardiovascular outcomes and none reported increased risks for individuals with diabetes. Toxicological studies also identified hyperthyroidism to be a factor warranting further examination. Future research will provide additional insight into whether these factors affect risk of O_3-related health effects.

8.13 References

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9 ENVIRONMENTAL EFFECTS: OZONE EFFECTS ON VEGETATION AND ECOSYSTEMS

9.1 Introduction

This chapter synthesizes and evaluates the relevant science to help form the scientific foundation for the review of a vegetation- and ecologically-based secondary NAAQS for O_3. The secondary NAAQS are based on welfare effects. The Clean Air Act (CAA) definition of welfare effects includes, but is not limited to, effects on soils, water, wildlife, vegetation, visibility, weather, and climate, as well as effects on materials, economic values, and personal comfort and well-being. The effects of O_3 as a greenhouse gas and its direct effects on climate are discussed in Chapter 10 of this document.

The intent of the ISA, according to the CAA, is to "accurately reflect the latest scientific knowledge expected from the presence of [a] pollutant in ambient air" (42 U.S.C.7408 and 42 U.S.C.7409 (1999). This chapter of the ISA includes scientific research from biogeochemistry, soil science, plant physiology, and ecology conducted at multiple scales (e.g., organ, organism, population, community, ecosystem). Key information and judgments formerly found in the AQCDs regarding O_3 effects on vegetation and ecosystems are found in this chapter. This chapter of the O_3 ISA serves to update and revise Chapter 9 and AX9 of the 2006 O_3 AQCD (U.S. EPA, 2006b).

Numerous studies of the effects of O_3 on vegetation and ecosystems were reviewed in the 2006 O_3 AQCD. That document concluded that the effects of ambient O_3 on vegetation and ecosystems appear to be widespread across the U.S., and experimental studies demonstrated plausible mechanisms for these effects. Ozone effect studies published from 2005 to July 2011 are reviewed in this document in the context of the previous O_3 AQCDs. From 2005 to 2011, some areas have had very little new research published and the reader is referred back to sections of the 2006 O_3 AQCD for a more comprehensive discussion of those subjects. This chapter is focused on studies of vegetation and ecosystems that occur in the U.S. and that report endpoints or processes most relevant to the review of the secondary standard. Many studies have been published about vegetation and ecosystems outside of the U.S. and North America, largely in Europe and Asia. This document includes discussion of studies of vegetation and ecosystems outside of North America only if those studies contribute to the general understanding of O_3 effects across species and ecosystems. For example, studies outside North America are discussed that consider physiological and biochemical processes that contribute to the understanding of effects of O_3 across species. Also, ecosystem studies outside of North America that

contribute to the understanding of O_3 effects on general ecosystem processes are discussed in the chapter.

Sections of this chapter first discuss exposure methods, followed by effects on vegetation and ecosystems at various spatial scales and ends with policy-relevant discussions of exposure indices and exposure-response. Figure 9-1 is a simplified illustrative diagram of the major pathway through which O_3 enters plants and the major endpoints O_3 may affect. First, Section 9.2 presents a brief overview of various methodologies that have been, and continue to be, central to quantifying O_3 effects on vegetation (AX9.1 of the 2006 O_3 AQCD for more detailed discussion) (U.S. EPA, 2006b). Sections 9.3 through 9.4 begin with a discussion of effects at the cellular and subcellular level followed by consideration of the O_3 effects on plant and ecosystem processes (Figure 9-1). In Section 9.3, research is reviewed from the molecular to the biochemical and physiological levels in impacted plants, offering insight into the mode of action of O_3. Section 9.4 provides a review of the effects of O_3 exposure on major endpoints at the whole plant scale including growth, reproduction, visible foliar injury and leaf gas exchange in woody and herbaceous plants in the U.S., as well as a brief discussion of O_3 effects on agricultural crop yield and quality. Section 9.4 also integrates the effects of O_3 on individual plants in a discussion of available research for assessing the effect of O_3 on ecosystems, along with available studies that could inform assessments of various ecosystem services (See section 9.4.1.2). The development of indices of O_3 exposure and dose modeling is discussed in Section 9.5. Finally, exposure-response relationships for a number of tree species, native vegetation, and crop species and cultivars are reviewed, tabulated, and compared in Section 9.6 to form the basis for an assessment of the potential risk to vegetation from current ambient levels of O_3.

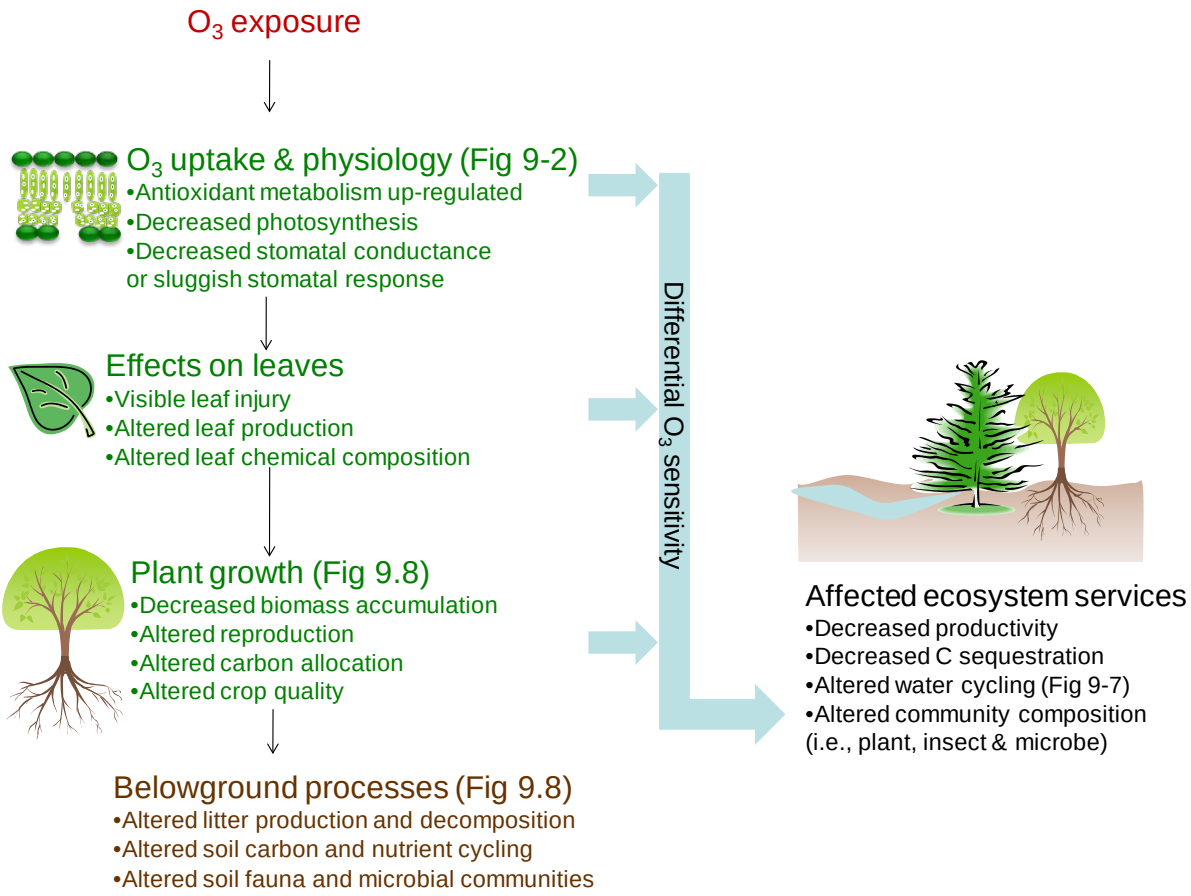


Figure 9-1 An illustrative diagram of the major pathway through which O_3 enters plants and the major endpoints that O_3 may affect in plants and ecosystems.

9.2 Experimental Exposure Methodologies

9.2.1 Introduction

A variety of methods for studying plant response to O_3 exposures have been developed over the last several decades. Methodological advancements since 2006 have not fundamentally altered our understanding of O_3 effects on plants or ecosystems. The majority of methodologies currently used have been discussed in detail in the 1996 O_3 AQCD and 2006 O_3 AQCD. This section will serve as a short overview of the methodologies and the reader is referred to the previous O_3 AQCDs for more in-depth discussion.

9.2.2 "Indoor," Controlled Environment, and Greenhouse Chambers

The earliest experimental investigations of the effects of O_3 on plants utilized simple glass or plastic-covered chambers, often located within greenhouses, into which a flow of O_3-enriched air or oxygen could be passed to provide the exposure. The types, shapes, styles, materials of construction, and locations of these chambers have been numerous. Hogsett et al. (1987a) have summarized the construction and performance of more elaborate and better instrumented chambers since the 1960s, including those installed in greenhouses (with or without some control of temperature and light intensity).

One greenhouse chamber approach that continues to yield useful information on the relationships of O_3 uptake to both physiological and growth effects employs continuous stirred tank reactors (CSTRs) first described by Heck et al. (1978). Although originally developed to permit mass-balance studies of O_3 flux to plants, their use has more recently widened to include short-term physiological and growth studies of $O_3 \times CO_2$ interactions (Loats and Rebbeck, 1999; Reinert et al., 1997; Rao et al., 1995; Reinert and Ho, 1995; Heagle et al., 1994a), and validation of visible foliar injury on a variety of plant species (Kline et al., 2009; Orendovici et al., 2003). In many cases, supplementary lighting and temperature control of the surrounding structure have been used to control or modify the environmental conditions (Heagle et al., 1994a).

Many investigations have utilized commercially available controlled environment chambers and walk-in rooms adapted to permit the introduction of a flow of O_3 into the controlled air-volume. Such chambers continue to find use in genetic screening and in physiological and biochemical studies aimed primarily at improving our understanding of modes of action. For example, some of the studies of the O_3 responses of common plantain (*Plantago major*) populations have been conducted in controlled environment chambers (Whitfield et al., 1996; Reiling and Davison, 1994).

More recently, some researchers have been interested in attempting to investigate direct O_3 effects on reproductive processes, separate from the effects on vegetative processes (Black et al., 2010). For this purpose, controlled exposure systems have been employed to expose the reproductive structures of annual plants to gaseous pollutants independently of the vegetative component (Black et al., 2010; Stewart et al., 1996).

9.2.3 Field Chambers

In general, field chamber studies are dominated by the use of various versions of the open top chamber (OTC) design, first described by Heagle et al. (1973) and Mandl et al. (1973). The OTC method continues to be a widely used technique in the U.S. and Europe

for exposing plants to varying levels of O_3. Most of the new information confirms earlier conclusions and provides additional support for OTC use in assessing plant species and in developing exposure-response relationships. Chambers are generally ~3 m in diameter with 2.5-m-high walls. Hogsett et al. (1987b) described in detail many of the various modifications to the original OTC designs that appeared subsequently, e.g., the use of larger chambers for exposing small trees (Kats et al., 1985) or grapevines (Mandl et al., 1989), the addition of a conical baffle at the top to improve ventilation (Kats et al., 1976), a frustum at the top to reduce ambient air incursions, and a plastic rain-cap to exclude precipitation (Hogsett et al., 1985). All versions of OTCs included the discharge of air via ports in annular ducting or interiorly perforated double-layered walls at the base of the chambers to provide turbulent mixing and the upward mass flow of air.

Chambered systems, including OTCs, have several advantages. For instance, they can provide a range of treatment levels including charcoal-filtered (CF), clean-air control, and several above ambient concentrations for O_3 experiments. Depending on experimental intent, a replicated, clean-air control treatment is an essential component in many experimental designs. The OTC can provide a consistent, definable exposure because of the constant wind speed and delivery systems. Statistically robust concentration-response (C-R) functions can be developed using such systems for evaluating the implications of various alternative air quality scenarios on vegetation response. Nonetheless, there are several characteristics of the OTC design and operation that can lead to exposures that might differ from those experienced by plants in the field. First, the OTC plants are subjected to constant air flow turbulence, which, by lowering the boundary layer resistance to diffusion, may result in increased uptake. This may lead to an overestimation of effects relative to areas with less turbulence (Krupa et al., 1995; Legge et al., 1995). However, other research has found that OTC's may slightly change vapor pressure deficit (VPD) in a way that may decrease the uptake of O_3 into leaves (Piikki et al., 2008b). As with all methods that expose vegetation to modified O_3 concentrations in chambers, OTCs create internal environments that differ from ambient air. This so-called "chamber effect" refers to the modification of microclimatic variables, including reduced and uneven light intensity, uneven rainfall, constant wind speed, reduced dew formation, and increased air temperatures (Fuhrer, 1994; Manning and Krupa, 1992). However, in at least one case where canopy resistance was quantified in OTCs and in the field, it was determined that gaseous pollutant exposure to crops in OTCs was similar to that which would have occurred at the same concentration in the field (Unsworth et al., 1984a, b). Because of the standardized methodology and protocols used in National Crop Loss Assessment Network (NCLAN) and other programs, the database can be assumed to be internally consistent.

While it is clear that OTCs can alter some aspects of the microenvironment and plant growth, it is important to establish whether or not these differences affect the relative response of a plant to O_3. As noted in the 1996 O_3 AQCD, evidence from a number of comparative studies of OTCs and other exposure systems suggested that responses were essentially the same regardless of exposure system used and chamber effects did not significantly affect response. For example, a study of chamber effects examined the responses of tolerant and sensitive white clover clones (*Trifolium repens*) to ambient O_3 in greenhouse, open top, and ambient plots (Heagle et al., 1996). The response found in OTCs was the same as in ambient plots.

Another type of field chamber called a "terracosm" has been developed and used in recent studies (Lee et al., 2009a). Concern over the need to establish realistic plant-litter-soil relationships as a prerequisite to studies of the effects of O_3 and CO_2 enrichment on ponderosa pine (*Pinus ponderosa*) seedlings led Tingey et al. (1996) to develop closed, partially environmentally controlled, sun-lit chambers ("terracosms") incorporating 1-m-deep lysimeters containing forest soil in which the appropriate horizon structure was retained.

Other researchers have recently published studies using another type of out-door chamber called recirculating Outdoor Plant Environment Chambers (OPECs) (Flowers et al., 2007). These closed chambers are approximately 2.44 m×1.52 m with a growth volume of approximately 3.7 m^3 in each chamber. These chambers admit 90% of full sunlight and control temperature, humidity and vapor pressure (Fiscus et al., 1999).

9.2.4 Plume and FACE-Type Systems

Plume systems are chamberless exposure facilities in which the atmosphere surrounding plants in the field is modified by the injection of pollutant gas into the air above or around them from multiple orifices spaced to permit diffusion and turbulence, so as to establish relatively homogeneous conditions as the individual plumes disperse and mix with the ambient air. They can only be used to increase the O_3 levels in the ambient air.

The most common plume system used in the U.S. is a modification of the free-air carbon-dioxide/ozone enrichment (FACE) system (Hendrey et al., 1999; Hendrey and Kimball, 1994). Although originally designed to provide chamberless field facilities for studying the CO_2 effects of climate change, FACE systems have been adapted to include the dispensing of O_3 (Karnosky et al., 1999). This method has been employed in Illinois (SoyFACE) to study soybeans (Morgan et al., 2004; Rogers et al., 2004) and in Wisconsin (Aspen FACE) to study trembling aspen (*Populus tremuloides*), birch (*Betula papyrifera*) and maple (*Acer saccharum*) (Karnosky et al., 1999). Volk et al. (2003) also

described a similar system for exposing grasslands that uses 7-m diameter plots. FACE systems discharge the pollutant gas (O_3 and/or CO_2) through orifices spaced along an annular ring (or torus) or at different heights on a ring of vertical pipes. Computer-controlled feedback from the monitoring of gas concentration regulates the feed rate of enriched air to the dispersion pipes. Feedback of wind speed and direction information ensures that the discharges only occur upwind of the treatment plots, and that discharge is restricted or closed down during periods of low wind speed or calm conditions. The diameter of the arrays and their height (25-30 m) in some FACE systems requires large throughputs of enriched air per plot, particularly in forest tree systems. The cost of the throughputs tends to limit the number of enrichment treatments, although Hendrey et al. (1999) argued that the cost on an enriched volume basis is comparable to that of chamber systems.

Although plume systems make virtually none of the modifications to the physical environment that are inevitable with chambers, their successful use depends on selecting the appropriate numbers, sizes, and orientations of the discharge orifices to avoid "hot-spots" resulting from the direct impingement of jets of pollutant-enriched air on plant foliage (Werner and Fabian, 2002). Because mixing is unassisted and completely dependent on wind turbulence and diffusion, local gradients are inevitable especially in large-scale systems. FACE systems have provisions for shutting down under low wind speed or calm conditions and for an experimental area that is usually defined within a generous border in order to strive for homogeneity of the exposure concentrations within the treatment area. They are also dependent upon continuous computer-controlled feedback of the O_3 concentrations in the mixed treated air and of the meteorological conditions. Plume and FACE systems also are unable to reduce O_3 levels below ambient in areas where O_3 concentrations are phytotoxic.

9.2.5 Ambient Gradients

Ambient O_3 gradients that occur in the U.S. hold potential for the examination of plant responses over multiple levels of exposure. However, few such gradients can be found that meet the rigorous statistical requirements for comparable site characteristics such as soil type, temperature, rainfall, radiation, and aspect (Manning and Krupa, 1992); although with small plants, soil variability can be avoided by the use of plants in large pots. The use of soil monoliths transported to various locations along natural O_3 gradients is another possible approach to overcome differences in soils; however, this approach is also limited to small plants.

Studies in the 1970s used the natural gradients occurring in southern California to assess yield losses of alfalfa and tomato (Oshima et al., 1977; Oshima et al., 1976). A transect study of the impact of O_3 on the growth of white clover and barley in the U.K. was confounded by differences in the concurrent gradients of SO_2 and NO_2 pollution (Ashmore et al., 1988). Studies of forest tree species in national parks in the eastern U.S. (Winner et al., 1989) revealed increasing gradients of O_3 and visible foliar injury with increased elevation.

Several studies have used the San Bernardino Mountains Gradient Study in southern California to study the effects of O_3 and N deposition on forests dominated by ponderosa and Jeffrey pine (Jones and Paine, 2006; Arbaugh et al., 2003; Grulke, 1999; Miller and Elderman, 1977). However, it is difficult to separate the effects of N and O_3 in some instances in these studies (Arbaugh et al., 2003). An O_3 gradient in Wisconsin has been used to study foliar injury in a series of trembling aspen clones (*Populus tremuloides*) differing in O_3 sensitivity (Maňkovská et al., 2005; Karnosky et al., 1999).

More recently, studies have been published that have used natural gradients to study a variety of endpoints and species. For example, Gregg et al. (2003) studied cottonwood saplings grown in an urban to rural gradient of O_3 in the New York City area. The secondary nature of the reactions of O_3 formation and NO_X titration reactions within the city center resulted in significantly higher cumulative O_3 exposures in the rural sites. The results of this gradient study were similar to those of a parallel OTC study. Also, the U.S. forest service Forest Inventory and Analysis (FIA) program uses large-scale O_3 exposure patterns across the continental U.S. to study occurrences of foliar injury due to O_3 exposure (Smith et al., 2003) (Section 9.4.2). Finally, McLaughlin et al. (2007a; 2007b) used spatial and temporal O_3 gradients to study forest growth and water use in the southern Appalachians. These studies found varying O_3 exposures between years and between sites.

9.2.6 Comparative Studies

All experimental approaches used to expose plants to O_3 have strengths and weaknesses. One potential weakness of laboratory, greenhouse, or field chamber studies is the potential effect of the chamber on micrometeorology. In contrast, plume, FACE and gradient systems are limited by the very small number of possible exposure levels (almost always no more than two), small replication and an inability to reduce O_3 levels below ambient. In general, experiments that aim at characterizing the effect of a single variable, e.g., exposure to O_3, must not only manipulate the levels of that variable, but also control potentially interacting variables and confounders, or else account for them.

However, while increasing control of environmental variables makes it easier to discern the effect of the variable of interest, it must be balanced with the ability to extend conclusions to natural, non-experimental settings. More naturalistic exposure systems, on the other hand, let interacting factors vary freely, resulting in greater unexplainable variability. The various exposure methodologies used with O_3 vary in the balance each strikes between control of environmental inputs, closeness to the natural environment, noisiness, and ability to make general inferences.

Studies have examined the comparability of results obtained though the various exposure methodologies. As noted in the 1996 O_3 AQCD, evidence from the comparative studies of OTCs and from closed chamber and O_3-exclusion exposure systems on the growth of alfalfa (*Medicago sativa*) by Olszyk et al. (1986) suggested that, since significant differences were found for fewer than 10% of the growth parameters measured, the responses were, in general, essentially the same regardless of exposure system used, and chamber effects did not significantly affect response. In 1988, Heagle et al. (1988) concluded: "Although chamber effects on yield are common, there are no results showing that this will result in a changed yield response to O_3." A study of the effects of an enclosure examined the responses of tolerant and sensitive white clover clones (*Trifolium repens*) to ambient O_3 in a greenhouse, open-top chamber, and ambient (no chamber) plots (Heagle et al., 1996). For individual harvests, greenhouse O_3 exposure reduced the forage weight of the sensitive clone 7 to 23% more than in OTCs. However, the response in OTCs was the same as in ambient plots. Several studies have shown very similar response of yield to O_3 for plants grown in pots or in the ground, suggesting that even such a significant change in environment does not alter the proportional response to O_3, providing that the plants are well watered (Heagle et al., 1983; Heagle, 1979).

A few recent studies have compared results of O_3 experiments between OTCs, FACE experiments, and gradient studies. For example, a series of studies undertaken at Aspen FACE (Isebrands et al., 2001; Isebrands et al., 2000) showed that O_3 symptom expression was generally similar in OTCs, FACE, and ambient O_3 gradient sites, and supported the previously observed variation among trembling aspen clones using OTCs (Maňkovská et al., 2005; Karnosky et al., 1999). In the SoyFACE experiment in Illinois, soybean (Pioneer 93B15 cultivar) yield loss data from a two-year study was published (Morgan et al., 2006). This cultivar is a recent selection and, like most modern cultivars, has been selected under an already high current O_3 exposure. It was found to have average sensitivity to O_3 compared to 22 other cultivars tested at SoyFACE. In this experiment, ambient hourly O_3 concentrations were increased by approximately 20% and measured yields were decreased by 15% in 2002 as a result of the increased O_3 exposure (Morgan et al., 2006). To compare these results to chamber studies, Morgan et al. (2006) calculated the expected yield loss from a linear relationship constructed from chamber

data using seven-hour seasonal averages (Ashmore, 2002). They calculated an 8% expected yield loss from the 2002 O_3 exposure using that linear relationship. In another study, Gregg et al. (2006, 2003) found similar O_3 effects on cottonwood sapling biomass growth along an ambient O_3 gradient in the New York City area and a parallel OTC study.

Finally, EPA conducted comparisons of exposure-response model predictions based on OTC studies, and more recent FACE observations. These comparisons include yield of annual crops, and biomass growth of trees. They are presented in section 9.6.3 of this document.

9.3 Mechanisms Governing Vegetation Response to Ozone

9.3.1 Introduction

This section focuses on the effects of O_3 stress on plants and their responses to that stress on the molecular, biochemical and physiological levels. First, the pathway of O_3 uptake into the leaf and the initial chemical reactions occurring in the substomatal cavity and apoplast will be described (Section 9.3.2); additionally, direct effects of O_3 on the stomatal apparatus will be discussed. Once O_3 has entered the substomatal cavity and apoplast, it is thought that the cell must be able to sense the presence of O_3 or its breakdown products in order to initiate the rapid changes in signaling pathways and gene expression that have been measured in O_3-treated plants. While it remains unclear exactly how O_3 and/or its breakdown products are sensed in the apoplast, much progress has been made in examining several different mechanisms that may contribute both to sensing the presence of O_3 and its breakdown products, and also initiating a signal transduction cascade, which will be described in Section 9.3.3.1. The next section focuses on changes in gene and protein expression measured in plants exposed to O_3, with particular emphasis on results from transcriptome (all RNA molecules produced in a cell) and proteome (all proteins produced in a cell) analyses (Section 9.3.3.2). Subsequently, the role of phytohormones such as salicylic acid (SA), ethylene (ET), jasmonic acid (JA), and abscisic acid (ABA) and their interactions in both signal transduction processes and in determining plant response to O_3 is discussed in Section 9.3.3.3. After O_3 uptake and sensing, some plants can respond to the oxidative stress with detoxification to minimize damage. These mechanisms of detoxification, with particular emphasis on antioxidant enzymes and metabolites, are reviewed in Section 9.3.4. The next section focuses on changes in primary and secondary metabolism in plants exposed to O_3, looking at photosynthesis, respiration and several secondary metabolites, some of which may also

act as antioxidants and protect the plant from oxidative stress (Section 9.3.5). For many of these topics, information from the 2006 O_3 AQCD has been summarized, as this information is still valid and supported by more recent findings. For other topics, such as genomics and proteomics, which have arisen due to the availability of new technologies, the information is based solely on new publications with no reference to the 2006 O_3 AQCD.

As Section 9.3 focuses on mechanisms underlying effects of O_3 on plants and their response to it, the conditions that are used to study these mechanisms do not always reflect conditions that a plant may be exposed to in an agricultural setting or natural ecosystem. The goal of many of these studies is to generate an O_3 effect in a relatively short period of time and not always to simulate ambient O_3 exposures. Therefore, plants are often exposed to unrealistically high O_3 concentrations for several hours or days (acute exposure), and only in some cases to ambient or slightly elevated O_3 concentrations for longer time periods (chronic exposure). Additionally, the plant species utilized in these studies are often not agriculturally important or commonly found as part of natural ecosystems. Model organisms such as *Arabidopsis thaliana* are used frequently as they are easy to work with, and mutants or transgenic plants are easy to develop or have already been developed. Furthermore, the *Arabidopsis* genome has been sequenced, and much is known about the molecular basis of many biochemical and cellular processes.

Many of the studies described in this section focus on changes in the expression of genes in O_3-treated plants. Changes in gene expression (i.e., either up- or down-regulation of gene expression) do not always translate into changes in protein quantity and/or activity, as there are many levels of post-transcriptional and post-translational modifications which impact protein quantity and activity. Many studies do not evaluate whether the observed changes in gene expression lead to changes at the protein level and, therefore, it is not always clear how relevant the changes in gene expression are in determining plant response to O_3. However, with the advent of proteomics, some very recent studies have evaluated changes in protein expression for large numbers of proteins in O_3 treated plants, and the findings from these studies support the previous results regarding changes in gene expression studies as a result of O_3 exposure. The next step in the process is to determine the implications of the measured changes occurring at the cellular level to whole plants and ecosystems, which is an important topic of study which has not been widely addressed.

The most significant new body of research since the 2006 O_3 AQCD is on the understanding of molecular mechanisms underlying how plants are affected by O_3; a significant number of recent studies reviewed here focus on changes in gene expression

in plants exposed to elevated O_3. Conclusions from the 2006 O_3 AQCD have been supported by these new studies, and the advent of new technologies has allowed for a more comprehensive understanding of the mechanisms governing how plants are affected by O_3.

In summary, these new studies have increased knowledge of the molecular, biochemical and cellular mechanisms occurring in plants in response to O_3 by often using artificial exposure conditions and model organisms. This information adds to the understanding of the basic biology of how plants are affected by oxidative stress in the absence of any other potential stressors. The results of these studies provide important insights, even though they may not always directly translate into effects observed in other plants under more realistic exposure conditions.

9.3.2 Ozone Uptake into the Leaf

Appendix AX9.2.3 of the 2006 O_3 AQCD clearly described the process by which O_3 enters plant leaves through open stomata (U.S. EPA, 2006b). This information continues to be valid and is only summarized here.

Stomata provide the principal pathway for O_3 to enter and affect plants (Massman and Grantz, 1995; Fuentes et al., 1992; Reich, 1987; Leuning et al., 1979). Ozone moves into the leaf interior by diffusing through open stomata, and environmental conditions which promote high rates of gas exchange will favor the uptake of the pollutant by the leaf. Factors that may limit uptake include boundary layer resistance and the size of the stomatal aperture (Figure 9-2) (U.S. EPA, 2006b). Once inside the substomatal cavity, O_3 is thought to rapidly react with the aqueous apoplast to form breakdown products known as reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2), superoxide (O_2^-), hydroxyl radicals ($HO^{\cdot}$) and peroxy radicals ($HO_2^{\cdot}$) (Figure 9-3). Hydrogen peroxide is not only a toxic breakdown product of O_3, but has been shown to function as a signaling molecule, which is activated in response to both biotic and abiotic stressors. The role of H_2O_2 in signaling was described in detail in the 2006 O_3 AQCD. Additional organic molecules present in the apoplast or cell wall, such as those containing double bonds or sulfhydryls that are sensitive to oxidation, could also be converted to oxygenated molecules after interacting with O_3 (Figure 9-4). These reactions are not only pH dependent, but are also influenced by the presence of other molecules in the apoplast (U.S. EPA, 2006b). The 2006 O_3 AQCD provided a comprehensive summary of what is known about the possible interactions of O_3 with other biomolecules (U.S. EPA, 2006b). It is in the apoplast that initial detoxification reactions by antioxidant metabolites and enzymes take place, and these initial reactions are critical to reduce concentrations of the

oxidative breakdown products of O_3; these reactions are described in more detail in Section 9.3.4 of this document.

9.3.2.1 Changes in Stomatal Function

The effects of O_3 exposure on stomatal conductance have been reviewed in detail in previous O_3 AQCDs. Although the nature of these effects depends upon many different factors, including the plant species, concentration and duration of the O_3 exposure, and prevailing meteorological conditions, stomatal conductance is often negatively affected by plant exposure to O_3 (Wittig et al., 2007). Decreases in conductance have been shown to result from declines in photosynthetic carboxylation capacity, leading to a buildup of CO_2 in the substomatal cavity and subsequent stomatal closure (Wittig et al., 2007). However, results from the use of Arabidopsis mutants and new technologies, which allow for analysis of guard cell function in whole plants rather than in isolated guard cells or epidermal peels, suggest that O_3 may also have a direct impact on stomatal guard cells, leading to alterations in stomatal conductance. The use of a new simultaneous O_3 exposure/gas exchange device has demonstrated that exposure of *Arabidopsis* ecotypes Col-0 and Ler to 150 ppb O_3 resulted in a 60-70% decline in stomatal conductance within 9-12 minutes of beginning the exposure. Twenty to thirty minutes later, stomatal conductance had returned to its initial value, even with continuing exposure to O_3, indicating a rapid direct effect of O_3 on stomatal function (Kollist et al., 2007). This transient decrease in stomatal conductance was not observed in the abscisic acid insensitive (ABI2) Arabidopsis mutant. As the ABI2 protein is thought to regulate the signal transduction process involved in stomatal response downstream of ROS production, the authors suggest that the transient decrease in stomatal conductance in the Col-0 and Ler ecotypes results from the biological action of ROS in transducing signals, rather than direct physical damage to guard cells by ROS (Kollist et al., 2007). This rapid transient decrease in stomatal conductance was also not observed when exposing the Arabidopsis mutant slac1 (slow anion channel-associated 1) to 200 ppb O_3 (Vahisalu et al., 2008). The SLAC1 protein was shown to be essential for guard cell slow anion channel functioning and for stomatal closure in response to O_3. Based on additional studies using a variety of Arabidopsis mutants impaired in various aspects of stomatal function, Vahisalu et al. (2010) suggest that the presence of ROS in the guard cell apoplast (formed either by O_3 breakdown or through ROS production from NADPH oxidase activity) leads to the activation of a signaling pathway in the guard cells, which includes SLAC1, and results in stomatal closure.

A review by McAinsh et al. (2002) discusses the role of calcium as a part of the signal transduction pathway involved in regulating stomatal responses to pollutant stress. A

number of studies in this review provide some evidence that exposure to O_3 increases the cytosolic free calcium concentration ($[Ca^{2+}]$cyt) in guard cells, which may result in an inhibition of the plasma membrane inward-rectifying K^+ channels in guard cells, which allow for the K^+ uptake needed for stomatal opening (McAinsh et al., 2002; Torsethaugen et al., 1999). This would compromise the ability of the stomata to respond to various stimuli, including light, CO2 concentration and drought. Pei et al. (2000) reported that the presence of H_2O_2 activated Ca^{2+} -permeable channels, which mediate increases in $[Ca^{2+}]$cyt in guard cell plasma membranes of Arabidopsis. They also determined that abscisic acid (ABA) induced H_2O_2 production in guard cells, leading to ABA-induced stomatal closure via activation of the membrane Ca^{2+} channels. Therefore, it is possible that H_2O_2, a byproduct of O_3 breakdown in the apoplast, could disrupt the Ca^{2+}-ABA signaling pathway that is involved in regulating stomatal responses (McAinsh et al., 2002). The studies described here provide some evidence to suggest that O_3 and its breakdown products can directly affect stomatal functioning by impacting the signal transduction pathways which regulate guard cells. Stomatal sluggishness has been described as a delay in stomatal response to changing environmental conditions in sensitive species exposed to higher concentrations and/or longer-term O_3 exposures (Paoletti and Grulke, 2010, 2005; McAinsh et al., 2002). It is possible that the signaling pathways described above could be involved in mediating this stomatal sluggishness in some plant species under certain O_3 exposure conditions (Paoletti and Grulke, 2005; McAinsh et al., 2002).

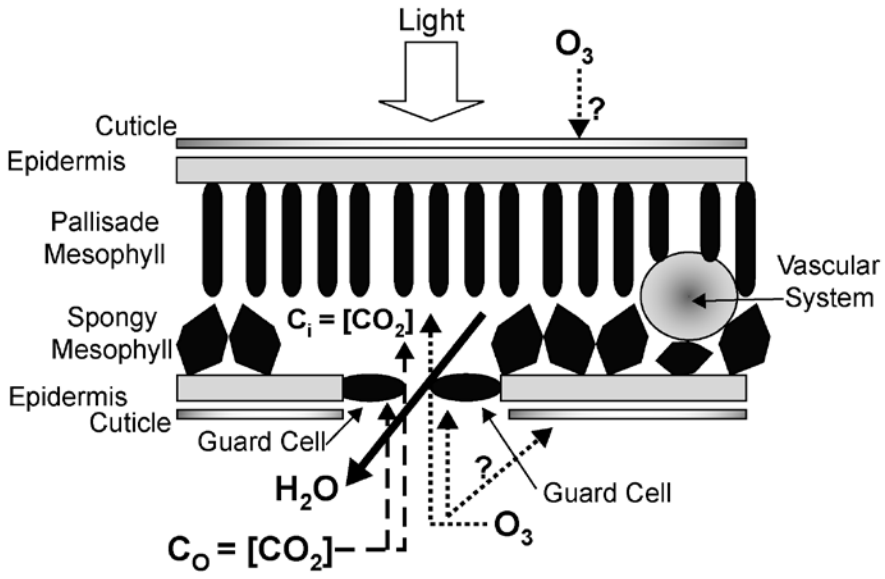


Figure 9-2 **The microarchitecture of a dicot leaf. While details among species vary, the general overview remains the same. Light that drives photosynthesis generally falls upon the upper (adaxial) leaf surface. Carbon dioxide and ozone enter through the stomata on the lower (abaxial) leaf surface, while water vapor exits through the stomata (transpiration).**

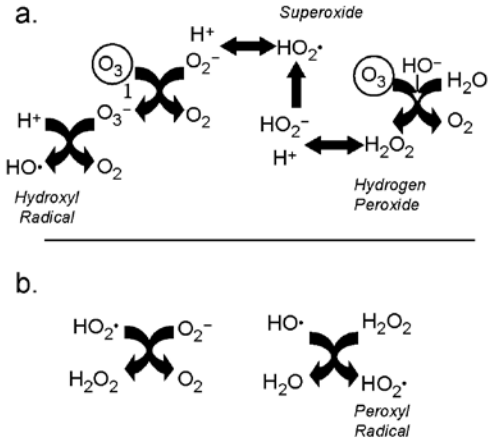
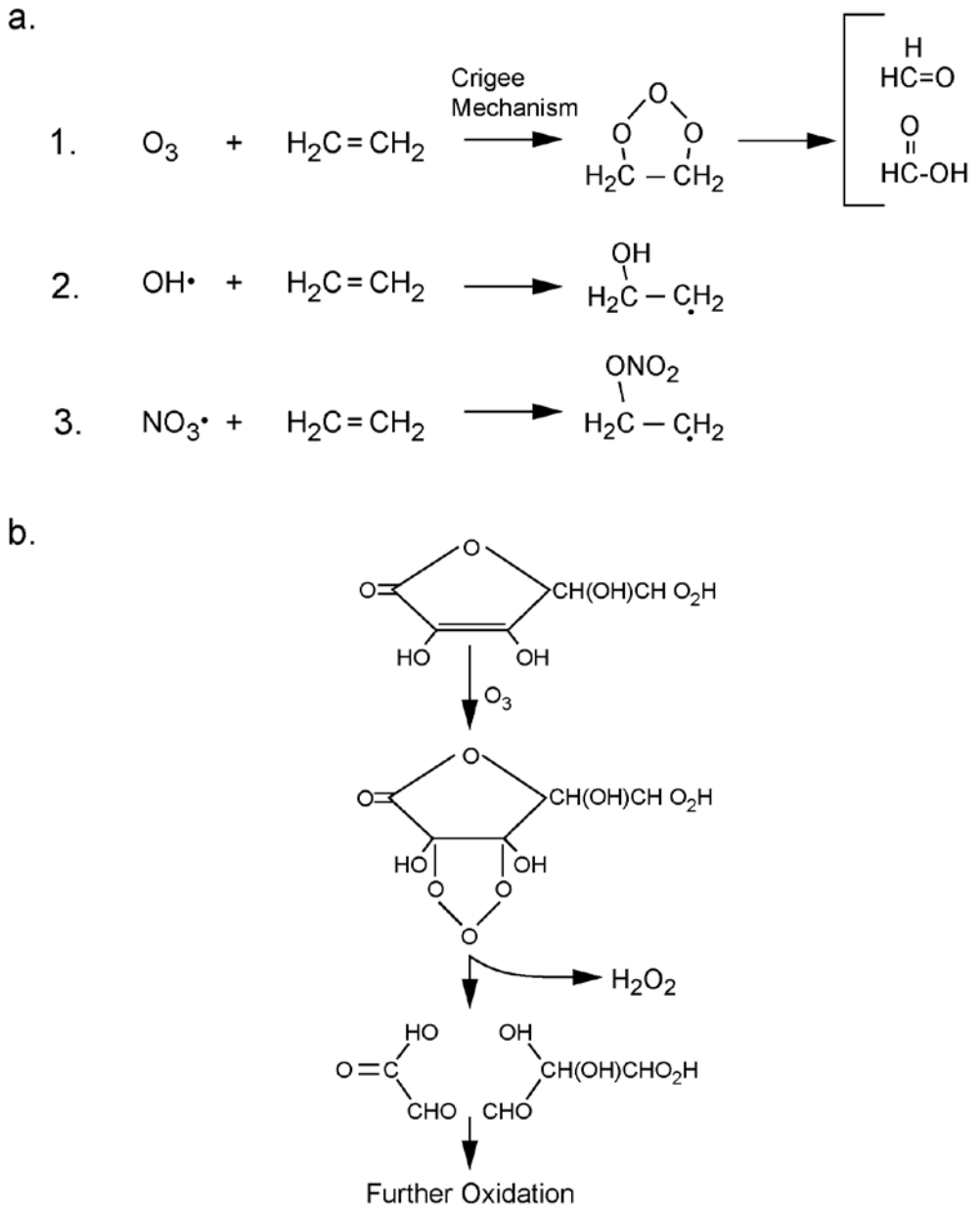


Figure 9-3 **Possible reactions of ozone within water. (a) Ozone reacts at the double bonds to form carbonyl groups. (b) Under certain circumstances, peroxides are generated.**



Source: Adapted from Mudd (1996).

Figure 9-4 The Crigee mechanism of ozone attack of a double bond. (a) The typical Crigee mechanism is shown in which several reactions paths from the initial product is shown. (b) Typical reaction of ascorbic acid with ozone.

9.3.3 Cellular to Systemic Responses

9.3.3.1 Ozone Sensing and Signal Transduction

New technologies allowing for large-scale analysis of oxidative stress-induced changes in gene expression have facilitated the study of signal transduction processes associated with the perception and integration of responses to the stress. Many of these studies have been conducted using *Arabidopsis* or tobacco plants, for which a variety of mutants are available and/or which can be easily genetically modified to generate either loss-of-function or over-expressing genotypes. Several comprehensive review articles provide an overview of what is known of O_3-induced signal transduction processes and how they may help to explain differential sensitivity of plants to the pollutant (Ludwikow and Sadowski, 2008; Baier et al., 2005; Kangasjarvi et al., 2005). Additionally, analysis of several studies of transcriptome changes has also allowed for the compilation of these data to determine an initial time-course for O_3-induced activation of various signaling compounds (Kangasjarvi et al., 2005).

A number of different mechanisms for plant sensing of O_3 have been proposed; however, there is still much that is not known about this process. Some of the earliest events that occur in plants exposed to O_3 have been described in the guard cells of stomata. Reactive oxygen species were observed in the chloroplasts of guard cells in the O_3 tolerant Col-0 *Arabidopsis thaliana* ecotype plants within 5 minutes of plant exposure to 350 ppb O_3 (Joo et al., 2005). Reactive oxygen species from the breakdown of O_3 in the apoplast are believed to activate GTPases (G-proteins), which, in turn, activate several intracellular sources of ROS, including ROS derived from the chloroplasts. G-proteins are also believed to play a role in activating membrane-bound NADPH oxidases to produce ROS and, as a result, propagate the oxidative burst to neighboring cells (Joo et al., 2005). Therefore, G-proteins are recognized as important molecules involved in plant responses to O_3 and may play a role in perceiving ROS from the breakdown of O_3 in the apoplast (Kangasjarvi et al., 2005; Booker et al., 2004b).

A change in the redox state of the plant and the oxidation of sensitive molecules in itself may represent a means of perception and signaling of oxidative stress in plants. Disulfide-thiol conversions in proteins and the redox state of the glutathione pool may be important components of redox sensing and signal transduction (Foyer and Noctor, 2005a, b).

Calcium (Ca^{2+}) has also been implicated in the transduction of signals to the nucleus in response to oxidative stress. The influx of Ca^{2+} from the apoplast into the cell occurs early during plant exposure to O_3, and it is thought to play a role in regulating the activity

of protein kinases, which are discussed below (Baier et al., 2005; Hamel et al., 2005). Calcium channel blockers inhibited O_3-induced activation of protein kinases in tobacco suspension cells exposed to 500 ppb O_3 for 10 minutes, indicating that the opening of Ca^{2+} channels is an important upstream signaling event or that the as yet unknown upstream process has a requirement for Ca^{2+} (Samuel et al., 2000).

Further transmission of information regarding the presence of ROS to the nucleus t involves mitogen-activated protein kinases (MAPK), which phosphorylate proteins and activate various cellular responses (Hamel et al., 2005). Mitogen-activated protein kinases are induced in several different plant species in response to O_3 exposure, including tobacco (Samuel et al., 2005), *Arabidopsis* (Ludwikow et al., 2004), the shrub *Phillyrea latifolia* (Paolacci et al., 2007) and poplar (Hamel et al., 2005). Disruption of these signal transduction pathways by over-expressing or suppressing MAP kinase activity in different Arabidopsis and tobacco lines resulted in increased plant sensitivity to O_3 (Miles et al., 2005; Samuel and Ellis, 2002). Additionally, greater O_3 tolerance of several Arabidopsis ecotypes was correlated with greater up-regulation of MAP kinase signaling pathways upon O_3 exposure than in more sensitive Arabidopsis ecotypes (Li et al., 2006b; Mahalingam et al., 2006; Overmyer et al., 2005), indicating that determination of plant sensitivity and plant response to O_3 may, in part, be determined not only by whether these pathways are turned on, but also by the magnitude of the signals moving through these communication channels.

In conclusion, experimental evidence suggests that there are likely several different mechanisms by which the plant senses the presence of O_3 or its breakdown products. These mechanisms may vary by species or developmental stage of the plant, or may co-exist and be activated by different exposure conditions. Calcium and protein kinases are likely involved in relaying information about the presence of the stressor to the nucleus and other cellular compartments as a first step in determining whether and how the plant will respond to the stress.

9.3.3.2 Gene and Protein Expression Changes in Response to Ozone

The advent of DNA microarray technology has allowed for the study of gene expression in cells on a large scale. Rather than assessing changes in gene expression of individual genes, DNA microarrays facilitate the evaluation of entire transcriptomes, providing a comprehensive picture of simultaneous alterations in gene expression. In addition, these studies have provided more insight into the complex interactions between molecules, how those interactions lead to the communication of information in the cell (or between

neighboring cells) , and which role these interactions play in determining tolerance or sensitivity and how a plant may respond to stresses such as O_3 (Ludwikow and Sadowski, 2008). Transcriptome analysis of O_3-treated plants has been performed in several species, including *Arabidopsis thaliana* (Li et al., 2006b; Tosti et al., 2006; Heidenreich et al., 2005; Mahalingam et al., 2005; Tamaoki et al., 2003), pepper (*Capsicum annuum)* (Lee and Yun, 2006), clover (*Medicago truncatula*) (Puckette et al., 2008), *Phillyrea latifolia* (Paolacci et al., 2007), poplar (Street et al., 2011), and European beech (*Fagus sylvatica*) (Olbrich et al., 2010; Olbrich et al., 2009; Olbrich et al., 2005). In some cases, researchers compared transcriptomes of two or more cultivars, ecotypes or mutants that differed in their sensitivity to O_3 (Puckette et al., 2008; Rizzo et al., 2007; Lee and Yun, 2006; Li et al., 2006b; Tamaoki et al., 2003). Species, O_3 exposure conditions (concentration, duration of exposure) and sampling times varied significantly in these studies. However, functional classification of the genes that were either up- or down-regulated by plant exposure to O_3 exhibited common trends. Genes involved in plant defense, signaling and those associated with the synthesis of plant hormones and secondary metabolism were generally up-regulated, while those related to photosynthesis and general metabolism were typically down-regulated in O_3-treated plants (Puckette et al., 2008; Lee and Yun, 2006; Li et al., 2006b; Tosti et al., 2006; Olbrich et al., 2005; Tamaoki et al., 2003).

Analysis of the transcriptome has been used to evaluate differences in gene expression between O_3 sensitive and tolerant plants. In pepper, 67% of the 180 genes studied that were affected by O_3 were differentially regulated in the sensitive and tolerant cultivars. At both 0 hours and 48 hours after a 3-day exposure at 150 ppb, O_3 responsive genes were either up- or down-regulated more markedly in the sensitive than in the tolerant cultivar (Lee and Yun, 2006). Transcriptome analysis also revealed differences in timing and magnitude of changes in gene expression between sensitive and tolerant clovers. Acute exposure (300 ppb O_3 for 6 hours) led to the production of an oxidative burst in both clovers (Puckette et al., 2008). However, the sensitive Jemalong cultivar exhibited a sustained ROS burst and a concomitant down-regulation of defense response genes at 12 hours after the onset of exposure, while the tolerant JE 154 accession showed much more rapid and large-scale transcriptome changes than the Jemalong cultivar (Puckette et al., 2008).

Arabidopsis ecotypes WS and Col-0 were exposed to 1.2 × ambient O_3 concentrations for 8-12 days at the SoyFACE site (Li et al., 2006b). The sensitive WS ecotype showed a far greater number of changes in gene expression in response to this low-level O_3 exposure than the tolerant Col-0 ecotype. In a different study, exposure of the WS ecotype to 300 ppb O_3 for 6 hours showed a rapid induction of genes leading to cell death, such as

proteases, and down-regulation or inactivation of cell signaling genes, demonstrating an ineffective defense response in this O_3 sensitive ecotype (Mahalingam et al., 2006).

The temporal response of plants to O_3 exposure was evaluated in the *Arabidopsis* Col-0 ecotype during a 6-h exposure at 350 ppb O_3 and for 6 hours after the exposure was completed. Results of this study, shown in Figure 9-5, indicate that genes associated with signal transduction and regulation of transcription were in the class of early up-regulated genes, while genes associated with redox homeostasis and defense/stress response were in the class of late up-regulated genes (Mahalingam et al., 2005).

A few studies have been conducted to evaluate transcriptome changes in response to longer term chronic O_3 exposures in woody plant species. Longer term exposures resulted in the up-regulation of genes associated with secondary metabolites, including isoprenoids, polyamines and phenylpropanoids in 2-year-old seedlings of the Mediterranean shrub *Phillyrea latifolia* exposed to 110 ppb O_3 for 90 days (Paolacci et al., 2007). In 3-year-old European beech saplings exposed to O_3 for 20 months, with monthly average twice ambient O_3 concentrations ranging from 11 to 80 ppb, O_3-induced changes in gene transcription were similar to those observed for herbaceous species (Olbrich et al., 2009). Genes encoding proteins associated with plant stress response, including ethylene biosynthesis, pathogenesis-related proteins and enzymes detoxifying ROS, were up-regulated. Some genes associated with primary metabolism, cell structure, cell division and cell growth were reduced (Olbrich et al., 2009). In a similar study using adult European beech trees, it was determined that the magnitude of the transcriptional changes described above was far greater in the saplings than in the adult trees exposed to the same O_3 concentrations for the same time period (Olbrich et al., 2010).

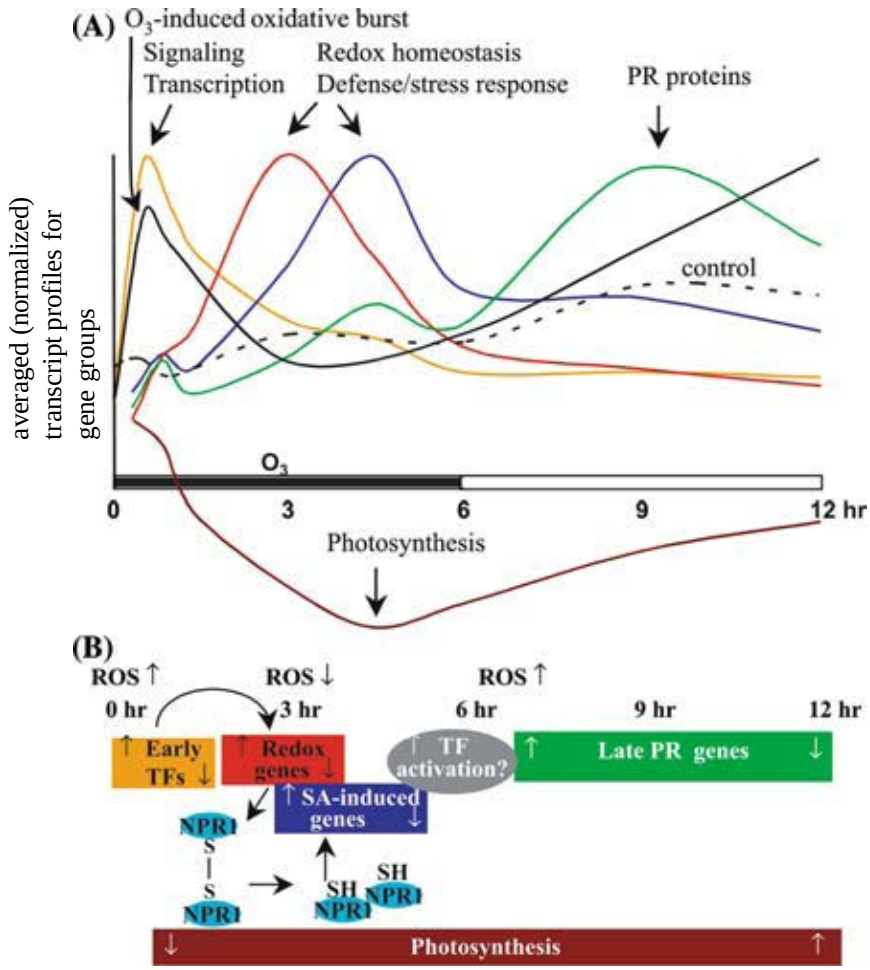
The results from transcriptome studies described above have been substantiated by results from proteome analysis in rice, poplar, European beech, wheat, and soybean. Exposure of soybean to 120 ppb O_3 for 12-h/day for 3 days in growth chambers resulted in decreases in the quantity of proteins associated with photosynthesis, while proteins involved with antioxidant defense and carbon metabolism increased (Ahsan et al., 2010). Young poplar plants exposed to 120 ppb O_3 in a growth chamber for 35 days also showed significant changes in proteins involved in carbon metabolism (Bohler et al., 2007). Declines in enzymes associated with carbon fixation, the Calvin cycle and photosystem II were measured, while ascorbate peroxidase and enzymes associated with glucose catabolism increased in abundance. In another study to determine the impacts of O_3 on both developing and fully expanded poplar leaves, young poplars were exposed to 120 ppb O_3 for 13-h per day for up to 28 days (Bohler et al., 2010). Impacts on protein quantity only occurred after the plants had been exposed to O_3 for 14 days, and at this point in time, several Calvin cycle enzymes were reduced in quantity, while the effects on the light

reactions appeared later, at 21 days after beginning treatment. Some of the antioxidant enzymes increased in abundance with O_3 treatment, while others (ascorbate peroxidase) did not. In relationship to leaf expansion, it was shown that O_3 did not affect protein quantity until leaves had reached full expansion, after about 7 days (Bohler et al., 2010).

Two-week-old rice seedlings exposed to varying levels of O_3 (4, 40, 80, 120 ppb) in a growth chamber for 9 days showed reductions in quantities of proteins associated with photosynthesis and energy metabolism, and increases in some antioxidant and defense related proteins (Feng et al., 2008a). A subsequent study of O_3-treated rice seedlings (exposed to 200 ppb O_3 for 24-h) focusing on the integration of transcriptomics and proteomics, supported and further enhanced these results (Cho et al., 2008). The authors found that of the 22,000 genes analyzed from the rice genome, 1,535 were differentially regulated by O_3. Those differentially regulated genes were functionally categorized as transcription factors, MAPK cascades, those encoding for enzymes involved in the synthesis of jasmonic acid (JA),ethylene (ET), shikimate, tryptophan and lignin, and those involved in glycolysis, the citric acid cycle, oxidative respiration and photosynthesis. The authors determined that the proteome and metabolome (all small molecule metabolites in a cell) analysis supported the results of the transcriptome changes described above (Cho et al., 2008). This type of study, which ties together results from changes in gene expression, protein quantity and activity, and metabolite levels, provides the most complete picture of the molecular and biochemical changes occurring in plants exposed to a stressor such as O_3.

Sarkar et al. (2010) compared proteomes of two cultivars of wheat grown in OTCs at several O_3 concentrations, including filtered air, ambient O_3 (mean concentration 47 ppb), ambient + 10 ppb and ambient + 20 ppb for 5-h/day for 50 days. Declines in the rate of photosynthesis and stomatal conductance were related to decreases in proteins involved in carbon fixation and electron transport and increased proteolysis of photosynthetic proteins such as the large subunit of ribulose-1,6-bisphosphate carboxylase/oxygenase (Rubisco). Enzymes that take part in energy metabolism, such as ATP synthesis, were also down-regulated, while defense/stress related proteins were up-regulated in O_3 treated plants. In comparing the two wheat cultivars, Sarkar et al. (2010) found that while the qualitative changes in protein expression between the two cultivars were similar, the magnitude of these changes differed between the sensitive and tolerant wheat cultivars. Greater foliar injury and a smaller decline in stomatal conductance was observed in the sensitive cultivar as compared to the more tolerant cultivar, along with greater losses in photosynthetic enzymes and higher quantities of antioxidant enzymes. Results from a three year exposure of European beech saplings to elevated O_3 (AOT 40 value was 52.6 ul l-1-h for 2006 when trees were sampled) supported the results from the short-term exposure studies described above (Kerner et al., 2011). The O_3 treatment of

the saplings resulted in reductions in enzymes associated with the Calvin cycle, which could lead to reduced carbon fixation. Enzymes associated with carbon metabolism/catabolism were increased, and quantities of starch and sucrose were reduced in response to the O_3 treatment in these trees, indicating a potential impact of O_3 on overall carbon metabolism in long-term exposure conditions (Kerner et al., 2011).



Source: Used with permission from Springer (Mahalingam et al., 2005).

(A) Temporal profile of the oxidative stress response to ozone. The biphasic ozone-induced oxidative burst is represented in black, with the ROS control measurements shown as a broken line. Average transcript profiles are shown for early up-regulated genes (yellow, peaks at 0.5-1 hours), and the 3 hours (blue), 4.5 hours (red) and 9-12 hours (green) late up-regulated genes and for the down-regulated genes coding for photosynthesis proteins (brown). (B) Diagrammatic representation of redox regulation of the oxidative stress response.

Figure 9-5 Composite diagram of major themes in the temporal evolution of the genetic response to ozone stress. All of these studies describe common trends for changes in gene and protein expression which occur in a variety of plant species exposed to O_3. While genes associated with carbon assimilation and general metabolism are typically down-regulated, genes associated with signaling, catabolism, and defense are up-regulated. The magnitude of these changes in gene and protein expression appears to be related to plant species, age and their sensitivity or tolerance to O_3.

9.3.3.3 Role of Phytohormones in Plant Response to Ozone

Many studies of O_3 effects on plants have analyzed the importance of plant hormones such as SA, ET and JA in determining plant response to O_3; some of the roles of these hormones were described in the 2006 O_3 AQCD. Transcriptome analysis and the use of a variety of mutants have allowed for further elucidation of the complex interactions between SA, ET, JA and the role of abscisic acid (ABA) in mediating plant response to O_3 (Ludwikow and Sadowski, 2008). In addition to their roles in signaling pathways, phytohormones also appear to regulate, and be regulated by, the MAPK signaling cascades described previously. Most evidence suggests that while ET and SA are needed to develop O_3-induced leaf lesions, JA acts antagonistically to SA and ET to limit the lesions (Figure 9-6) (Kangasjarvi et al., 2005).

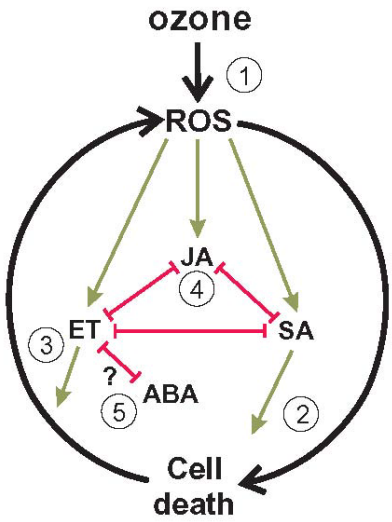
The rapid production of ET in O_3 treated plants has been described in many plant species and has been further characterized through the use of a variety of mutants that either over-produce or are insensitive to ET. Production of stress ET in O_3-treated plants, which is thought to be part of a wounding response, was found to be correlated to the degree of injury development in leaves (U.S. EPA, 2006b). More recent studies have supported these conclusions and have also focused on the interactions occurring between several oxidative-stress induced phytohormones. Yoshida et al. (2009) determined that ET likely amplifies the oxidative signal generated by ROS, thereby promoting lesion formation. By analyzing the O_3-induced transcriptome of several *Arabidopsis* mutants of the Col-0 ecotype, Tamaoki et al. (2003) determined that at 12 hours after initiating the O_3 exposure (200 ppb for 12 hours), the ET and JA signaling pathways were the main pathways used to activate plant defense responses, with a lesser role for SA. The authors also demonstrated that low levels of ET production could stimulate the expression of defense genes, rather than promoting cell death which occurs when ET production is high. Tosti et al. (2006) supported these findings by showing that plant exposure to O_3 not only results in activation of the biosynthetic pathways of ET, JA and SA, but also increases the expression of genes related to the signal transduction pathways of these phytohormones in O_3-treated *Arabidopsis* plants (300 ppb O_3 for 6 hours). Conversely, in the O_3 sensitive Ws ecotype, its sensitivity may, in part, be due to intrinsically high ET levels leading to SA accumulation, and the high ET and SA may act to repress JA-associated genes, which would serve to inhibit the spread of lesions (Mahalingam et al., 2006). Ogawa et al. (2005) found that increases in SA in O_3-treated plants leads to the formation of leaf lesions in tobacco plants exposed to 200 ppb O_3 for 6 hours. Furthermore, in transgenic tobacco plants with reduced levels of ET production in response to O_3 exposure, several genes encoding for enzymes in the biosynthetic pathway of SA were suppressed, suggesting that SA levels are, in part, controlled by ET in the presence of O_3.

Exposure of the *Arabidopsis* mutant rcd1 to acute doses of O_3 (250 ppb O_3 for 8-h/day for 3 days) resulted in programmed cell death (PCD) and the formation of leaf lesions (Overmyer et al., 2000). They determined that the observed induction of ET synthesis promotes cell death, and that ET perception and signaling are required for the accumulation of superoxide, which leads to cell death and propagation of lesions. . Jasmonic acid, conversely, contains the spread of leaf lesions (Overmyer et al., 2000). Transcriptome analysis of several Arabidopsis mutants, which are insensitive to SA, ET and JA, exposed to 12-h of 200 ppb O_3 showed that approximately 78 of the up-regulated genes measured in this study were controlled by ET and JA signaling pathways, while SA signaling pathways were suggested to antagonize ET and JA pathways (Tamaoki et al., 2003). In a subsequent transcriptome study on the Col-0 ecotype exposed to 150 ppb O_3 for 48-h, JA and ET synthesis was down-regulated, while SA was up-regulated in O_3-treated plants. In cotton plants exposed to a range of O_3 concentrations (0-120 ppb) and methyl jasmonate (MeJA), Grantz et al. (2010a) determined that exogenous applications of MeJA did not protect plants from chronic O_3 exposure.

Abscisic acid has been investigated for its role in regulating stomatal aperture and also for its contribution to signaling pathways in the plant. The role of ABA and the interaction between ABA and H_2O_2 in O_3-induced stomatal closure was described in the 2006 O_3 AQCD. More recently, it was determined that synthesis of ABA was induced in O_3-treated *Arabidopsis* plants (250-350 ppb O_3 for 6 hours), with a more pronounced induction in the O_3 sensitive rcd3 mutant as compared to the wildtype Col-0 (Overmyer et al., 2008). The rcd3 mutant also exhibited a lack of O_3-induced stomatal closure, and the RCD3 protein has been shown to be required for slow anion channels (Overmyer et al., 2008) (see Section 9.3.4.1). Ludwikow et al. (2009) used *Arabidopsis* ABI1td mutants, in which a key negative regulator of ABA action (abscisic acid insensitive1 protein phosphatase 2C) has been knocked out, to examine O_3 responsive genes in this mutant compared to the *Arabidopsis* Col-0. Results of this study indicate a role for ABI1 in negatively regulating the synthesis of both ABA and ET in O_3-treated plants (350 ppb O_3 for 9 hours). Additionally, ABI1 may stimulate JA-related gene expression, providing evidence for an antagonistic interaction between ABA and JA signaling pathways (Ludwikow et al., 2009).

Nitric oxide (NO) has also been shown to play a role in regulating gene expression in plants in response to O_3 exposure. However, little is known to date about NO and its role in the complex interactions of molecules in response to O_3. Exposure of tobacco to O_3 (150 ppb for 5 hours) stimulated NO and NO-dependent ET production, while NO production itself did not depend on the presence of ET (Ederli et al., 2006). Analysis of O_3-treated *Arabidopsis* indicated the possibility of a dual role for NO in the initiation of cell death and later lesion containment (Ahlfors et al., 2009).

While much work remains to be done to better elucidate how plants sense O_3, what determines their sensitivity to the pollutant and how they might respond to it, it is clear that the mechanism for O_3 sensing and signal transduction is very complex. Many of the phytohormones and other signaling molecules thought to be involved in these processes are interactive and depend upon a variety of other factors, which could be either internal or external to the plant. This results in a highly dynamic and complex system, capable of resulting in a spectrum of plant sensitivity to oxidative stress and generating a variety of plant responses to that stress.



Source: Used with permission from Blackwell Publishing Ltd. (Kangasjarvi et al., 2005).

Ozone-derived radicals induce endogenous ROS production (1) which results in salicylic acid (SA) accumulation and programmed cell death; (2) Cell death triggers ethylene (ET) production, which is required for the continuing ROS production responsible for the propagation of cell death; (3) Jasmonates counteract the progression of the cycle by antagonizing the cell death promoting function of SA and ET; (4) Abscisic acid (ABA) antagonizes ET function in many situations and might also have this role in ozone-induced cell death; (5) Mutually antagonistic interactions between ET, SA and jasmonic acid (JA) are indicated with red bars.

Figure 9-6 The oxidative cell death cycle. Detoxification

9.3.4.1 Overview of Ozone-Induced Defense Mechanisms

Plants are exposed to an oxidizing environment on a continual basis, and many reactions that are part of the basic metabolic processes, such as photosynthesis and respiration, generate ROS. As a result, there is an extensive and complex mechanism in place to detoxify these oxidizing radicals, including both enzymes and metabolites, which are located in several locations in the cell and also in the apoplast of the cell. As O_3 enters the leaf through open stomata, the first point of contact of O_3 with the plant is likely in the apoplast, where it breaks down to form oxidizing radicals such as H_2O_2, O_2^-, $HO\cdot$ and

HO_2. Another source of oxidizing radicals is an oxidative burst, generated by a membrane-bound NADPH oxidase enzyme, which is recognized as an integral component of the plant's defense system against pathogens (Schraudner et al., 1998). Antioxidant metabolites and enzymes located in the apoplast are thought to form a first line of defense by detoxifying O_3 and/or the ROS that are formed as breakdown products of O_3 (Section 9.3.2.). However, even with the presence of several antioxidants, including ascorbate, the redox buffering capacity of the apoplast is far less than that of the cytoplasm, as it lacks the regeneration systems necessary to retain a reduced pool of antioxidants (Foyer and Noctor, 2005b).

Redox homeostasis is regulated by the presence of a pool of antioxidants, which are typically found in a reduced state and detoxify ROS produced by oxidases or electron transport components. As ROS increase due to environmental stress such as O_3, it is unclear whether the antioxidant pool can maintain its reduced state (Foyer and Noctor, 2005b). As such, not only the quantity and types of antioxidant enzymes and metabolites present, but also the cellular ability to regenerate those antioxidants are important considerations in mechanisms of plant tolerance to oxidative stress (Dizengremel et al., 2008). Molecules such as glutathione (GSH), thioredoxins and NADPH play very important roles in this regeneration process; additionally, it has been hypothesized that alterations in carbon metabolism would be necessary to supply the needed reducing power for antioxidant regeneration (Dizengremel et al., 2008).

9.3.4.2 Role of Antioxidants in Plant Defense Responses

Ascorbate has been the focus of many different studies as an antioxidant metabolite that protects plants from exposure to O_3. It is found in several cellular locations, including the chloroplast, the cytosol and the apoplast (Noctor and Foyer, 1998). Ascorbate is synthesized in the cell and transported to the apoplast. Apoplastic ascorbate can be oxidized to dehydroascorbate (DHA) with exposure to O_3 and is then transported back to the cytoplasm. Here, DHA is reduced to ascorbate by the enzyme dehydroascorbate reductase (DHAR) and reduced GSH, which is part of the ascorbate-glutathione cycle (Noctor and Foyer, 1998). Many studies have focused on evaluating whether ascorbate is the primary determining factor in differential sensitivity of plants to O_3. An evaluation of several species of wildflowers in Great Smoky Mountains National Park showed a correlation between higher quantities of reduced apoplastic ascorbate and lower levels of foliar injury from O_3 exposure in the field in tall milkweed plants (*Asclepsias exaltata* L.) (Burkey et al., 2006; Souza et al., 2006). Cheng et al. (2007) exposed two soybean cultivars to elevated O_3 (77 ppb) and filtered air for 7-h/day for 6 days. The differences in sensitivity between the two cultivars could not be explained by differential O_3 uptake or

by the fraction of reduced ascorbate present in the apoplast. However, total antioxidant capacity of the apoplast was twofold higher in the tolerant Essex cultivar as compared to the sensitive Forrest cultivar, indicating that there may be other compounds in the leaf apoplast that scavenge ROS. D'Haese et al. (2005) exposed the NC-S (sensitive) and NC-R (resistant) clones of white clover (*Trifolium repens*) to 60 ppb O_3 for 7-h/day for 5 days in environmental chambers. Surprisingly, the NC-S clone had a higher constitutive concentration of apoplastic ascorbate with a higher redox status than the NC-R clone. However, the redox status of symplastic GSH was higher in NC-R, even though the concentration of GSH was not higher than in NC-S. In addition, total symplastic antioxidative capacity was not a determining factor in differential sensitivity between these two clones. Severino et al. (2007) also examined the role of antioxidants in the differential sensitivity of the two white clover clones by growing them in the field for a growing season and then exposing them to elevated O_3 (100 ppb for 8-h/day for 10 days) in OTC at the end of the field season. The NC-R clone had greater quantities of total ascorbate and total antioxidants than the NC-S clone at the end of the experiment. In snap bean, plants of the O_3 tolerant Provider cultivar had greater total ascorbate and more ascorbate in the apoplast than the sensitive S156 cultivar after exposure to 71 ppb O_3 for 10 days in OTC (Burkey et al., 2003). While most of the apoplastic ascorbate was in the oxidized form, the ratio of reduced ascorbate to total ascorbate was higher in Provider than S156, indicating that Provider is better able to maintain this ratio to maximize plant protection from oxidative stress. Exposure of two wheat varieties to ambient (7-h average 44 ppb O_3) and elevated (7-h average 56 ppb O_3) for 60 days in open-air field conditions showed higher concentrations of reduced ascorbate in the apoplast in the tolerant Y16 variety than the more sensitive Y2 variety, however no varietal differences were seen in the decrease in reduced ascorbate quantity in response to O_3 exposure (Feng et al., 2010). There is much evidence that supports an important role for ascorbate, particularly apoplastic ascorbate, in protecting plants from oxidative stressors such as O_3; however, it is also clear that there is much variation in the importance of ascorbate for different plant species and differing exposure conditions. Additionally, the work of several authors suggests that there may be other compounds in the apoplast which have the capacity to act as antioxidants.

While the quantities of antioxidant metabolites such as ascorbate are an important indicator of plant tolerance to O_3, the ability of the plant to recycle oxidized ascorbate efficiently also plays a large role in determining the plant's ability to effectively protect itself from sustained exposure to oxidative stress. Tobacco plants over-expressing DHAR were better protected from exposure to either chronic (100 ppb O_3 4-h/day for 30 days) or acute (200 ppb O_3 for 2 hours) conditions than control plants and those with reduced expression of DHAR (Chen and Gallie, 2005). The DHAR over-expressing plants exhibited an increase in guard cell ascorbic acid, leading to a decrease in stomatal

responsiveness to O_3 and an increase in stomatal conductance and O_3 uptake. Despite this, the presence of higher levels of ascorbic acid led to a lower oxidative load and a higher level of photosynthetic activity in the DHAR over-expressing plants (Chen and Gallie, 2005). A subsequent study with tobacco plants over-expressing DHAR confirmed some of these results. Levels of ascorbic acid were higher in the transgenic tobacco plants, and they exhibited greater tolerance to O_3 exposure (200 ppb O_3) as demonstrated by higher photosynthetic rates in the transgenic plants as compared to the control plants (Eltayeb et al., 2006). Over-expression of monodehydroascorbate reductase (MDAR) in tobacco plants also showed enhanced stress tolerance in response to O_3 exposure (200 ppb O_3), with higher rates of photosynthesis and higher levels of reduced ascorbic acid as compared to controls (Eltayeb et al., 2007). Results of these studies demonstrate the importance of ascorbic acid as a detoxification mechanism in some plant species, and also emphasize that the recycling of oxidized ascorbate to maintain a reduced pool of ascorbate is a factor in determining plant tolerance to oxidative stress.

The roles of other antioxidant metabolites and enzymes, including GSH, catalase (CAT), and superoxide dismutase (SOD), were comprehensively reviewed in the 2006 O_3 AQCD. Additional studies have supported the findings reported in that document. Superoxide dismutase (SOD) and peroxidase (POD) activities were measured in both the tolerant Bel B and sensitive Bel W3 tobacco cultivars exposed to ambient O_3 concentrations for 2 weeks 3 times throughout a growing season (Borowiak et al., 2009). In this study, SOD and POD activity, including that of several different isoforms, increased in both the sensitive and tolerant tobacco cultivars with exposure to O_3, however the isoenzyme composition for POD differed between the sensitive and tolerant tobacco cultivars (Borowiak et al., 2009) Tulip poplar (*Liriodendron tulipifera*) trees exposed to increasing O_3 concentrations (from 100 to 300 ppb O_3 during a 2-week period) showed increases in activities of SOD, ascorbate peroxidase (APX), glutathione reductase (GR), MDAR, DHAR, CAT and POD in the 2-week period, although individual enzyme activities increased at different times during the 2-week period (Ryang et al., 2009).

Longer, chronic O_3 exposures in trees revealed increases in SOD and APX activity in *Quercus mongolica* after 45 days of plant exposure to 80 ppb O_3, which were followed by declines in the activities and quantities of these enzymes after 75 days of exposure (Yan et al., 2010). Similarly, activities of SOD, APX, DHAR, MDAR, and GR increased in *Gingko biloba* trees during the first 50 days of exposure to 80 ppb O_3, followed by decreases in activity below control values after 50 days of exposure (He et al., 2006). Soybean plants exposed to 70 or 100 ppb O_3 for 4-h/day over the course of a growing season showed elevated POD activity and a decrease in CAT activity at 40 and 60 days after germination (Singh et al., 2010a).

Antioxidant enzymes and metabolites have been shown to play an important role in determining plant tolerance to O_3 and mediating plant responses to O_3. However, there is also some evidence to suggest that the direct reaction of ascorbate with O_3 could lead to the formation of secondary toxicants, such as peroxy compounds, which may act upon signal transduction pathways and modulate plant response to O_3 (Sandermann, 2008). Therefore, the role of ascorbate and other antioxidants and their interaction with other plant responses to O_3, such as the activation of signal transduction pathways, is likely far more complex than is currently understood.

9.3.5 Effects on Primary and Secondary Metabolism

9.3.5.1 Light and Dark Reactions of Photosynthesis

Declines in the rate of photosynthesis and stomatal conductance in O_3-treated plants have been documented for many different plant species (Booker et al., 2009; U.S. EPA, 2006b) (Wittig et al., 2007). The 2006 O_3 AQCD outlined what is known about the effects of O_3 on carbon assimilation, and the more recent scientific literature confirms these findings. While several measures of the light reactions of photosynthesis are sensitive to exposure to O_3 (see below), photosynthetic carbon assimilation is generally considered to be more affected by pollutant exposure, resulting in an overall decline in photosynthesis (Guidi and Degl'lnnocenti, 2008; Heath, 2008; Fiscus et al., 2005). Loss of carbon assimilation capacity has been shown to result primarily from declines in the quantity of Rubisco (Singh et al., 2009; Calatayud et al., 2007a). Experimental evidence suggests that both decreases in Rubisco synthesis and enhanced degradation of the protein contribute to the measured reduction in its quantity (U.S. EPA, 2006b). Reduced carbon assimilation has been linked to reductions in biomass and yield (Wang et al., 2009b; He et al., 2007; Novak et al., 2007; Gregg et al., 2006; Keutgen et al., 2005). Recent studies evaluating O_3 induced changes in the transcriptome and proteome of several different species confirm these findings. Levels of mRNA for the small subunit of Rubisco (rbcS) declined in European beech saplings exposed to 300 ppb O_3 for 8-h/day for up to 26 days (Olbrich et al., 2005). Similar declines in rbcS mRNA were also measured in the beech saplings in a free air exposure system over a course of two growing seasons (Olbrich et al., 2009). Proteomics studies have also confirmed the effects of O_3 on proteins involved in carbon assimilation. Reductions in quantities of the small and large subunit (rbcL) of Rubisco and Rubisco activase were measured in soybean plants exposed to 120 ppb O_3 for 3 days in growth chambers (Ahsan et al., 2010). Exposure of young poplar trees to 120 ppb O_3 for 35 days in exposure chambers resulted in reductions of Rubisco, Rubisco activase, and up to 24 isoforms of Calvin cycle enzymes, most of which play a role in regenerating

the CO_2 acceptor molecule, ribulose-1.5-bisphosphate (Bohler et al., 2007). Reductions in protein quantity of both the small and large subunit of Rubisco were seen in wheat plants exposed to ambient (average concentration 47.3 ppb O_3) and elevated O_3 (ambient + 10 or 20 ppb O_3) in open-top chambers for 5-h/day for 50 days (Sarkar et al., 2010). Lettuce plants exposed to 100 ppb O_3 in growth chambers for 8-h/day for 3 weeks also showed reductions in transcript and protein levels of the small and large subunits of Rubisco and Rubisco activase (Goumenaki et al., 2010). The reductions in carbon assimilation have been associated with declines in both the mRNA of the small and large subunits of Rubisco, and with reductions in Rubisco activase mRNA and protein. Additionally, the reduction in Rubisco quantity has also been associated with the O_3-induced oxidative modification of the enzyme, which is evidenced by the increases in carbonyl groups on the protein after plant exposure to O_3.

In addition to impacts on carbon assimilation, the deleterious effects of O_3 on the photosynthetic light reactions have received more attention in recent years. Chlorophyll fluorescence provides a useful measure of changes to the photosynthetic process from exposure to oxidative stress. Decreases in the Fv/Fm ratio (a measure of the maximum efficiency of Photosystem II) in dark adapted leaves indicate a decline in the efficiency of the PSII photosystems and a concomitant increase in non-photochemical quenching (Guidi and Degl'lnnocenti, 2008; Scebba et al., 2006). Changes in these parameters have been correlated to differential sensitivity of plants to the pollutant. In a study to evaluate the response of 4 maple species to O_3 (exposed to an 8-h avg of 51 ppb for ambient and 79 ppb for elevated treatment in OTC), the 2 species which were most sensitive based on visible injury and declines in CO_2 assimilation also showed the greatest decreases in Fv/Fm in symptomatic leaves. In asymptomatic leaves, CO_2 assimilation decreased significantly but there was no significant decline in Fv/Fm (Calatayud et al., 2007a). Degl 'Innocenti et al. (2007) measured significant decreases in Fv/Fm in young and symptomatic leaves of a resistant tomato genotype (line 93.1033/1) in response to O_3 exposure (150 ppb O_3 for 3 hours in a growth chamber), but only minor decreases in asymptomatic leaves with no associated changes in net photosynthetic rate. In the O_3 sensitive tomato cultivar Cuor Di Bue, the Fv/Fm ratio did not change, while the photosynthetic rate declined significantly in asymptomatic leaves (Degl'Innocenti et al., 2007). In two soybean cultivars, Fv/Fm also declined significantly with plant exposure to O_3 (Singh et al., 2009). It appears that in asymptomatic leaves, photoinhibition, as indicated by a decrease in Fv/Fm, is not the main reason for a decline in photosynthesis.

An evaluation of photosynthetic parameters of two white clover (*Trifolium repens* cv. Regal) clones that differ in their O_3 sensitivity revealed that O_3 (40-110 ppb O_3 for 7-h/day for 5 days) increased the coefficient of non-photochemical quenching (q_{NP}) in both the resistant (NC-R) and sensitive (NC-S) clones, however q_{NP} was significantly lower

for the sensitive clone (Crous et al., 2006). Sensitive *Acer* clones had a lower coefficient of non-photochemical quenching, while exposure to O_3 increased q_{NP} in both sensitive and tolerant clones (Calatayud et al., 2007a). While exposure to O_3 also increased q_{NP} in tomato, there were no differences in the coefficient of photochemical quenching between cultivars thought to be differentially sensitive to O_3. (Degl'Innocenti et al., 2007). Higher q_{NP} as a result of exposure to O_3 indicates a reduction in the proportion of absorbed light energy being used to drive photochemistry. A lower coefficient of non-photochemical quenching in O_3 sensitive plants could indicate increased vulnerability to ROS generated during exposure to oxidative stress (Crous et al., 2006).

Most of the research on O_3 effects on photosynthesis has focused on C3 (Calvin cycle) plants because C4 (Hatch-Slack) plants have lower stomatal conductance and are, therefore, thought to be less sensitive to O_3 stress. However, a few studies have been conducted to evaluate the effects of O_3 on C4 photosynthesis. In older maize leaves, Leitao et al. (2007b; 2007c) found that the activity, quantity and transcript levels of both Rubisco and phosphoenolpyruvate carboxylase (PEPc) decreased as a function of rising O_3 concentration. In younger maize leaves, the quantity, activity, and transcript levels of the carboxylases were either increased or unaffected in plants exposed to 40 ppb O_3 for 7- h/day for 28-33 days, but decreased at 80 ppb (Leitao et al., 2007a; Leitao et al., 2007b).

9.3.5.2 Respiration and Dark Respiration

While much research emphasis regarding O_3 effects on plants has focused on the negative impacts on carbon assimilation, other studies have measured impacts on catabolic pathways such as shoot respiration and photorespiration. Generally, shoot respiration has been found to increase in plants exposed to O_3. Bean plants exposed to ambient (average 12-h mean 43 ppb) and twice ambient (average 12-h mean 80 ppb) O_3 showed increases in respiration. When mathematically partitioned, the maintenance coefficient of respiration was significantly increased in O_3 treated plants, while the growth coefficient of respiration was not affected (Amthor, 1988). Loblolly pines were exposed to ambient (12-h daily mean was 45 ppb) and twice ambient (12 hours daily mean was 86 ppb) O_3 for 12-h/day for approximately seven months per year for 3 and 4 years. While photosynthetic activity declined with the age of the needles and increasing O_3 concentration, enzymes associated with respiration showed higher levels of activity with increasing O_3 concentration (Dizengremel et al., 1994). In their review on the role of metabolic changes in plant redox status after O_3 exposure, Dizengremel et al. (2009) summarized multiple studies in which several different tree species were exposed to O_3 concentrations ranging from ambient to 200 ppb O_3 for at least several weeks. In all

cases, the activity of enzymes, including phosphofructokinase, pyruvate kinase and fumarase, which are part of several catabolic pathways, were increased in O_3 treated plants.

Photorespiration is a light-stimulated process which consumes O_2 and releases CO_2. While it has been regarded as a wasteful process, more recent evidence suggests that it may play a role in photoprotection during photosynthesis (Bagard et al., 2008). The few studies that have been conducted on O_3 effects on photorespiration suggest that rates of photorespiration decline concomitantly with rates of photosynthesis. Soybean plants were exposed to ambient (daily averages 43-58 ppb) and 1.5 ambient O_3 (daily averages 63-83 ppb) O_3 in OTCs for 12-h/day for 4 months. Rates of photosynthesis and photorespiration and photorespiratory enzyme activity declined only at the end of the growing season and did not appear to be very sensitive to O_3 exposure (Booker et al., 1997). Young hybrid poplars exposed to 120 ppb O_3 for 13-h/day for 35 days in phytotron chambers showed that effects on photorespiration and photosynthesis were dependent upon the developmental stage of the leaf. While young leaves were not impacted, reductions in photosynthesis and photorespiration were measured in fully expanded leaves (Bagard et al., 2008).

9.3.5.3 Secondary Metabolism

Transcriptome analysis of *Arabidopsis* plants has revealed modulation of several genes involved in plant secondary metabolism (Ludwikow and Sadowski, 2008). Phenylalanine ammonia lyase (PAL) has been the focus of many studies involving plant exposure to O_3 due to its importance in linking the phenylpropanoid pathway of plant secondary metabolism to primary metabolism in the form of the shikimate pathway. Genes encoding several enzymes of the phenylpropanoid pathway and lignin biosynthesis were up-regulated in transcriptome analysis of *Arabidopsis* plants (Col-0) exposed to 350 ppb O_3 for 6 hours, while 2 genes involved in flavonoid biosynthesis were down-regulated (Ludwikow et al., 2004). Exposure of *Arabidopsis* (Col-0) to lower O_3 concentrations (150 ppb for 8-h/day for 2 days) resulted in the induction of 11 transcripts involved in flavonoid synthesis. In their exposure of 2-year-old Mediterranean shrub *Phillyrea latifolia* to 110 ppb O_3 for 90 days, Paolacci et al. (2007) identified four clones that were up-regulated and corresponded to genes involved in the synthesis of secondary metabolites, such as isoprenoids, polyamines and phenylpropanoids. Up-regulation of genes involved in isoprene synthesis was also observed in *Medicago trunculata* exposed to 300 ppb O_3 for 6 hours, while genes encoding enzymes of the flavonoid synthesis pathway were either up- or down-regulated (Puckette et al., 2008). Exposure of red clover to 1.5 × ambient O_3 (average concentrations of 32.4 ppb) for up to 9 weeks in an open

field exposure system resulted in increases in leaf total phenolic content. However, the types of phenolics that were increased in response to O_3 exposure differed depending upon the developmental stage of the plant. While almost all of the 31 different phenolic compounds measured increased in quantity initially during the exposure, after 3 weeks the quantity of isoflavones decreased while other phenolics increased (Saviranta et al., 2010). Exposure of beech saplings to ambient and 2 × ambient O_3 concentrations over 2 growing seasons resulted in the induction of several enzymes which contribute to lignin formation, while enzymes involved in flavonoid biosynthesis were down-regulated (Olbrich et al., 2009). Exposure of tobacco Bel W3 to 160 ppb O_3 for 5 hours showed up-regulation of almost all genes encoding for enzymes which are part of the prechorismate pathway (Janzik et al., 2005). Isoprenoids can serve as antioxidant compounds in plants exposed to oxidative stress (Paolacci et al., 2007).

The prechorismate pathway is the pathway leading to the formation of chorismate, a precursor to the formation of the aromatic amino acids tryptophan, tyrosine and phenylalanine. These amino acids are precursors for the formation of many secondary aromatic compounds, and, therefore, the prechorismate pathway represents a branch-point in the regulation of metabolites into either primary or secondary metabolism (Janzik et al., 2005). Exposure of the O_3 sensitive Bel W3 tobacco cultivar at 160 ppb for 5 hours showed an increase in transcript levels of most of the genes encoding enzymes of the prechorismate pathway. However, shikimate kinase (SK) did not show any change in transcript levels and only one of three isoforms of DAHPS (3-deoxy-D-arabino-heptulosonat-7-phosphate synthase), the first enzyme in this pathway, was induced by O_3 exposure (Janzik et al., 2005). Differential induction of DAHPS isoforms was also observed in European beech after 40 days of exposure to 150-190 ppb O_3. At this time point in the beech experiment, transcript levels of shikimate pathway enzymes, including SK, were generally strongly induced after an only weak initial induction after the first 40 days of exposure. Both soluble and cell-wall bound phenolic metabolites showed only minimal increases in response to O_3 for the duration of the exposure period (Alonso et al., 2007). Total leaf phenolics decreased with leaf age in *Populus nigra* exposed to 80 ppb O_3 for 12-h/day for 14 days. Ozone increased the concentration of total leaf phenolics in newly expanded leaves, with the most significant increases occurring in compounds such as quercitin glycoside, which has a high antioxidant capacity (Fares et al., 2010b). While several phenylpropanoid pathway enzymes were induced in two poplar clones exposed to 60 ppb O_3 for 5-h/day for 15 days, the degree of induction differed between the two clones. In the tolerant I-214 clone, PAL activity increased nine fold in O_3-treated plants as compared to controls, while there was no significant difference in PAL activity in the sensitive Eridano clone (Di Baccio et al., 2008).

Polyamines such as putrescine, spermidine and spermine play a variety of roles in plants and have been implicated in plant defense responses to both abiotic and biotic stresses. They exist in both a free form and conjugated to hydroxycinnamic acids. Investigations on the role of polyamines have found that levels of putrescine increase in response to oxidative stress. This increase stems largely from the increase in the activity of arginine decarboxylase (ADC), a key enzyme in the synthesis of putrescine (Groppa and Benavides, 2008). Langebartels et al. (1991) described differences in putrescine accumulation in O_3-treated tobacco plants exposed to several O_3 concentrations, ranging from 0-400 ppb for 5-7 hours. A large and rapid increase in putrescine occurred in the tolerant Bel B cultivar and only a small increase in the sensitive Bel W3 cultivar, which occurred only after the formation of necrotic leaf lesions. Van Buuren et al. (2002) further examined the role of polyamines in these two tobacco cultivars during an acute (130 ppb O_3 for 7-h in a growth chamber) exposure. They found that while free putrescine accumulated in undamaged tissue of both cultivars, conjugated putrescine predominantly accumulated in tissues undergoing cell death after plant exposure to O_3 (van Buuren et al., 2002). The authors suggest that while free putrescine may not play a role in conferring tolerance in the Bel B cultivar, conjugated putrescine may play a role in O_3-induced programmed cell death in Bel W3 plants.

Isoprene is emitted by some plant species and represents the predominant biogenic source of hydrocarbon emissions in the atmosphere (Guenther et al., 2006). In the atmosphere, the oxidation of isoprene by hydroxyl radicals can enhance O_3 formation in the presence of NO_X, thereby impacting the O_3 concentration that plants are exposed to. While isoprene emission varies widely between species, it has been proposed to stabilize membranes and provide those plant species that produce it with a mechanism of thermotolerance (Sharkey et al., 2008). It has also been suggested that isoprene may act as an antioxidant compound to scavenge O_3 (Loreto and Velikova, 2001). Recent studies using a variety of plant species have shown conflicting results in trying to understand the effects of O_3 on isoprene emission. Exposure to acute doses of O_3 (300 ppb for 3-h) in detached leaves of *Phragmites australis* resulted in stimulation of isoprene emissions (Velikova et al., 2005). Similar increases in isoprene emissions were measured in *Populus nigra* after exposure to 100 ppb O_3 for 5 days continuously (Fares et al., 2008). Isoprene emission in attached leaves of *Populus alba*, which were exposed to 150 ppb O_3 for 11-h/day for 30 days inside cuvettes, was inhibited, while isoprene emission and transcript levels of isoprene synthase mRNA were increased in the leaves exposed to ambient O_3 (40 ppb), which were located above the leaves enclosed in the exposure cuvettes (Fares et al., 2006). Exposure of 2 genotypes of hybrid poplar to 120 ppb O_3 for 6-h/day for 8 days resulted in a significant reduction in isoprene emission in the O_3-sensitive but not the tolerant genotype (Ryan et al., 2009). Similarly, O_3 treatment (80 ppb 12-h/day for 14 days) of *Populus nigra* showed that isoprene emission was

reduced in the treated plants relative to the control plants (Fares et al., 2010b). Based on results of this and other studies, Fares et al. (2010b) concluded that the isoprenoid pathway may be induced in plants exposed to acute O_3 doses, while at lower doses isoprene emission may be inhibited. Vickers et al. (2009) developed transgenic tobacco plants with the isoprene synthase gene from *Populus alba* and exposed them to 120 ppb O_3 for 6-h/day for 2 days. They determined that the wildtype plants showed significantly more O_3 damage, including the development of leaf lesions and a decline in photosynthetic rates, than the transgenic, isoprene-emitting plants. Transgenic plants also accumulated less H_2O_2 and had lower levels of lipid peroxidation following exposure to O_3 than the wildtype plants (Vickers et al., 2009). These results indicate that isoprene may have a protective role for plants exposed to oxidative stress.

9.3.6 Summary

The results of recent studies on the effects of O_3 stress on plants support and strengthen those reported in the 2006 O_3 AQCD. The most significant new body of evidence since the 2006 O_3 AQCD comes from research on molecular mechanisms of the biochemical and physiological changes observed in many plant species in response to O_3 exposure. Recent studies have employed new techniques, such as those used in evaluating transcriptomes and proteomes to perform very comprehensive analyses of changes in gene transcription and protein expression in plants exposed to O_3. These newer molecular studies not only provide very important information regarding the many mechanisms of plant responses to O_3, they also allow for the analysis of interactions between various biochemical pathways which are induced in response to O_3. However, many of these studies have been conducted in artificial conditions with model plants, which are typically exposed to very high, short doses of O_3. Therefore, additional work remains to elucidate whether these plant responses are transferable to other plant species exposed to more realistic ambient conditions.

Ozone is taken up into leaves through open stomata. Once inside the substomatal cavity, O_3 is thought to rapidly react with the aqueous layer surrounding the cell (apoplast) to form breakdown products such as hydrogen peroxide (H_2O_2), superoxide ($O_2^{\cdot-}$), hydroxyl radicals ($HO^{\cdot}$) and peroxy radicals ($HO_2^{\cdot}$). Plants could be sensing the presence of O_3 and/or its breakdown products in a variety different ways, depending upon the plant species and the exposure parameters. Experimental evidence suggests that mitogen-activated protein kinases and calcium are important components of the signal transduction pathways, which communicate signals to the nucleus and lead to changes in gene expression in response to O_3. It is probable that there are multiple sensing mechanisms and signal transduction pathways, and their activation may depend upon the

plant species, its developmental stage and/or O_3 exposure conditions. Initiation of signal transduction pathways in O_3 treated plants has also been observed in stomatal guard cells. Reductions in stomatal conductance in have been described for many plant species exposed to O_3, and new experimental evidence suggests that this reduction may be due not only to a decrease in carboxylation efficiency, but also to a direct impact of O_3 on stomatal guard cell function, leading to a changes in stomatal conductance.

Alterations in gene transcription that have been observed in O_3-treated plants are now evaluated more comprehensively using DNA microarray studies, which measure changes in the entire transcriptome rather than measuring the transcript levels of individual genes. These studies have demonstrated very consistent trends, even though O_3 exposure conditions (concentration, duration of exposure), plant species and sampling times vary significantly. Genes involved in plant defense, signaling, and those associated with the synthesis of plant hormones and secondary metabolism are generally up-regulated in plants exposed to O_3, while those related to photosynthesis and general metabolism are typically down-regulated. Proteome studies support these results by demonstrating concomitant increases or decreases in the proteins encoded by these genes. Transcriptome analysis has also illuminated the complex interactions that exist between several different phytohormones and how they modulate plant sensitivity and response to O_3. Experimental evidence suggests that while ethylene and salicylic acid are needed to develop O_3-induced leaf lesions, jasmonic acid acts antagonistically to ethylene and salicylic acid to limit the spread of the lesions. Abscisic acid, in addition to its role in regulating stomatal aperture, may also act antagonistically to the jasmonic acid signaling pathway. Changes in the quantity and activity of these phytohormones and the interactions between them reveal some of the complexity of plant responses to an oxidative stressor such as O_3.

Another critical area of interest is to better understand and quantify the capacity of the plant to detoxify oxygen radicals using antioxidant metabolites, such as ascorbate and glutathione, and the enzymes that regenerate them. Ascorbate remains an important focus of research, and, due to its location in the apoplast in addition to other cellular compartments, it is regarded as a first line of defense against oxygen radicals formed in the apoplast. Most studies demonstrate that antioxidant metabolites and enzymes increase in quantity and activity in plants exposed to O_3, indicating that they play an important role in protecting plants from oxidative stress. However, attempts to quantify the detoxification capacity of plants have remained unsuccessful, as high quantities of antioxidant metabolites and enzymes do not always translate into greater protection of the plant. Considerable variation exists between plant species, different developmental stages, and the environmental and O_3 exposure conditions which plants are exposed to.

As indicated earlier, the described alterations in transcript levels of genes correlate with observed changes quantity and activity of the enzymes and metabolites involved in primary and secondary metabolism. In addition to the generalized up-regulation of the antioxidant defense system, photosynthesis typically declines in O_3 treated plants. Declines in C fixation due to reductions in quantity and activity of Rubisco were extensively described in the 2006 O_3 AQCD. More recent studies support these results and indicate that declines in Rubisco activity may also result from reductions in Rubisco activase enzyme quantity. Other studies, which have focused on the light reactions of photosynthesis, demonstrate that plant exposure to O_3 results in declines in electron transport efficiency and a decreased capacity to quench oxidizing radicals. Therefore, the overall declines in photosynthesis observed in O_3 -treated plants likely result from combined impacts on stomatal conductance, carbon fixation and the light reactions. While photosynthesis generally declines in plants exposed to O_3, catabolic pathways such as respiration have been shown to increase. It has been hypothesized that increased respiration may result from greater energy needs for defense and repair. Secondary metabolism is generally up-regulated in a variety of species exposed to O_3 as a part of a generalized plant defense mechanism. Some secondary metabolites, such as flavonoids and polyamines, are of particular interest as they are known to have antioxidant properties. The combination of decreases in C assimilation and increases in catabolism and the production of secondary metabolites would negatively impact plants by decreasing the energy available for growth and reproduction.

9.4 Nature of Effects on Vegetation and Ecosystems

9.4.1 Introduction

Ambient O_3 concentrations have long been known to cause visible symptoms, decreases in photosynthetic rates, decreases in growth and yield of plants as well as many other effects on ecosystems (U.S. EPA, 2006b, 1996c, 1986, 1978a). Numerous studies have related O_3 exposure to plant responses, with most effort focused on the yield of crops and the growth of tree seedlings. Many experiments exposed individual plants grown in pots or soil under controlled conditions to known concentrations of O_3 for a segment of daylight hours for some portion of the plant's life span. Information in this section also goes beyond individual plant scale responses to consider effects at the broader ecosystem scale, including effects related to ecosystem services.

This section will focus mainly on studies published since the release of the 2006 O_3 AQCD. However, because much O_3 research was conducted prior to the 2006 O_3 AQCD,

the present discussion of vegetation and ecosystem response to O_3 exposure is largely based on the conclusions of the 1978, 1986, 1996, and 2006 O_3 AQCDs.

9.4.1.1 Ecosystem Scale, Function, and Structure

Information presented in this section was collected at multiple spatial scales, ranging from the physiology of a given species to population, community, and ecosystem investigations. An ecological population is a group of individuals of the same species and a community is an assemblage of populations of different species interacting with one another that inhabit an area. For this assessment, "ecosystem" is defined as the interactive system formed from all living organisms and their abiotic (physical and chemical) environment within a given area (IPCC, 2007a). The boundaries of what could be called an ecosystem are somewhat arbitrary, depending on the focus of interest or study. Thus, the extent of an ecosystem may range from very small spatial scales to, ultimately, the entire Earth (IPCC, 2007a). All ecosystems, regardless of size or complexity, have interactions and physical exchanges between biota and abiotic factors, this includes both structural (e.g., soil type and food web trophic levels) and functional (e.g., energy flow, decomposition, nitrification) attributes.

Ecosystems are most often defined by their structure based on the number and type of species present. Structure may refer to a variety of measurements including the species richness, abundance, community composition and biodiversity as well as landscape attributes. Competition among and within species and their tolerance to environmental stressors are key elements of survivorship. When environmental conditions are shifted, for example, by the presence of anthropogenic air pollution, these competitive relationships may change and tolerance to stress may be exceeded. Ecosystems may also be defined on a functional basis. "Function" refers to the suite of processes and interactions among the ecosystem components and their environment that involve nutrient and energy flow as well as other attributes including water dynamics and the flux of trace gases. Plant processes including photosynthesis, respiration, C allocation, nutrient uptake and evaporation, are directly related to functions of energy flow and C, nutrient and water cycling. The energy accumulated and stored by vegetation (via photosynthetic C capture) is available to other organisms. Energy moves from one organism to another through food webs, until it is ultimately released as heat. Nutrients and water can be recycled. Air pollution alters the function of ecosystems when elemental cycles or the energy flow are altered. This alteration can also be manifested in changes in the biotic composition of ecosystems.

There are at least three levels of ecosystem response to pollutants: (1) the individual organism and its environment; (2) the population and its environment; and (3) the biological community composed of many species and their environment (Billings, 1978). Individual organisms within a population vary in their ability to withstand the stress of environmental change. The response of individual organisms within a population is based on their genetic constitution, stage of growth at time of exposure to stress, and the microhabitat in which they are growing (Levine and Pinto, 1998). The stress range within which organisms can exist and function determines the ability of the population to survive. Those best able to cope with environmental stressors survive and reproduce. Competition among different species results in succession (community change over time) and, ultimately, sensitive species may be progressively replaced and communities shift to favor those species that may have the capability to tolerate stressors such as O_3 (Rapport and Whitford, 1999; Guderian, 1985).

9.4.1.2 Ecosystem Services

Ecosystem structure and function may be translated into ecosystem services. Ecosystem services are the benefits people obtain from ecosystems (UNEP, 2003). Ecosystems provide many goods and services that are of vital importance for the functioning of the biosphere and provide the basis for the delivery of tangible benefits to human society. Hassan et al. (2005) define these benefits to include supporting, provisioning, regulating, and cultural services:

- Supporting services are necessary for the production of all other ecosystem services. Some examples include biomass production, production of atmospheric O_2, soil formation and retention, nutrient cycling, water cycling, and provisioning of habitat. Biodiversity is a supporting service that is increasingly recognized to sustain many of the goods and services that humans enjoy from ecosystems. These provide a basis for three higher-level categories of services.
- Provisioning services, such as products (Gitay et al., 2001), i.e., food (including game, roots, seeds, nuts and other fruit, spices, fodder), water, fiber (including wood, textiles), and medicinal and cosmetic products (such as aromatic plants, pigments).
- Regulating services that are of paramount importance for human society such as (1) C sequestration, (2) climate and water regulation, (3) protection from natural hazards such as floods, avalanches, or rock-fall, (4) water and air purification, and (5) disease and pest regulation.

- Cultural services that satisfy human spiritual and aesthetic appreciation of ecosystems and their components including recreational and other nonmaterial benefits.

In the sections that follow, available information on individual, population and community response to O_3 will be discussed. Effects of O_3 on productivity and C sequestration, water cycling, below-ground processes, competition and biodiversity, and insects and wildlife are considered below and in the context of ecosystem services where appropriate.

9.4.2 Visible Foliar Injury and Biomonitoring

Visible foliar injury resulting from exposure to O_3 has been well characterized and documented over several decades on many tree, shrub, herbaceous, and crop species (U.S. EPA, 2006b, 1996b, 1984, 1978a). Visible foliar injury symptoms are considered diagnostic as they have been verified experimentally in exposure-response studies, using exposure methodologies such as CSTRs, OTCs, and free-air fumigation (see Section 9.2 for more detail on exposure methodologies). Several pictorial atlases and guides have been published, providing details on diagnosis and identification of O_3-induced visible foliar injury on many plant species throughout North America (Flagler, 1998; NAPAP, 1987) and Europe (Innes et al., 2001; Sánchez et al., 2001). Typical visible injury symptoms on broad-leaved plants include: stippling, flecking, surface bleaching, bifacial necrosis, pigmentation (e.g., bronzing), chlorosis, and/or premature senescence. Typical visible injury symptoms for conifers include: chlorotic banding, tip burn, flecking, chlorotic mottling, and/or premature senescence of needles. Although common patterns of injury develop within a species, these foliar lesions can vary considerably between and within taxonomic groups. Furthermore, the degree and extent of visible foliar injury development varies from year to year and site to site (Orendovici-Best et al., 2008; Chappelka et al., 2007; Smith et al., 2003), even among co-members of a population exposed to similar O_3 levels, due to the influence of co-occurring environmental and genetic factors. Nevertheless, Chappelka et al. (2007) reported that the average incidence of O_3-induced foliar injury was 73% on milkweed in the Great Smoky Mountains National Park in the years 1992-1996.

Although the majority of O_3-induced visible foliar injury occurrence has been observed on seedlings and small plants, many studies have reported visible injury of mature coniferous trees, primarily in the western U.S. (Arbaugh et al., 1998) and to mature deciduous trees in eastern North America (Schaub et al., 2005; Vollenweider et al., 2003;

Chappelka et al., 1999a; Chappelka et al., 1999b; Somers et al., 1998; Hildebrand et al., 1996).

It is important to note that visible foliar injury occurs only when sensitive plants are exposed to elevated O_3 concentrations in a predisposing environment. A major modifying factor for O_3-induced visible foliar injury is the amount of soil moisture available to a plant during the year that the visible foliar injury is being assessed. This is because lack of soil moisture generally decreases stomatal conductance of plants and, therefore, limits the amount of O_3 entering the leaf that can cause injury (Matyssek et al., 2006; Panek, 2004; Grulke et al., 2003a; Panek and Goldstein, 2001; Temple et al., 1992; Temple et al., 1988). Consequently, many studies have shown that dry periods in local areas tend to decrease the incidence and severity of O_3-induced visible foliar injury; therefore, the incidence of visible foliar injury is not always higher in years and areas with higher O_3, especially with co-occurring drought (Smith et al., 2003). Other factors such as leaf age influence the severity of symptom expression with older leaves showing greater injury severity as a result of greater seasonal exposure (Zhang et al., 2010a).

Although visible injury is a valuable indicator of the presence of phytotoxic concentrations of O_3 in ambient air, it is not always a reliable indicator of other negative effects on vegetation. The significance of O_3 injury at the leaf and whole plant levels depends on how much of the total leaf area of the plant has been affected, as well as the plant's age, size, developmental stage, and degree of functional redundancy among the existing leaf area. Previous O_3 AQCDs have noted the difficulty in relating visible foliar injury symptoms to other vegetation effects such as individual plant growth, stand growth, or ecosystem characteristics (U.S. EPA, 2006b, 1996b). As a result, it is not presently possible to determine, with consistency across species and environments, what degree of injury at the leaf level has significance to the vigor of the whole plant. However, in some cases, visible foliar symptoms have been correlated with decreased vegetative growth (Somers et al., 1998; Karnosky et al., 1996; Peterson et al., 1987; Benoit et al., 1982) and with impaired reproductive function (Chappelka, 2002; Black et al., 2000). Conversely, the lack of visible injury does not always indicate a lack of phytotoxic concentrations of O_3 or a lack of non-visible O_3 effects (Gregg et al., 2006, 2003).

9.4.2.1 Biomonitoring

The use of biological indicators to detect phytotoxic levels of O_3 is a longstanding and effective methodology (Chappelka and Samuelson, 1998; Manning and Krupa, 1992). A plant bioindicator can be defined as a vascular or nonvascular plant exhibiting a typical

and verifiable response when exposed to a plant stress such as an air pollutant (Manning, 2003). To be considered a good indicator species, plants must (1) exhibit a distinct, verified response; (2) have few or no confounding disease or pest problems; and (3) exhibit genetic stability (U.S. EPA, 2006b). Such sensitive plants can be used to detect the presence of a specific air pollutant such as O_3 in the ambient air at a specific location or region and, as a result of the magnitude of their response, provide unique information regarding specific ambient air quality. Bioindicators can be either introduced sentinels, such as the widely used tobacco (*Nicotiana tabacum*) variety Bel W3 (Calatayud et al., 2007b; Laffray et al., 2007; Nali et al., 2007; Gombert et al., 2006; Kostka-Rick and Hahn, 2005; Heggestad, 1991) or detectors, which are sensitive native plant species (Chappelka et al., 2007; Souza et al., 2006). The approach is especially useful in areas where O_3 monitors are not operated (Manning, 2003). For example, in remote wilderness areas where instrument monitoring is generally not available, the use of bioindicator surveys in conjunction with the use of passive samplers (Krupa et al., 2001) may be a useful methodology (Manning, 2003). However, it requires expertise in recognizing those signs and symptoms uniquely attributable to exposure to O_3 as well as in their quantitative assessment.

Since the 2006 O_3 AQCD, new sensitive plant species have been identified from field surveys and verified in controlled exposure studies (Kline et al., 2009; Kline et al., 2008). Several multiple-year field surveys have also been conducted at National Wildlife Refuges in Maine, Michigan, New Jersey, and South Carolina (Davis, 2009, 2007a, b; Davis and Orendovici, 2006).

The USDA Forest Service through the Forest Health Monitoring Program (FHM) (1990 - 2001) and currently the Forest Inventory and Analysis (FIA) Program has been collecting data regarding the incidence and severity of visible foliar injury on a variety of O_3 sensitive plant species throughout the U.S. (Coulston et al., 2003; Smith et al., 2003). The plots where these data are taken are known as biosites. These biosites are located throughout the country and analysis of visible foliar injury within these sites follows a set of established protocols. For more details, see http://www.nrs.fs.fed.us/fia/topics/ozone/ (USDA, 2011). The network has provided evidence of O_3 concentrations high enough to induce visible symptoms on sensitive vegetation. From repeated observations and measurements made over a number of years, specific patterns of areas experiencing visible O_3 injury symptoms can be identified. Coulston et al. (2003) used information gathered over a 6-year period (1994-1999) from the network to identify several species that were sensitive to O_3 over a regional scale including sweetgum (*Liquidambar styraciflua*), loblolly pine (*Pinus taeda*), and black cherry (*Prunus serotina*). In a study of the west coast of the U.S, Campbell et al. (2007) reported O_3 injury in 25-37% of biosites in California forested ecosystems from 2000-2005.

A study by Kohut (2007) assessed the risk of O_3-induced visible foliar injury on bioindicator plants (NPS, 2006) in 244 national parks in support of the National Park Service's Vital Signs Monitoring Network (NPS, 2007). The risk assessment was based on a simple model relating response to the interaction of species, level of O_3 exposure, and exposure environment. Kohut (2007) concluded that the risk of visible foliar injury was high in 65 parks (27%), moderate in 46 parks (19%), and low in 131 parks (54%). Some of the well-known parks with a high risk of O_3-induced visible foliar injury include Gettysburg, Valley Forge, Delaware Water Gap, Cape Cod, Fire Island, Antietam, Harpers Ferry, Manassas, Wolf Trap Farm Park, Mammoth Cave, Shiloh, Sleeping Bear Dunes, Great Smoky Mountains, Joshua Tree, Sequoia and Kings Canyon, and Yosemite.

Lichens have also long been used as biomonitors of air pollution effects on forest health (Nash, 2008). It has been suspected, based on field surveys in the San Bernardino Mountains surrounding the Los Angeles air basin, that declines in lichen diversity and abundance were correlated with measured O_3 gradients (Gül et al., 2011). Several recent studies in North America (Geiser and Neitlich, 2007; Gombert et al., 2006; Jovan and McCune, 2006) and Europe (Nali et al., 2007; Gombert et al., 2006) have used lichens as biomonitors of atmospheric deposition (e.g., N and S) and O_3 exposure. Nali et al. (2007) found that epiphytic lichen biodiversity was not related to O_3 geographical distribution. In addition, a recent study by Riddell et al. (2010) found that lichen species, *Ramalina menziesii*, showed no decline in physiological response to low and moderate concentrations of O_3 and may not be a good indicator for O_3 pollution. Mosses have also been used as biomonitors of air pollution; however, there remains a knowledge gap in the understanding of the effects of ozone on mosses as there has been very little information available on this topic in recent years.

9.4.2.2 Summary

Visible foliar injury resulting from exposure to O_3 has been well characterized and documented over several decades of research on many tree, shrub, herbaceous, and crop species (U.S. EPA, 2006b, 1996b, 1984, 1978a). Ozone-induced visible foliar injury symptoms on certain bioindicator plant species are considered diagnostic as they have been verified experimentally in exposure-response studies, using exposure methodologies such as continuous stirred tank reactors (CSTRs), OTCs, and free-air fumigation. Experimental evidence has clearly established a consistent association of visible injury with O_3 exposure, with greater exposure often resulting in greater and more prevalent injury. Since the 2006 O_3 AQCD, several multi-year field surveys of O_3-induced visible foliar injury have been conducted at National Wildlife Refuges in Maine, Michigan, New

Jersey, and South Carolina. New sensitive species showing visible foliar injury continue to be identified from field surveys and verified in controlled exposure studies.

The use of biological indicators in field surveys to detect phytotoxic levels of O_3 is a longstanding and effective methodology. The USDA Forest Service through the Forest Health Monitoring (FHM) Program (1990-2001) and currently the Forest Inventory and Analysis (FIA) Program has been collecting data regarding the incidence and severity of visible foliar injury on a variety of O_3 sensitive plant species throughout the U.S. The network has provided evidence that O_3 concentrations were high enough to induce visible symptoms on sensitive vegetation. From repeated observations and measurements made over a number of years, specific patterns of areas experiencing visible O_3 injury symptoms can be identified. As noted in the preceding section, a study of 244 national parks indicated that the risk of visible foliar injury was high in 65 parks (27%), moderate in 46 parks (19%), and low in 131 parks (54%).

Evidence is sufficient to conclude that there is a causal relationship between ambient O_3 exposure and the occurrence of O_3-induced visible foliar injury on sensitive vegetation across the U.S.

9.4.3 Growth, productivity and carbon storage in natural ecosystems

Ambient O_3 concentrations have long been known to cause decreases in photosynthetic rates, decreases in growth, and decreases in yield (U.S. EPA, 2006b, 1996c, 1986, 1978a). The O_3-induced damages at the plant scale may translate to the ecosystem scale, and cause changes in productivity and C storage. This section focuses on the responses of C cycling to seasonal or multi-year exposures to O_3 from the plant to ecosystem scale. Quantitative responses include changes in plant growth, plant biomass allocation, ecosystem production and ecosystem C sequestration. Because of the available information, most of discussion at the plant scale focuses on the response of individual plants, especially tree seedlings and crops, with limited discussion of mixtures of herbaceous species. Changes at the ecosystem scale are difficult to evaluate directly due to the complexity and the large spatial and temporal scale. The discussion of ecosystem effects focuses on the new studies at the large-scale FACE experiments and on ecological model simulations.

9.4.3.1 Plant growth and biomass allocation

The previous O_3 AQCDs concluded that there is strong evidence that exposure to O_3 decreases photosynthesis and growth in numerous plant species (U.S. EPA, 2006b,

1996b, 1984, 1978a). Studies published since the last review support those conclusions and are summarized below.

In general, research conducted over several decades has indicated that exposure to O_3 alters stomatal conductance and reduces photosynthesis in a wide variety of plant species. In a review of more than 55 studies, Wittig et al. (2007) reported that current O_3 concentrations in the northern hemisphere are decreasing stomatal conductance (13%) and photosynthesis (11%) across tree species. It was also found that younger trees (<4 year) were affected less by O_3 than older trees. Further, the authors also found that decreases in photosynthesis are consistent with the cumulative uptake of O3 into the leaf. In contrast, several studies reported that O_3 exposure may result in loss of stomatal control, incomplete stomatal closure at night and a decoupling of photosynthesis and stomatal conductance, which may have implications for whole- plant water use (Section 9.4.5).

In a recently published meta-analysis, Wittig et al. (2009) quantitatively compiled peer reviewed studies from the past 40 years on the effect of current and future O_3 exposures on the physiology and growth of forest species. Wittig et al. (2009) reported that current ambient O_3 concentrations as reported in those studies (~40 ppb) significantly decreased annual total biomass growth (7%) across 263 studies. However, this effect could be greater (11 to 17%) in areas that have higher O_3 concentrations and as background O_3 increases in the future (Wittig et al., 2009). This meta-analysis demonstrates the coherence of O_3 effects across numerous studies and species that used a variety of experimental techniques, and these results support the conclusion of the previous AQCD.

In two companion papers, McLaughlin et al. (2007a; 2007b) investigated the effects of ambient O_3 on tree growth and hydrology at forest sites in the southern Appalachian Mountains. The authors reported that the cumulative effects of ambient levels of O_3 decreased seasonal stem growth by 30-50% for most trees species in a high O_3 year in comparison to a low O_3 year (McLaughlin et al., 2007a). The authors also report that high ambient O_3 concentrations can disrupt whole-tree water use and in turn reduce late-season streamflow (McLaughlin et al., 2007b); see Section 9.4.5 for more on water cycling.

Since the 2006 O_3 AQCD, several new studies based on the Aspen FACE "free air" O_3 and CO_2 exposure experiment in a forest in Wisconsin were published (Darbah et al., 2008; Riikonen et al., 2008; Darbah et al., 2007; Kubiske et al., 2007; Kubiske et al., 2006; King et al., 2005). Over the first seven years of stand development , Kubiske et al. (2006) observed that elevated O_3 decreased tree heights, diameters, and main stem volumes in the aspen community by 11, 16, and 20%, respectively. In addition, Kubiske et al. (2007) reported that elevated O_3 may change the intra- and inter-species

competition. For example, O_3 treatments increased the rate of conversion from a mixed aspen-birch community to a birch dominated community. In a comparison presented in Section 9.6.3 of this document, EPA found that effects on biomass accumulation in aspen during the first seven years closely agreed with the exposure-response function based on data from earlier OTC experiments.

Several studies at the Aspen FACE site also considered other growth-related effects of elevated O_3. Darbah et al. (2008; 2007) reported that O_3 treatments decreased paper birch seed weight and seed germination and that this would likely lead to a negative impact of regeneration for that species. Riikonen et al. (2008) found that elevated O_3 decreased the amount of starch in birch buds by 16%, and reduced aspen bud size, which may have been related to the observed delay in spring leaf development. The results suggest that elevated O_3 concentrations have the potential to alter C metabolism of overwintering buds, which may have carry-over effects in the subsequent growing season (Riikonen et al., 2008).

Effects on growth of understory vegetation were also investigated at Aspen FACE. Bandeff et al. (2006) found that the effects of elevated CO_2 and O_3 on understory species composition, total and individual species biomass, N content, and ^{15}N recovery were a result of overstory community responses to those treatments; however, there were no apparent direct treatment effects due to high variability of the data. Total understory biomass increased with increasing light and was greatest under the open canopy of the aspen/maple community, as well as the more open canopy of the elevated O_3 treatments (Bandeff et al., 2006). Similarly, data from a study by Awmack et al. (2007) suggest that elevated CO_2 and O_3 may have indirect growth effects on red (*Trifolium pratense*) and white (*Trifolium repens*) clover in the understory via overstory community effects; however, no direct effects of elevated O_3 were observed.

Overall, the studies at the Aspen FACE experiment are consistent with many of the OTC studies that were evaluated in previous O_3 AQCDs. These results strengthen our understanding of O_3 effects on forests and demonstrate the relevance of the knowledge gained from trees grown in open-top chamber studies.

For some annual species, particularly crops, the endpoint for an assessment of the risk of O_3 exposure is yield or growth, e.g., production of grain. For plants grown in mixtures such as hayfields, and natural or semi-natural grasslands (including native nonagricultural species), endpoints other than production of biomass may be important. Such endpoints include biodiversity or species composition, and effects may result from competitive interactions among plants in mixed-species communities. Most of the available data on non-crop herbaceous species are for grasslands, with many of the recent studies

conducted in Europe. See Section 9.4.7 for a review of the recent literature on O_3 effects on competition and biodiversity in grasslands.

Root Growth

Although O_3 does not penetrate soil, it could alter root development by decreasing C assimilation via photosynthesis leading to less C allocation to the roots (Andersen, 2003). The response of root development to O_3 exposure depends on available photosynthate within the plant and could vary over time. Many biotic and abiotic factors, such as community dynamics and drought stress, have been found to alter root development under elevated O_3. An earlier study at the Aspen FACE experiment found that elevated O_3 reduced coarse root and fine roots biomass in young stands of paper birch and trembling aspen (King et al., 2001). However, this reduction disappeared several years later. Ozone significantly increased fine-root (<1.0 mm) in the aspen community (Pregitzer et al., 2008). This increase in fine root production was due to changes in community composition, such as better survival of the O_3-tolerant aspen genotype, birch, and maple, rather than changes in C allocation at the individual tree level (Pregitzer et al., 2008; Zak et al., 2007). In an adult European beech/Norway spruce forest in Germany, drought was found to nullify the O_3-driven stimulation of fine root growth. Ozone stimulated fine-root production of beech during the humid year, but had no significant impact on fine root production in the dry year (Matyssek et al., 2010; Nikolova et al., 2010).

Using a non-destructive method, Vollsnes et al. (2010) studied the in vivo root development of subterranean clover (*Trifolium subterraneum*) before, during and after short-term O_3 exposure. It was found that O_3 reduced root tip formation, root elongation, the total root length, and the ratios between below- and above-ground growth within one week after exposure. Those effects persisted for up to three weeks; however, biomass and biomass ratios were not significantly altered at the harvest five weeks after exposure.

Several recent meta-analyses have generally indicated that O_3 reduced C allocated to roots. In one meta-analysis, Grantz et al. (2006) estimated the effect of O_3 on the root:shoot allometric coefficient (k), the ratio between the relative growth rate of the root and shoot. The results showed that O_3 reduced the root:shoot allometric coefficient by 5.6%, and the largest decline of the root:shoot allometric coefficient was observed in slow-growing plants. In another meta-analysis including 263 publications, Wittig et al. (2009) found that current O_3 exposure had no significant impacts on root biomass and root:shoot ratio when compared to pre-industrial O_3 exposure. However, if O_3 concentrations rose to 81-101 ppb (projected O_3 levels in 2100), both root biomass and root:shoot ratio were found to significantly decrease. Gymnosperms and angiosperms

differed in their responses, with gymnosperms being less sensitive to elevated O_3. In two other meta-analyses, Wang et al. (2010) found elevated O_3 reduced biomass allocation to roots by 8.3% at ambient CO_2 and 6.0% at elevated CO_2, and Morgan et al. (2003) found O_3 reduced root dry weight of soybean. While there is clear evidence that O_3 reduced C allocation to roots, results of recent individual studies have been mixed, showing negative (Jones et al., 2010), non-significant (Andersen et al., 2010; Phillips et al., 2009) and positive effects (Pregitzer et al., 2008; Grebenc and Kraigher, 2007) on root biomass and root: shoot ratio.

9.4.3.2 Summary

The previous O_3 AQCDs concluded that there is strong and consistent evidence that ambient concentrations of O_3 decrease photosynthesis and growth in numerous plant species across the U.S. Studies published since the last review continue to support that conclusion.

The meta-analysis by Wittig et al.(2007) and (2009) demonstrates the coherence of O_3 effects on plant photosynthesis and growth across numerous studies and species using a variety of experimental techniques. Since the 2006 O_3 AQCD, several studies were published based on the Aspen FACE experiment using "free air," O_3, and CO_2 exposures in a forest in Wisconsin. Overall, the studies at the Aspen FACE experiment were consistent with many of the open-top chamber (OTC) studies that were the foundation of previous O_3 NAAQS reviews. These results strengthen our understanding of O_3 effects on forests and demonstrate the relevance of the knowledge gained from trees grown in open-top chamber studies.

In recent studies, O_3 was shown to have either negative, non-significant, or positive effects on root biomass and root:shoot ratio. While the findings of individual studies were mixed, recent meta-analyses have generally indicated that O_3 reduced C allocated to roots (Wittig et al., 2009; Grantz et al., 2006).

Evidence is sufficient to conclude that there is a causal relationship between O_3 exposure and reduced growth of woody and herbaceous vegetation.

9.4.3.3 Reproduction

Studies during recent decades have demonstrated O_3 effects on various stages of plant reproduction. The impacts of O_3 on reproductive development, as reviewed by Black et al. (2000), can occur by influencing (1) age at which flowering occurs, particularly in

long-lived trees that often have long juvenile periods of early growth without flower and seed production; (2) flower bud initiation and development; (3) pollen germination and pollen tube growth; (4) seed, fruit, or cone yields; and (5) seed quality (Table 9-1) (U.S. EPA, 2006b). Several recent studies since the 2006 O_3 AQCD further demonstrate the effects of O_3 on reproductive processes in herbaceous and woody plant species. Although there have been documented effects of ozone on reproductive processes, a knowledge gap still exists pertaining to the exact mechanism of these responses.

Rämö et al. (2007) exposed several meadow species to elevated O_3 (40-50 ppb) and CO_2 (+100 ppm), both individually and combined, over three growing seasons in ground-planted mesocosms, using OTCs. Elevated O_3 delayed flowering of *Campanula rotundifolia* and *Vicia cracca*. Ozone also reduced the overall number of produced flowers and decreased fresh weight of individual *Fragaria vesca* berries.

Black et al. (2007) exposed *Brassica campestris* to 70 ppb for two days during late vegetative growth or ten days during most of the vegetative phase. The two-day exposure had no effect on growth or reproductive characteristics, while the 10 day exposure reduced vegetative growth and reproductive site number on the terminal raceme, emphasizing the importance of exposure duration and timing. Mature seed number and weight per pod were unaffected due to reduced seed abortion, suggesting that, although O_3 affected reproductive processes, indeterminate species such as *B. campestris* possess enough compensatory flexibility to avoid reduced seed production (Black et al., 2007).

In the determinate species, *Plantago major*, Black et al. (2010) found that O_3 may have direct effects on reproductive development in populations of differing sensitivity. Only the first flowering spike was exposed to 120 ppb O_3 for 7 hours per day on 9 successive days (corresponding to flower development) while the leaves and second spike were exposed to charcoal-filtered air. Exposure of the first spike to O_3 affected seed number per capsule on both spikes even though spike two was not exposed. The combined seed weight of spikes one and two was increased by 19% in the two resistant populations, suggesting an overcompensation for injury; whereas, a decrease of 21% was observed in the most sensitive population (Black et al., 2010). The question remains as to whether these effects are true direct ozone-induced effects or compensatory responses.

A study by Darbah et al. (2008; 2007) of paper birch (*Betula papyrifera*) trees at the Aspen FACE site in Rhinelander, WI investigated the effects of elevated O_3 and/or CO_2 on reproductive fitness. Elevated O_3 increased flowering, but decreased seed weight and germination success rate of seeds from the exposed trees. These results suggest that O_3 can dramatically affect flowering, seed production, and seed quality of paper birch, ultimately affecting its reproductive fitness (Darbah et al., 2008; Darbah et al., 2007).

Table 9-1 Ozone effects on plant reproductive processes (derived from Table AX9-22 of the 2006 ozone AQCD)

Species	Condition Measures	References
Apocynun androsaemifolium	Flowering time	Bergweiler and Manning (1999)
Buddleia davidii	Flowering time	Findley et al. (1997)
Rubus cuneifolius	Pollen germination	Chappelka (2002)
Plantago major	Pollen tube elongation	Stewart (1998)
Fragaria × *ananassa*	Fruit yield	Drogoudi and Ashmore (2001); Drogoudi and Ashmore (2000)
Plantago major	Seed yield	Lyons and Barnes (1998); Pearson et al. (1996); Reiling and Davison (1992); Whitfield et al. (1997)
Understory herbs	Seed yield	Harward and Treshow (1975)

Source: Adapted from 2006 O_3 AQCD

9.4.3.4 Ecosystem Productivity and Carbon Sequestration

During the previous NAAQS review, there were limited studies that investigated the effect of O_3 exposure on ecosystem productivity and C sequestration. Recent studies from long-term FACE experiments provide more evidence of the association of O_3 exposure and changes in productivity at the ecosystem scale. In addition to experimental studies, model studies also assessed the impact of O_3 exposure on productivity and C sequestration from stand to global scales.

Two types of models are most often used to study the ecological consequences of O_3 exposure: (1) single plant growth models such as TREGRO and PnET–II (Hogsett et al., 2008; Martin et al., 2001; Ollinger et al., 1997b), and (2) process-based ecosystem models such as PnET-CN, Dynamic Land Ecosystem Model (DLEM), Terrestrial Ecosystem Model (TEM), or Met Office Surface Exchange Scheme - Top-down Representation of Interactive Foliage and Flora Including Dynamics (MOSES-TRIFFID) (Felzer et al., 2009; Ren et al., 2007a; Sitch et al., 2007; Ollinger et al., 2002) (Table 9-2). In these models, carbon uptake is simulated through photosynthesis (TREGRO, PnET – II, PnET- CN, DLEM and MOSES-TRIFFID) or gross primary production (TEM). Photosynthesis rate at leaf level is modeled by a function of stomatal conductance and other parameters in TREGRO, PnET –II, PnET- CN, DLEM and MOSES-TRIFFID. Photosynthesis at canopy level is calculated by summing either photosynthesis of different leaf types (TREGRO, DLEM, and MOSES-TRIFFID) or photosynthesis of different canopy layers (PnET –II, PnET- CN). The detrimental effect of O_3 on plant growth is often simulated by multiplying photosynthesis rate by a coefficient that is dependent on stomatal conductance and cumulative O_3 uptake (Table 9-2). Different

plant functional groups (PFTs, such as deciduous trees, coniferous trees or crops) show different responses to O_3 exposure. PnET-II, PnET-CN, TEM, DLEM and MOSES-TRIFFID estimate this difference by modifying net photosynthesis with coefficients that represent the O_3 induced fractional reduction of photosynthesis for each functional group. The coefficients used in PnET-II, PnET-CN, TEM, DLEM are derived from the functions of O_3 exposure (AOT40) versus photosynthesis reduction from Reich (1987) and Tjoelker et al. (1995). The coefficients used in MOSES-TRIFFID are derived from the O_3 dose-photosynthesis response function from Pleijel et al. (2004a) and Karlsson et al. (2004), where O_3 dose is estimated by a metric named CUOt (cumulative stomatal uptake of O_3). The O_3 threshold of CUOt is 1.6 nmol/m^2/s for woody PFT and 5 nmol/m^2/s for grass PFT, and is different from AOT40, which has an O_3 threshold level of 40 ppb for all PFTs. Experimental and model studies on ecosystem productivity and C sequestration at the forest stand scale as well as regional and global scales are reviewed in the following section.

Table 9-2 Comparison of models used to simulate the ecological consequences of O_3 exposure

Model	Model feature	Carbon uptake	Ozone effect	Reference
TREGRO	Hourly or daily step, single plant model simulating vegetation growth process	Leaf: leaf photosynthesis is a function of stomatal conductance, mesophyll conductance and the gradient of CO_2 from atmosphere to the mesophyll cells Canopy: Leaf is divided into different ages. The canopy photosynthesis rate is the sum the photosynthesis of all foliage groups	The effect of O_3 on photosynthesis is simulated by reducing mesophyll conductance, and increasing respiration. The degree of O_3 damage is determined by ambient O_3 exposure, and the threshold O_3 concentration below which O_3 does not affect mesophyll conductance and respiration	Hogsett et al. (2008); Weinstein et al. (2005); Tingey et al. (2004)
PnET-II and PnET -CN	PnET-II: monthly time-step, single plant model PnET –CN: monthly time-step, ecosystem mode	Leaf: Maximum photosynthesis rate is determined by a function of foliar N concentration, and stomatal conductance is determined by a function of the actual rate of the photosynthesis. Canopy: canopy is divided into multiple, even-mass layers and photosynthesis is simulated by a multilayered canopy submodel	The effect of O_3 on photosynthesis is simulated by an equation of stomatal conductance and O_3 dose (AOT40). The model assumes that photosynthesis and stomatal conductance remain coupled under O_3 exposure, with a reduction in photosynthesis for a given month causing a proportion reduction in stomatal conductance.	Ollinger et al. (2002; 1997b); Pan et al. (2009)
TEM	monthly time-step, ecosystem mode	Ecosystem: TEM is run at a 0.5*0.5 degree resolution. Each grid cell is classified by vegetation type and soil texture, and vegetations and detritus are assumed to distribute homogeneously within grid cells. Carbon flows into ecosystem via gross primary production, which is a function of maximum rate of assimilation, photosynthetically active radiation, the leaf area relative to the maximum annual leaf area, mean monthly air temperate, and nitrogen availability.	The direct O_3 reduction on GPP is simulated by multiplying GPP by $f(O_3)t$, where $f(O_3)t$ is determined by evapotranspiration, mean stomatal conductance, ambient AOT40, and empirically O_3 response coefficient derived from previous publications.	Felzer et al. (2005; 2004)
DLEM	daily time-step ecosystem model	Leaf: photosynthesis is a function of 6 parameters: photosynthetic photon flux density, stomatal conductance, daytime temperature, the atmospheric CO_2 concentration, the leaf N content and the length of daytime. Canopy: Photosynthetic rates for sunlit leaf and shaded leaf scale up to the canopy level by multiplying the estimated leaf area index Ecosystem: GPP is the sum of gross C fixation of different plant function groups	The detrimental effect of O_3 is simulated by multiplying the rate of photosynthesis by O_3eff, where O_3eff is a function of stomatal conductance, ambient AOT40, and O_3 sensitive coefficient. Ozone's indirect effect on stomatal conductance is also simulated, with a reduction in photosynthesis for a given month causing a reduction in stomatal conductance, and therefore canopy conductance.	Ren et al. (2007a; 2007b); Zhang et al. (2007a)
MOSES-TRIFFID	30 minutes time-step, dynamic global vegetation model	Leaf: photosynthesis is a function of environmental and leaf parameters and stomatal conductance; Stomatal conductance is a function of the concentration of CO_2 and H_2O in air at the leaf surface and the current rate of photosynthesis of the leaf Canopy: Photosynthetic rates scale up to the canopy level by multiplying a function of leaf area index and PAR extinction coefficient Ecosystem: GPP is the sum of gross C fixation of different plant function groups	The effect of O_3 is simulated by multiplying the rate of photosynthesis by F, where F depends upon stomatal conductance, O_3 exposure, a critical threshold for O_3 damage, and O_3 sensitive coefficient (functional type dependent)	Sitch et al. (2007)

Local Scale

The above- and below-ground biomass and net primary production (NPP) were measured at the Aspen FACE site after 7 years of O_3 exposure. Elevated O_3 caused 23, 13 and 14% reductions in total biomass relative to the control in the aspen, aspen–birch and aspen–maple communities, respectively (King et al., 2005). At the Kranzberg Forest FACE experiment in Germany, O_3 reduced annual volume growth by 9.5 m^3/ha in a mixed mature stand of Norway spruce and European beech (Pretzsch et al., 2010). At the grassland FACE experiment at Alp Flix, Switzerland, O_3 reduced the seasonal mean rates of ecosystem respiration and GPP by 8%, but had no significant impacts on aboveground dry matter productivity or growing season net ecosystem production (NEP) (Volk et al., 2011). Ozone also altered C accumulation and turnover in soil, as discussed in Section 9.4.6.

Changes in forest stand productivity under elevated O_3 were assessed by several model studies. TREGRO (Table 9-2) has been widely used to simulate the effects of O_3 on the growth of several species in different regions in the U.S. Hogsett et al. (2008) used TREGRO to evaluate the effectiveness of various forms and levels of air quality standards for protecting tree growth in the San Bernardino Mountains of California. They found that O_3 exposures at the Crestline site resulted in a mean 20.9% biomass reduction from 1980 to 1985 and 10.3% biomass reduction from 1995 to 2000, compared to the ‘‘background’’ O_3 concentrations (O_3 concentration in Crook County, Oregon). The level of vegetation protection projected was different depending on the air quality scenarios under consideration. Specifically, when air quality was simulated to just meet the California 8-h average maximum of 70 ppb and the maximum 3 months 12-h SUM06 of 25 ppm-h, annual growth reductions were limited to 1% or less, while air quality that just met a previous NAAQS (the second highest 1-h max [125 ppb]) resulted in 6-7% annual reduction in growth, resulting in the least protection relative to background O_3 (Hogsett et al., 2008).

ZELIG is a forest succession gap model, and has been used to evaluate the dynamics of natural stand succession. Combining TREGRO with ZELIG, Weinstein et al. (2005) simulated the effects of different O_3 levels (0.5, 1.5, 1.75, and 2 times ambient) on the growth and competitive interactions of white fir and ponderosa pine at three sites in California: Lassen National Park, Yosemite National Park, and Crestline. Their results suggested that O_3 had little impact on white fir, but greatly reduced the growth of ponderosa pine. If current O_3 concentrations continue over the next century, ambient O_3 exposure (SUM06 of 110 ppm-h) at Crestline was predicted to decrease individual tree C budget by 10% and decrease ponderosa pine abundance by 16%. Effects at Lassen

National Park and Yosemite National Park sites were found to be smaller because of lower O_3 exposure levels (Weinstein et al., 2005).

The effects of O_3 on stand productivity and dynamics were also studied by other tree growth or stand models, such as ECOPHYS, INTRASTAND and LINKAGES. ECOPHYS is a functional-structural tree growth model. The model used the linear relationship between the maximum capacity of carboxylation and O_3 dose to predict the relative effect of O_3 on leaf photosynthesis (Martin et al., 2001). Simulations with ECOPHYS found that O_3 decreased stem dry matter production, stem diameter and leaf dry matter production, induced earlier leaf abscission, and inhibited root growth (Martin et al., 2001). INTRASTAND is an hourly time step model for forest stand carbon and water budgets. LINKAGES is a monthly time step model simulating forest growth and community dynamics. Linking INTRASTAND with LINKAGES, Hanson et al. (2005) found that a simulated increase in O_3 concentration in 2100 (a mean 20-ppb increase over the current O_3 concentration) yields a 35% loss of net ecosystem C exchange (NEE) with respect to the current conditions (174 g C/m^2/year).

Regional and Global Scales

Since the publication of the 2006 O_3 AQCD, there is additional evidence suggesting that O_3 exposure alters ecosystem productivity and biogeochemical cycling at the regional and continental scale. Most of those studies were conducted by using process-based ecosystem models (Table 9-2) and are briefly reviewed in the following sections.

Ollinger et al. (1997a) simulated the effect of O_3 on hardwood forest productivity of 64 hardwood sites in the northeastern U.S. with PnET-II (Table 9-2). Their simulations indicated that O_3 caused a 3-16% reduction in NPP from 1987 to 1992 (Table 9-3). The interactive effects of O_3, N deposition, elevated CO_2 and land use history on C dynamics were estimated by PnET-CN (Table 9-2) (Ollinger et al., 2002). The results indicated that O_3 offset the increase in net C exchange caused by elevated CO_2 and N deposition by 13% (25.0 g C/m^2/year) under agriculture site history, and 23% (33.6 g C/m^2/year) under timber harvest site history. PnET-CN was also used to assess changes in C sequestration of U.S. Mid-Atlantic temperate forest. Pan et al. (2009) designed a factorial modeling experiment to separate the effects of changes in atmospheric composition, historical climatic variability and land-disturbances on the C cycle. They found that O_3 acted as a negative factor, partially offsetting the growth stimulation caused by elevated CO_2 and N deposition in U.S. Mid-Atlantic temperate forest. Ozone decreased NPP of most forest types by 7-8%. Among all the forest types, spruce-fir forest was most resistant to O_3 damage, and NPP decreased by only 1% (Pan et al., 2009).

Felzer et al. (2004) developed TEM 4.3 (Table 9-2) to simulate the effects of O_3 on plant growth and estimated effects of O_3 on NPP and C sequestration of deciduous trees, conifers and crops in the conterminous U.S. The results indicated that O_3 reduced NPP and C sequestration in the U.S. (Table 9-3) with the largest decreases (over 13% in some locations) in NPP occurring in the Midwest agricultural lands during the mid-summer. TEM was also used to evaluate the magnitude of O_3 damage at the global scale (Table 9-3) (Felzer et al., 2005). Simulations for the period 1860 to 1995 show that the largest reductions in NPP and net C exchange occurred in the mid western U.S., eastern Europe, and eastern China (Felzer et al., 2005). DLEM (Table 9-2) was developed to simulate the detrimental effect of O_3 on ecosystems, and has been used to examine the O_3 damage on NPP and C sequestration in Great Smoky Mountains National Park (Zhang et al., 2007a), grassland ecosystems and terrestrial ecosystems in China (Ren et al., 2007a; Ren et al., 2007b). Results of those simulations are listed in Table 9-3.

Instead of using AOT40 as their O_3 exposure metric as PnET, TEM and DLEM did, Sitch et al. (2007) incorporated a different O_3 metric named CUOt (cumulative stomatal uptake of O_3), derived from Pleijel et al. (2004a), into the MOSES-TRIFFID coupled model (Table 9-2). In the CUOt metric, the fractional reduction of plant production is dependent on O_3 uptake by stomata over a critical threshold for damage with this threshold level varying by plant functional type. Consistent with previous studies, their model simulation indicated that O_3 reduced global gross primary production (GPP), C exchange rate and C sequestration (Table 9-3). The largest reductions in GPP and land-C storage were projected over North America, Europe, China and India. In the model, reduced ecosystem C uptake due to O_3 damage, results in additional CO_2 accumulation in the atmosphere and an indirect radiative forcing of climate change. Their simulations indicated that the indirect radiative forcing caused by O_3 (0.62-1.09 W/m^2) could have even greater impact on global warming than the direct radiative forcing of O_3 (0.89 W/m^2) (Sitch et al., 2007).

Results from the various model studies presented in Table 9-3 are difficult to compare because of the various spatial and temporal scales used in these studies. However, all the studies showed that O_3 exposure decreased ecosystem productivity and C sequestration. These results are consistent and coherent with experimental results from the leaf, plant and ecosystem scales (Sitch et al., 2007; Felzer et al., 2005). Many of the models use the same underlying function to simulate the effect of O_3 exposure to C uptake. For example the functions of O_3 exposure (AOT40) versus photosynthesis reduction for PnET-II, PnET-CN, TEM, DLEM were all from Reich (1987) and Tjoelker et al. (1995). Therefore, it is not surprising that the results are similar. While these models can be improved and more evaluation with experimental data can be done, these models

represent the state of the science for estimating the effect of O_3 exposure on productivity and C sequestration.

9.4.3.5 Summary

During the previous NAAQS reviews, there were very few studies that investigated the effect of O_3 exposure on ecosystem productivity and C sequestration. Recent studies from long-term FACE experiments, such as Aspen FACE, SoyFACE and the Kranzberg Forest (Germany), provided evidence of the association of O_3 exposure and reduced productivity at the ecosystem level. Studies at the leaf and plant scales showed that O_3 reduced photosynthesis and plant growth, which provided coherence and biological plausibility for the decrease in ecosystem productivity. Results across different ecosystem models, such as TREGRO, PnET, TEM and DLEM, were consistent with the FACE experimental evidence, which showed that O_3 reduced ecosystem productivity.

Although O_3 generally causes negative effects on plant growth, the magnitude of the response varies among plant communities. For example, O_3 had little impact on white fir, but greatly reduced growth of ponderosa pine in southern California (Weinstein et al., 2005). Ozone decreased net primary production (NPP) of most forest types in Mid-Atlantic region, but had small impacts on spruce-fir forest (Pan et al., 2009).

In addition to plant growth, other indicators that are typically estimated by model studies include net ecosystem CO_2 exchange (NEE), C sequestration, and crop yield. Model simulations consistently found that O_3 exposure caused negative impacts on those indicators, but the severity of these impacts was influenced by multiple interactions of biological and environmental factors. The suppression of ecosystem C sinks results in more CO_2 accumulation in the atmosphere. Globally, the indirect radiative forcing caused by O_3 exposure through lowering ecosystem C sink could have an even greater impact on global warming than the direct radiative forcing of O_3 (Sitch et al., 2007). Ozone could also affect regional C budgets through interacting with multiple factors, such as N deposition, elevated CO_2 and land use history. Model simulations suggested that O_3 partially offset the growth stimulation caused by elevated CO_2 and N deposition in both Northeast- and Mid-Atlantic-region forest ecosystems of the U.S. (Pan et al., 2009; Ollinger et al., 2002).

The evidence is sufficient to infer that there is a causal relationship between O_3 exposure and reduced productivity, and a likely causal relationship between O_3 exposure and reduced carbon sequestration in terrestrial ecosystems.

Table 9-3 Modeled effects of ozone on primary production, C exchange, and C sequestration

	Scale	Model	Index	Ozone Impacts	Reference
GPP	Global	MOSES-TRIFFID	CUOta	Decreased by 14-23% over the period 1901-2100	Sitch et al. (2007)
NPP	Global	TEM	AOT40	Decreased by 0.8% without agricultural management and a decrease of 2.9% with optimal agricultural management	Felzer et al. (2005)
	U.S.	TEM	AOT40	Reduced by 2.3% without optimal N fertilization and 7.2% with optimal N fertilization from 1983-1993	Felzer et al. (2005)
	U.S.	TEM	AOT40	Reduced by 2.6–6.8% during the late 1980s-early 1990s.	Felzer et al. (2004)
	Northeastern U.S.	PnET	AOT40	A reduction of 3-16% from 1987-1992	Ollinger et al. (1997a)
	U.S. Mid-Atlantic	PnET	AOT40	Decreased NPP of most forest types by 7-8%	Pan et al. (2009)
	China	DLEM	AOT40	Reduced NPP of grassland in China by 8.5 Tg C from 1960s to 1990s	Ren et al. (2007b)
C exchange	Global	TEM	AOT40	Reduced net C exchange (1950–1995) by 0.1 Pg C/yr without agricultural management and 0.3 Pg C/yr with optimal agricultural management	Felzer et al. (2005)
	Global	MOSES-TRIFFID	CUOt	Decreased global mean land–atmosphere C fluxes by 1.3 Pg C/yr and 1.7 Pg C/yr for the 'high' and 'low' plant O_3 sensitivity models, respectively	Sitch et al. (2007)
C sequestration	Global	MOSES-TRIFFID	CUOt	Reduced land-C storage accumulation by between 143 Pg C/yr and 263 Pg C/yr from 1900–2100	Sitch et al. (2007)
	U.S.	TEM	AOT40	Reduced C sequestration by 18–38 Tg C/yr from 1950 to 1995	Felzer et al. (2004)
	GSM National Park	DLEM	AOT40	Decreased the ecosystem C storage of deciduous forests by 2.5% and pine forest by 1.4% from 1971 to 2001	Zhang et al. (2007a)
	China	DLEM	AOT40	Reduced total C storage by 0.06% in 1960s and 1.6% in 1990s in China's terrestrial ecosystems	Ren et al. (2007a)
	China	DLEM	AOT40	O3 exposure reduced the net C sink of China's terrestrial ecosystem by 7% from 1961 to 2005	Tian et al. (2011)
	China	DLEM	AOT40	Ozone induced net carbon exchange reduction ranged from 0.4-43.1% , depending on different forest type	Ren et al. (2011)

[a]CUOt is defined as the cumulative stomatal uptake of O_3, using a constant O_3-uptake rate threshold of t nmol/m^2/s.
[d]Pg equals 1×10^{15} grams.

9.4.4 Crop yield and quality in agricultural systems

The detrimental effect of O_3 on crop production has been recognized since the 1960s and a large body of research has stemmed from that recognition. Previous O_3 AQCDs have extensively reviewed this body of literature. Table 9-4 summarizes recent experimental studies of O_3 effects on agricultural crops, exclusive of growth and yield. Growth and yield results are summarized in Table 9-17.

The actual concentration and duration threshold for O_3 damage varies from species to species and sometimes even among genotypes of the same species (Guidi et al., 2009; Sawada and Kohno, 2009; Biswas et al., 2008; Ariyaphanphitak et al., 2005; Dalstein and Vas, 2005; Keutgen et al., 2005). A number of comprehensive reviews and meta-analyses have recently been published discussing both the current understanding of the quantitative effects of O_3 concentration on a variety of crop species and the potential focus areas for biotechnological improvement to a future growing environment that will include higher O_3 concentrations (Bender and Weigel, 2011; Booker et al., 2009; Van Dingenen et al., 2009; Ainsworth, 2008; Feng et al., 2008b; Hayes et al., 2007; Mills et al., 2007b; Grantz et al., 2006; Morgan et al., 2003). Since the 2006 O_3 AQCD(U.S. EPA, 2006b), exposure-response indices for a variety of crops have been suggested (Mills et al., 2007b) and many reports have investigated the effects of O_3 concentration on seed or fruit quality to extend the knowledge base beyond yield quantity. This section will outline the key findings from these papers as well as highlight some of the recent research addressing the endpoints such as yields and crop quality.

This section will also highlight recent literature that focuses on O_3 damage to crops as influenced by other environmental factors. Genetic variability is not the only factor that determines crop response to O_3 damage. Ozone concentration throughout a growing-season is not homogeneous and other environmental conditions such as elevated CO_2 concentrations, drought, cold or nutrient availability may alleviate or exacerbate the oxidative stress response to a given O_3 concentration.

9.4.4.1 Yield

It is well known that yield is negatively impacted in many crop species in response to high O_3 concentration. However, the concentrations at which damage is observed vary from species to species. Numerous analyses of experiments conducted in OTCs and with naturally occurring gradients demonstrate that the effects of O_3 exposure also vary depending on the growth stage of the plant; plants grown for seed or grain are often most sensitive to exposure during the seed or grain-filling period (Soja et al., 2000; Pleijel et al., 1998; Younglove et al., 1994; Lee et al., 1988a). AX9.5.4.1 of the 2006 O_3 AQCD summarized many previous studies on crop yield.

Field studies and meta-analyses

The effect of O_3 exposure on U.S. crops remains an important area of research and several studies have been published on this topic since the 2006 O_3 AQCD (U.S. EPA, 2006b) (Table 9-4 and 9-17). For example, one study with cotton in a crop-weed

interaction study (Grantz and Shrestha, 2006) utilizing OTCs suggests that 12-hour average O_3 concentrations of 79.9 ppb decreased cotton biomass by 25% and 12-hour average O_3 concentration of 122.7 ppb decreased cotton biomass by 75% compared to charcoal filtered control (12-h avg: 12.8 ppb). Further, this study suggests that the weed, yellow nutsedge, was less sensitive to increasing O_3 concentration, which would increase weed competition (Grantz and Shrestha, 2006). In a study of peanuts in North Carolina, near ambient and elevated exposures of O_3 reduced photosynthesis and yield compared to very low O_3 conditions (Booker et al., 2007; Burkey et al., 2007). In another study, Grantz and Vu (2009) reported that sugarcane biomass growth significantly declined under O_3 exposure.

The average yield loss reported across a number of meta-analytic studies have been published recently for soybean (Morgan et al., 2003), wheat (Feng et al., 2008b), rice (Ainsworth, 2008), semi-natural vegetation (Hayes et al., 2007), potato, bean and barley (Feng and Kobayashi, 2009). Meta-analysis allows for the objective development of a quantitative consensus of the effects of a treatment across a wide body of literature. Further, this technique allows for a compilation of data across a range of O_3 fumigation techniques, durations and concentrations in order to assemble the existing literature in a meaningful manner.

Morgan et al. (2003) reported an average seed yield loss for soybean of 24% compared to charcoal filtered air across all O_3 concentrations used in the 53 compiled studies. The decrease in seed yield appeared to be the product of nearly equal decreases (7-12%) in seed weight, seed number and pod number. As would be expected, the lowest O_3 concentration (30-59 ppb) resulted in the smallest yield losses, approximately 8%, while the highest O_3 concentration (80-120 ppb) resulted in the largest yield losses, approximately 35% (Morgan et al., 2003). Further, the oil/protein ratio within the soybean seed was altered due to growth at elevated O_3 concentrations, with a decrease in oil content. The studies included in this meta-analysis all used enclosed fumigation systems or growth chambers which may have altered the coupling of the atmosphere to the lower plant canopy (McLeod and Long, 1999) , although the results of Morgan et al. (2006), Betzelberger et al. (2010), and the comparisons presented in Section 9.6.3 strongly suggest that decreases in yield between ambient and elevated exposures are not affected by exposure method. Utilizing the Soybean Free Air gas Concentration Enrichment Facility (SoyFACE; www.soyface.illinois.edu), Morgan et al. (2006) report a 20% seed yield loss due to a 23% increase in average daytime O_3 concentration (56-69 ppb) within a single soybean cultivar across two growing seasons in Illinois, which lies within the range predicted by the meta-analysis. A further breakdown of the effects of current O_3 concentrations (AOT40 of 4.7 ppm-h) on bean seed quality (*Phaseolus vulgaris*) has identified that growth at current O_3 concentrations compared to

charcoal-filtered air raised total lipids, total crude protein and dietary fiber content (Iriti et al., 2009). An increase in total phenolics was also observed, however the individual phenolics compounds responded differently, with significant decreases in anthocyanin content. The seeds from ambient O_3 exposed plants also displayed increased total antioxidant capacity compared to charcoal-filtered air controls (Iriti et al., 2009). Betzelberger et al. (2010) has recently utilized the SoyFACE facility to compare the impact of elevated O_3 concentrations across 10 soybean cultivars to investigate intraspecific variability of the O_3 response to find physiological or biochemical markers for eventual O_3 tolerance breeding efforts (Betzelberger et al., 2010). They report an average 17% decrease in yield across all 10 cultivars across two growing seasons due to a doubling of ambient O_3 concentrations, with the individual cultivar responses ranging from -7% to -36%. The exposure-response functions derived for these 10 current cultivars were similar to the response functions derived from the NCLAN studies conducted in the 1980s (Heagle, 1989) suggesting there has not been any selection for increased tolerance to O_3 in more recent cultivars. More complete comparisons between yield predictions based on data from cultivars used in NCLAN studies, and yield data for modern cultivars from SoyFACE are reported in Section 9.6.3 of this document. They confirm that the response of soybean yield to O_3 exposure has not changed in current cultivars.

A meta-analysis has also been performed on studies investigating the effects of O_3 concentrations on wheat (Feng et al., 2008b). Across 23 studies included, elevated O_3 concentrations (ranging from a 7-h daily average of 31-200 ppb) decreased grain yield by 29%. Winter wheat and spring wheat did not differ in their responses; however the response in both varieties to increasing O_3 concentrations resulted in successively larger decreases in yield, from a 20% decrease in 42 ppb to 60% in 153 ppb O_3. These yield losses were mainly caused by a combination of decreases in individual grain weight (-18%), ear number per plant (-16%), and grain number per ear (-11%). Further, the grain starch concentration decreased by 8% and the grain protein yield decreased by 18% due to growth at elevated O_3 concentrations as well. However, increases in grain calcium and potassium levels were reported (Feng et al., 2008b).

A recent meta-analysis found that growth at elevated O_3 concentrations negatively impacts nearly every aspect of rice performance as well (Ainsworth, 2008). While rice is not a major crop in the U.S., it provides a staple food for over half of the global population (IRRI, 2002) and the effects of rising O_3 concentrations on rice yields merits consideration. On average, rice yields decreased 14% in 62 ppb O_3 compared to charcoal-filtered air. This yield loss was largely driven by a 20% decrease in grain number (Ainsworth, 2008).

Feng and Kobayashi (2009) have recently compiled yield data for six major crop species, potato, barley, wheat, rice, bean and soybean and grouped the O_3 treatments used in those studies into three categories: baseline O_3 concentrations (<26 ppb), current ambient 7- or 12-h daily O_3 concentrations (31-50 ppb), and future ambient 7- or 12-h daily O_3 concentrations (51-75 ppb). Using these categories, they have effectively characterized the effects of current O_3 concentrations and the effects of future O_3 concentrations compared to baseline O_3 concentrations. At current O_3 concentrations, which ranged from 41-49 ppb in the studies included, soybean (-7.7%), bean (-19.0%), barley (-8.9%), wheat (-9.7%), rice (-17.5%) and potato (-5.3%) all had yield losses compared to the baseline O_3 concentrations (<26 ppb). At future O_3 concentrations, averaging 63 ppb, soybean (-21.6%), bean (-41.4%), barley (-14%), wheat (-28%), rice (-17.5%) and potato (-11.9%) all had significantly larger yield losses compared to the losses at current O_3 concentrations (<26 ppb) (Feng and Kobayashi, 2009).

A review of OTC studies has determined the AOT40 critical level that causes a 5% yield reduction across a variety of agricultural and horticultural species (Mills et al., 2007b). The authors classify the species studied into three groups: sensitive, moderate and tolerant. The sensitive crops, including watermelon, beans, cotton, wheat, turnip, onion, soybean, lettuce, and tomato, respond with a 5% reduction in yield under a 3-month AOT40 of 6 ppm-h. Watermelon was the most sensitive with a critical level of 1.6 ppm-h. The moderately sensitive crops, including sugar beet, oilseed rape, potato, tobacco, rice, maize, grape and broccoli, responded with a 5% reduction in yield between 8.6 and 20 ppm-h. The crops classified as tolerant, including strawberry, plum and barley, responded with a 5% yield reduction between 62-83.3 ppm-h (Mills et al., 2007b).

Feng and Kobayashi (2009) compared their exposure-response results to those published by Mills et al. (2007b) and found the ranges of yield loss to be similar for soybean, rice and bean. However, Feng and Kobayasi (2009) reported smaller yield losses for potato and wheat and larger yield losses for barley compared to the dose-response functions published by Mills et al. (2007b), which they attributed to their more lenient criteria for literature inclusion.

While the studies investigating the impact of various O_3 concentrations on yield are important and aid in determining the vulnerability of various crops to a variety of O_3 concentrations, there is still uncertainty as to how these crops respond under field conditions with interacting environmental factors such as temperature, soil moisture, CO_2 concentration, and soil fertility (Booker et al., 2009). Further, there appears to be a distinct developmental and genotype dependent influence on plant sensitivity to O_3 that has yet to be fully investigated across O_3 concentrations in a field setting. The potentially mitigating effect of breeding selection for O_3 resistance has received very little attention

in the published scientific literature. Anecdotal reports suggest that such selection may have occurred in recent decades for some crops in areas of the country with high ambient exposures. However, the only published literature available is on soybean and these studies indicate that sensitivity has not changed in cultivars of soybean between the 1980s and the 2000s (Betzelberger et al., 2010). This conclusion for soybeans is confirmed by comparisons presented in Section 9.6.3 of this document.

Yield loss at regional and global scales

Because O_3 is heterogeneous in both time and space and O_3 monitoring stations are predominantly near urban areas, the impacts of O_3 on current crop yields at large spatial scales are difficult to estimate. Fishman et al. (2010) have used satellite observations to estimate O_3 concentrations in the contiguous tri-state area of Iowa, Illinois and Indiana and have combined that information with other measured environmental variables to model the historical impact of O_3 concentrations on soybean yield across the 2002-2006 growing seasons. When soybean yield across Iowa, Indiana and Illinois was modeled as a function of seasonal temperature, soil moisture and O_3 concentrations, O_3 had the largest contribution to the variability in yield for the southern-most latitudes included in the dataset. Fishman et al. (2010) determined that O_3 concentrations significantly reduced soybean yield by 0.38 to 1.63% for every additional ppb of exposure across the 5 years. This value is consistent with previous chamber studies (Heagle, 1989) and results from SoyFACE (Morgan et al., 2006). Satellite estimates of tropospheric O_3 concentrations exist globally (Fishman et al., 2008), therefore utilizing this historical modeling approach is feasible across a wider geographical area, longer time-span and perhaps for more crop species.

The detrimental effects of O_3 on crop production at regional or global scales were also assessed by several model studies. Two large scale field studies were conducted in the U.S. (NCLAN) and in Europe (European Open Top Chamber Programme, EOTCP) to assess the impact of O_3 on crop production. Ozone exposure-response regression models derived from the two programs have been widely used to estimate crop yield loss (Avnery et al., 2011a, b; Van Dingenen et al., 2009; Tong and Mauzerall, 2008; Wang and Mauzerall, 2004). Those studies found that O_3 generally reduced crop yield and that different crops showed different sensitivity to O_3 pollution (Table 9-5). Ozone was calculated to induce a possible 45-82 million metric tons loss for wheat globally. Production losses for rice, maize and soybean were on the order of 17-23 million metric tons globally (Van Dingenen et al., 2009). The largest yield losses occur in high-production areas exposed to high O_3 concentrations, such the Midwest and the Mississippi Valley regions in the U.S., Europe, China and India (Van Dingenen et al., 2009; Tong et al., 2007).

9.4.4.2 Crop Quality

In general, it appears that increasing O_3 concentrations above current ambient concentrations can cause species-dependent biomass losses, decreases in root biomass and nutritive quality, accelerated senescence and shifts in biodiversity. A study conducted with highbush blackberry has demonstrated decreased nutritive quality with increasing O_3 concentration despite no change in biomass between charcoal-filtered control, ambient O_3 and 2 × ambient O_3 exposures (Ditchkoff et al., 2009). A study conducted with sedge using control (30 ppb), low (55 ppb), medium (80 ppb) and high (105 ppb) O_3 treatments has demonstrated decreased root biomass and accelerated senescence in the medium and high O_3 treatments (Jones et al., 2010). Alfalfa showed no biomass changes across two years of double ambient O_3 concentrations (AOT40 of 13.9 ppm-h) using FACE fumigation (Maggio et al., 2009). However a modeling study has demonstrated that 84% of the variability in the relative feed value in high-yielding alfalfa was due to the variability in mean O_3 concentration from 1998-2002 (Lin et al., 2007). Further, in a managed grassland FACE system, the reduction in total biomass harvest over five years decreased twice as fast in the elevated treatment (AOT40 of 13-59 ppm-h) compared to ambient (AOT40 of 1-20.7 ppm-h). Compared with the ambient control, loss in annual dry matter yield was 23% after 5 year. Further, functional groups were differentially affected, with legumes showing the strongest negative response (Volk et al., 2006). However, a later study by Stampfli and Fuhrer (2010) at the same site suggested that Volk et al.(2006) was likely overestimated the effects of O_3 on yield reduction because the overlapping effects of species dynamics caused by heterogeneous initial conditions and a change in management were not considered in Volk et al. (2006). An OTC study conducted with *Trifolium subterraneum* exposed to filtered (<15 ppb), ambient, and 40 ppb above ambient O_3 demonstrates decreases in biomass in the highest O_3 treatment as well as 10-20% decreased nutritive quality which was mainly attributed to accelerated senescence (Sanz et al., 2005). A study conducted with Eastern gamagrass and big bluestem in OTCs suggested that big bluestem is not sensitive to O_3, but gamagrass displayed decreased nutritive quality in the 2 × ambient O_3 treatment, due to higher lignin content and decreased N, (Lewis et al., 2006).

9.4.4.3 Summary

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

watermelon, beans, turnip, onion, lettuce, and tomato. Continued increases in O_3 concentration may further decrease yield in these sensitive crops. Despite the well-documented yield losses due to increasing O_3 concentration, there is still a knowledge gap pertaining to the exact mechanisms of O_3-induced yield loss. Research has linked increasing O_3 concentration to decreased photosynthetic rates and accelerated senescence, which are related to yield.

New research is beginning to consider the mechanism of damage caused by prolonged, lower O_3 concentration (so-called chronic exposure) compared to short, very high O_3 concentration (so-called acute exposure). Both types of O_3 exposure cause damage to agricultural crops, but through very different mechanisms. Historically, most research on the mechanism of O_3 damage used acute exposure studies. During the last decade, it has become clear that the cellular and biochemical processes involved in the response to acute O_3 exposure are not involved in response to chronic O_3 exposure, even though both cause yield loss in agriculturally important crops.

In addition, new research has highlighted the effects of O_3 on crop quality. Increasing O_3 concentration decreases nutritive quality of grasses, decreases macro- and micro-nutrient concentrations in fruits and vegetable crops, and decreases cotton fiber quality. These areas of research require further investigation to determine mechanisms and exposure-response relationships.

During the previous NAAQS reviews, there were very few studies that estimated O_3 impacts on crop yields at large spatial scales. Recent modeling studies found that O_3 generally reduced crop yield, but the impacts varied across regions and crop species. For example, the largest O_3-induced crop yield losses occurred in high-production areas exposed to high O_3 concentrations, such the Midwest and the Mississippi Valley regions of the U.S. (Van Dingenen et al., 2009). Among crop species, the estimated yield loss for wheat and soybean were higher than for rice and maize (Van Dingenen et al., 2009). Using satellite air-column observations with direct air-sampling O_3 data, Fishman et al. (2010) modeled the yield-loss due to O_3 over the continuous tri-state area of Illinois, Iowa and Wisconsin. They determined that O_3 concentrations significantly reduced soybean yield, which further reinforces previous results from FACE-type experiments and OTC experiments.

Evidence is sufficient to conclude that there is a causal relationship between O_3 exposure and reduced yield and quality of agricultural crops.

Table 9-4 Summary of recent studies of ozone effects on crops (exclusive of growth and yield)

Species Facility Location	Exposure Duration	Ozone Exposure[a] (Additional treatment)	Variable(s) measured	percent change from CF[b] (percent change from ambient)	Reference
Alfalfa (*Medicago sativa* cv. Beaver) Growth chambers	1, 2 or 4 days	3, 5 or - h/day 85 ppb (Exposure duration)	Relative feed value	n.s. *high variability among treatment groups (N/A)	Muntifering et al. (2006)
Bean (*Phaseolus vulgaris* l. cv Borlotto) OTC, ground-planted Curno, Italy	4 months	Seasonal AOT40: CF = 0.5 ppm-h; Ambient = 4.6 ppm-h (N/A)	Seed lipid, Protein content Fiber content	+28.5 (N/A) +7.88 (N/A) +14.54 (N/A)	Iriti et al. (2009)
Big Blue Stem (*Andropogon gerardii*) OTC Alabama, U.S.	4 months	12-h avg: CF = 14 ppb; Ambient = 29 ppb; Elevated = 71 ppb (N/A)	Relative feed value	n.s. (n.s.)	Lewis et al. (2006)
Brassica napus Growth chambers Belgium	4 days	CF & 176 ppb for 4 h/day (N/A)	Glucosinolates	−41 (N/A)	Gielen et al. (2006)
Brassica napus cv. Westar Growth chambers Finland	17-26 days	8-h avg: CF & 100 ppb (Bt/non-Bt; herbivory)	VOC emissions	−30.7 (N/A); −34 (N/A)	Himanen et al. (2009b)
Eastern Gamagrass (*Tripsacum dactyloides*) OTC Alabama, U.S.	4 months	12-h avg: CF = 14 ppb; Ambient = 29 ppb; Elevated = 71 ppb (N/A)	Relative feed value	−17 (−12)	Lewis et al. (2006)
Lettuce (*Lactuca sativa*) OTC Carcaixent Experimental Station, Spain	30 days	12-h mean: CF = 10.2 ppb; NF = 30.1 ppb; NF+O_3 = 62.7 ppb (4 cultivars)	Lipid peroxidation; Root length	+77 (+38) −22 (−14)	Calatayud et. al. (2002)
Peanut (*Arachis hypogaea*) OTC Raleigh, NC; U.S.	3 yr	12-h avg: CF = 22 ppb; Ambient = 46 ppb; Elevated = 75 ppb (CO_2: 375 ppm; 548 ppm; 730 ppm)	Harvest biomass	−40 (−10)	Booker et al. (2007)
Poa pratensis OTC Braunschweig, Germany	3 yr; 4-5 wk in the spring	8-h avg: CF+25 = 21.7 ppb; NF+50 = 73.1 ppb (Competition)	Relative feed value	N/A (n.s.; −8)	Bender et al. (2006)
Potato (*Solanum tuberosum* cv. Bintje OTC Sweden & Finland	2 yr	CF = 10 ppb; Ambient = 25 ppb); Ambient(+) = (36 ppb); Ambient(++) = (47 ppb) (N/A)	[K], [Ca], [Mg], [P], [N] per dry weight of tubers *dose-response regression, report significant positive or negative slope with increasing [O_3]	[N] [P] [Ca] n.s.; [K] & [Mg] sig + (N/A)	Piikki et al. (2007)
Potato (Solanum tuberosum cv. Indira) Climate chambers Germany	8 wk	CF = 10 ppb; Ambient = 50 ppb; 2×Ambient = 100 ppb (CO_2: 400 ppm & 700 ppm)	Pathogen infestation using % necrosis	+52 (n.s.)	Plessl et al. (2007)
Soybean OTC Italy	3 yr	AOT40: CF = 0 ppm-h; Ambient = 3.4 ppm-h; Elevated = 9.0 ppm-h (Well-watered & water-stressed)	Daily evapotranspiration	−28 (−14)	Jaude et al. (2008)

Species Facility Location	Exposure Duration	Ozone Exposure[a] (Additional treatment)	Variable(s) measured	percent change from CF[b] (percent change from ambient)	Reference
Soybean (*Glycine max* cv. 93B15) SoyFACE Urbana, IL; U.S.	3 yr May-Oct	AOT40: Ambient = 5-22 ppm-h; Elevated = 20-43 ppm-h (CO_2: 550 ppm; environmental variability)	Photosynthesis in new leaves,	N/A (n.s.)	Bernacchi et al. (2006)
Soybean (*Glycine max* cv. 93B15) SoyFACE Urbana, IL; U.S.	4 months	8-h avg: Ambient = 38.5 ppb; Elevated = 52 ppb (Herbivory)	Herbivory defense-related genes	N/A (N/A)	Casteel et al. (2008)
Soybean (*Glycine max* cv. Essex) OTC, ground-planted Raleigh, NC; U.S.	2 yr	12-h avg: CF = 21 ppb; 1.5×Ambient = 74 ppb (CO_2: 370 ppm & 714 ppm)	Post-harvest residue	N/A (−15.46)	Booker et al. (2005)
Soybean (*Glycine max* cv. Essex) OTCs, 21 L pots Raleigh, NC; U.S.	2×3 months	12-h avg: CF = 18 ppb); Elevated = 72 ppb) (CO_2: 367 & 718)	Water-use efficiency	n.s. (N/A)	Booker et al. (Booker et al., 2004a)
Soybean (*Glycine max*) 10 cultivars) SoyFACE Urbana, IL; U.S.	2 yr	8-h avg (ppb): Ambient = 46.3 & 37.9; Elevated = 82.5 & 61.3 (Cultivar comparisons)	Total antioxidant capacity	N/A (+19)	Betzelberger et al. (2010)
Spring Wheat (*Triticum aestivum* cv. Minaret; Satu; Drabant; Dragon) OTCs Belgium, Finland, & Sweden	7 yr	Seasonal AOT40s ranged from 0 to16 ppm-h (N/A)	Seed protein content; 1,000-seed weight regressed across all experiments	N/A (Significant negative correlation) N/A (Significant negative correlation)	Piikki et al. (2008a)
Strawberry (*Fragaria x ananassa* Duch. Cv. Korona & Elsanta) Growth chambers Bonn, Germany	2 months	8-h avg: CF = 0 ppb; Elevated = 78 ppb (N/A)	Total leaf area	−16 (N/A)	Keutgen et al. (2005)
Sweet Potato Growth Chambers Bonn, Germany	4 wk	8-h avg: CF = 0 ppb; Ambient < 40 ppb; Elevated = 255 ppb (N/A)	Tuber weight	−14 (−11.5)	Keutgen et al. (2008)
Tomato (*Lycopersicon esculentum*) OTC Valencia, Spain	133 days	8- mean: CF = 16.3 ppb; NF = 30.1 ppb; NF(+) = 83.2 ppb (Various cultivars; early & late harvest)	Brix degree	−7.2 (−3.6)	Calvo, et al. (2005)
Trifolium repens & *Trifolium pretense* Aspen FACE Rhinelander, WI; U.S.	3 months	3-mo daylight avg: Ambient = 34.8 ppb; 1.2×Ambient = 42.23 ppb (CO_2; 560 ppm)	Lignin; Dry-matter digestibility	N/A (+19.3) N/A (−4.2)	Muntifering et al. (2006)

[a]Ozone exposure in ppb unless otherwise noted.

[b]CF = Carbon-filtered air.

NF = Non-filtered air.

Table 9-5 Modeled effects of ozone on crop yield loss at regional and global scales

Scale	Index	Ozone Impacts	Reference
Global	M7a; M12b; AOT40	Reduced by 7.3% to 12.3% for wheat, 5.4% to 15.6% for soybean, 2.8% to 3.7% for rice, and 2.4% to 4.1% for maize in year 2000.	Van Dingenen et al. (2009)
Global	M12b; AOT40	O_3-induced global yield reductions ranged from 8.5-14% for soybean, 3.9-15% for wheat, and 2.2-5.5% for maize in year 2000. Global crop production losses totaled 79-121 million metric tons, worth $11-18 billion annually (USD2000).	Avnery et al. (2011a)
U.S.	M7; M12; AOT40	Reduced by 4.1% to 4.4% for wheat, 7.1% to 17.7% for soybean, 2.6% to 3.2% for rice, and 2.2% to 3.6% for maize in year 2000.	Van Dingenen et al. (2009)
U.S.	SUM06	Caused a loss of 53.8 million to 438 million bushels in soybean production, which account for 1.7–14.2% of total U.S. soybean production in 2005	Tong et al. (2007)
East Asia	M7; M12	Reduced the yield of wheat, rice and corn by 1–9% and soybean by 23–27% in China, Japan and South Korea in 1990	Wang and Mauzerall (2004)

[a]M7 is defined as 7-h mean O_3 concentration (ppb).

[b]M12 is defined as 12-h mean O_3 concentration (ppb).

9.4.5 Water Cycling

Ozone can affect water use in plants and ecosystems through several mechanisms including damage to stomatal functioning and loss of leaf area. Section 9.3.2 reviewed possible mechanisms for effects of O_3 exposure on stomatal functioning including build-up of CO_2 in substomatal cavity, impacts on signal transduction pathways, and direct O_3 impact on guard cells. Regardless of the mechanism, O_3 exposure has been shown to alter stomatal performance, which may affect plant and stand transpiration and therefore could affect hydrological cycling (Figure 9-7).

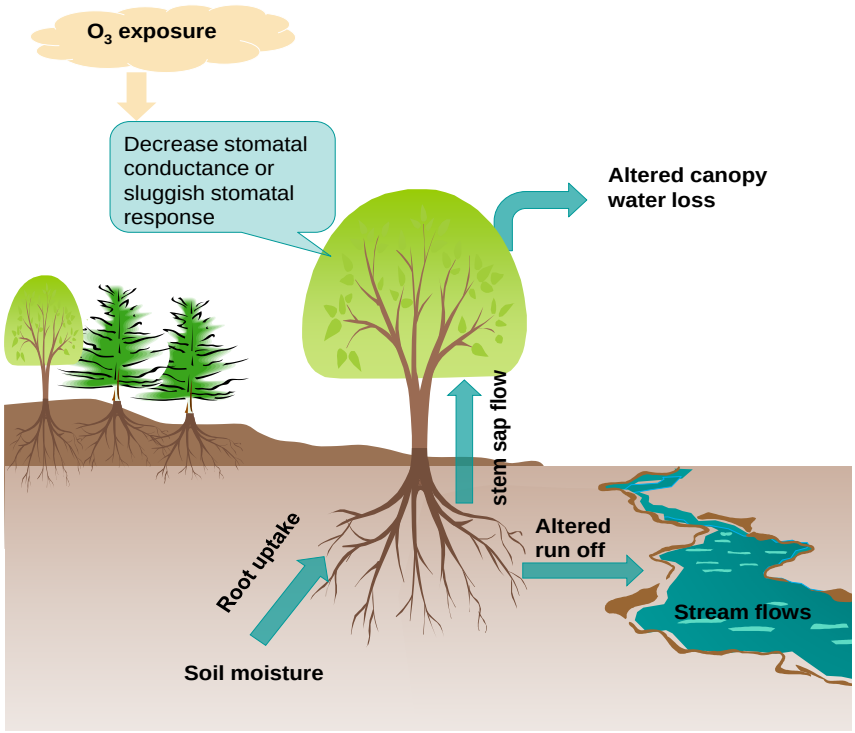


Figure 9-7 The potential effects of ozone exposure on watering cycling.

In the literature, there is not a clear consensus on the nature of leaf-level stomatal conductance response to O_3 exposure. At the leaf level, O_3 exposure is known to result in stomatal patchiness (Paoletti and Grulke, 2005; Omasa et al., 1987; Ellenson and Amundson, 1982), i.e., the heterogeneous aperture of stomata on the leaf surface, and, as a result, the collective response of groups of stomata on leaves and canopies determines larger-scale responses to O_3. When measured at steady-state high light conditions, leaf-level stomatal conductance is often found to be reduced when exposed to O_3. For example, a meta-analysis of 55 studies found that O_3 reduced stomatal conductance by 11% (Wittig et al., 2007). However, these steady-state measurements were generally taken at saturating light conditions and steady-state vapor pressure deficit (VPD). Saturating light and steady-state VPD conditions are not common in the field since many parts of the plant canopy are shaded throughout the day. When studied under varying environmental conditions, many studies have reported incomplete stomatal closure with elevated O_3 exposure during the day (Mills et al., 2009; Grulke et al., 2007b; Matyssek et al., 1995; Wieser and Havranek, 1995) or at night (Grulke et al., 2004). This may be due to sluggish stomatal response. Sluggish stomatal response, defined as a delay in stomatal response to changing environmental factors relative to controls (Paoletti and Grulke, 2010) has also been documented by several researchers (Grulke et al., 2007c; Matyssek et

al., 1995; Pearson and Mansfield, 1993; Wallin and Skärby, 1992; Lee et al., 1990; Skarby et al., 1987; Keller and Häsler, 1984; Reich and Lassoie, 1984). Sluggish stomatal response associated with O_3 exposure suggests an uncoupling of the normally tight relationship between carbon assimilation and stomatal conductance as measured under steady-state conditions (Gregg et al., 2006; Paoletti and Grulke, 2005). Several tree and ecosystem models, such as TREGRO, PnET and DLEM, rely on this tight relationship to simulate water and carbon dynamics. The O_3-induced impairment of stomatal control may be more pronounced for plants growing under water stress (Wilkinson and Davies, 2010; Grulke et al., 2007a; Paoletti and Grulke, 2005; Bonn et al., 2004; Kellomaki and Wang, 1997; Tjoelker et al., 1995; Reich and Lassoie, 1984). Since leaf-level stomatal regulation is usually assessed in a steady state rather than as a dynamic response to changing environmental conditions, steady state measurements cannot detect sluggish stomatal response. Because of sluggish stomatal responses, water loss from plants may be greater under dynamic environmental conditions over days and months.

In addition to the impacts on stomatal performance, O_3-induced physiological changes, such as reduced leaf area index and accelerated leaf senescence could alter water use efficiency. It is well established from chamber and field studies that O_3 exposure is correlated with lower foliar retention (Karnosky et al., 2003; Topa et al., 2001; Pell et al., 1999; Grulke and Lee, 1997; Karnosky et al., 1996; Miller et al., 1972; Miller et al., 1963). However, Lee et al. (2009a) did not find changes in needle area of ponderosa pine and reported that greater canopy conductance followed by water stress under elevated O_3 may have been caused by stomatal dysfunction. At the Aspen FACE experiment, stand-level water use, as indicated by sap flux per unit ground area, was not significantly affected by elevated O_3 despite a 22% decrease in leaf area index and 20% decrease in basal area (Uddling et al., 2008). The lack of negative effect of elevated O_3 on stand water use may be due to the substantially increased whole plant hydraulic conductance per unit leaf area under elevated O_3, as indicated by the sap flux per unit total leaf area (kl) (Uddling et al., 2009). The increased kl may be caused by the sluggish of stomatal response. In pure aspen stands, the stomatal closure response to increasing vapor pressure deficit was less sensitive and mid-day leaf water potential was lower under elevated O_3, suggesting O_3 impaired stomatal control over transpiration (Uddling et al., 2009). Other potential factors contributing to the unchanged stand-level water use included the higher proportion of sun leaves, and similar or even increased fine root biomass under elevated O_3 (Uddling et al., 2008). Elevated O_3 could also affect evapotranspiration by altering tree crown interception of precipitation. Ozone has been shown to change branch architectural parameters, and the effects were species-dependent at the Aspen FACE experiment (Rhea et al., 2010). The authors found that there was a significant correlation between canopy architecture parameters and stem flow for birch but not aspen.

It is difficult to scale up physiology measurements from leaves to ecosystems. Thus, the current understanding of how stomatal response at leaf scale is integrated at the scale of whole forest canopies, and therefore how it influences tree and forest stand water use is limited. Field studies by McLaughlin et al. (2007a; 2007b) provided valuable insight into the possible consequences of stomatal sluggishness for ecosystem water cycling. McLaughlin et al. (2007a; 2007b) indicated that O_3 increased water use in a mixed deciduous forest in eastern Tennessee. McLaughlin et al. (2007a; 2007b) found that O_3, with daily maximum levels ranging from 69.2 to 82.9 ppb, reduced stem growth by 30-50% in the high-O_3 year 2002. The decrease in growth rate was caused in part by amplification of diurnal cycles of water loss and recovery. Peak hourly O_3 exposure increased the rate of water loss through transpiration as indicated by the increased stem sap flow. The authors suggested that a potential mechanism for the increased sap flow could be altered stomatal regulation from O_3 exposure, but this was inferred through sap flow measurements and was not directly measured. The increased canopy water loss resulted in higher water uptake by the trees as reflected in the reduced soil moisture in the rooting zone. The change in tree water use led to further impacts on the hydrological cycle at the landscape level. Increased water use under high O_3 exposure was reported to reduce late-season modeled streamflow in three forested watersheds in eastern Tennessee (McLaughlin et al., 2007b).

Felzer et al. (2009) used TEM-Hydro to assess the interactions of O_3, climate, elevated CO_2 and N limitation on the hydrological cycle in the eastern U.S. They found that elevated CO_2 decreased evapotranspiration by 2-4% and increased runoff by 3-7%, as compared to the effects of climate alone. When O_3 damage and N limitation were included, evapotranspiration was reduced by an additional 4-7% and runoff was increased by an additional 6-11% (Felzer et al., 2009). Based upon simulation with INTRAST and LINKAGES, Hanson et al. (2005) found that increasing O_3 concentration by 20 ppb above the current ambient level yields a modest 3% reduction in water use. Those ecological models were generally built on the assumption that O_3 induces stomatal closure and have not incorporated possible stomatal sluggishness due to O_3 exposure. Because of this assumption, results of those models normally found that O_3 reduced water use.

9.4.5.1 Summary

Although the evidence was from a limited number of field and modeling studies, findings showed an association between O_3 exposure and alteration of water use and cycling in vegetation and at the ecosystem level. There is not a clear consensus on the nature of leaf-level stomatal conductance response to O_3 exposure. When measured under steady-

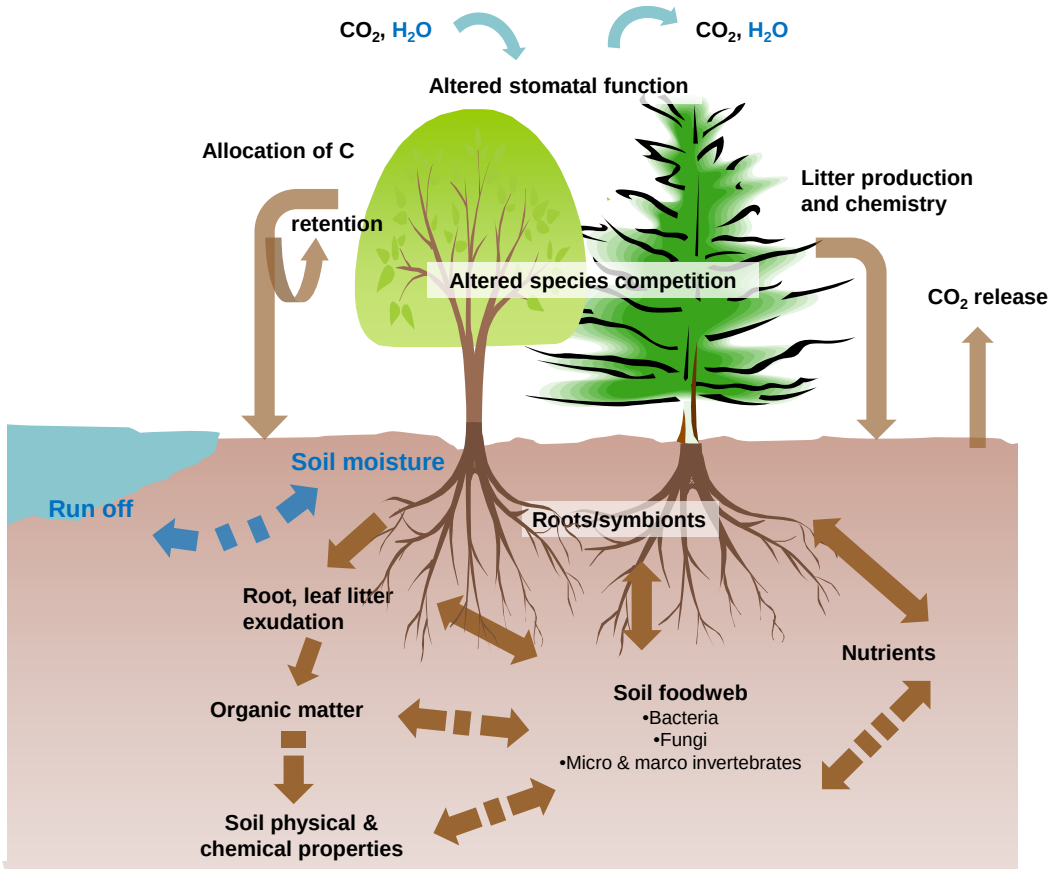
state high light conditions, leaf-level stomatal conductance is often found to be reduced when plants are exposed to O_3. However, measurements of stomatal conductance under dynamic light and VPD conditions indicate sluggish responses under elevated O_3 exposure, which could potentially lead to increased water loss from vegetation. Field studies conducted by McLaughlin et al. (2007a; 2007b) suggested that peak hourly O_3 exposure increased the rate of water loss from several tree species, and led to a reduction in the late-season modeled stream flow in three forested watersheds in eastern Tennessee. Sluggish stomatal responses during O_3 exposure was suggested as a possible mechanism for increased water loss during peak O_3 exposure. Currently, the O_3-induced reduction in stomatal aperture is the biological assumption for most process-based models. Because of this assumption, results of those models normally found that O_3 reduced water loss. For example, Felzer (2009) found that O_3 damage and N limitation together reduced evapotranspiration and increased runoff.

Although the direction of the response differed among studies, **the evidence is sufficient to conclude that there is likely to be a causal relationship between O_3 exposure and the alteration of ecosystem water cycling.**

9.4.6 Below-Ground Processes

Above-ground and below-ground processes are tightly interconnected. Because roots and soil organisms are not exposed directly to O_3, below-ground processes are affected by O_3 through alterations in the quality and quantity of C supply from photosynthates and litterfall (Andersen, 2003). Ozone can decrease leaf C uptake by reducing photosynthesis (Section 9.3). Ozone can also increase metabolic costs by stimulating the production of chemical compounds for defense and repair processes, and by increasing the synthesis of antioxidants to neutralize free radicals (see Section 9.3), both of which increase the consumption of carbon for above-ground processes. Therefore, O_3 could significantly reduce the amount of C available for allocation to below-ground by decreasing C uptake while increasing C consumption of above-ground processes (Andersen, 2003).

Since the 2006 O_3 AQCD, there is additional evidence for O_3 effects on below-ground processes. Ozone has been found to alter root growth, soil food web structure, decomposer activities, C turnover, water cycling and nutrient flow (Figure 9-8). Ozone effects on root development and root biomass production and soil food web structure are reviewed in sections 9.4.3.1 and 9.4.9.2, respectively. The focus in this section is on the response of litter input, decomposer activities, soil respiration, soil C formation and nutrient cycling.



Source: Modified from Andersen (2003)

Arrows denote C flux pathways that are affected by ozone. Dashed lines indicate where the impact of ozone is suspected but unknown.

Figure 9-8 Conceptual diagram showing where ozone alters C, water and nutrient flow in a tree-soil system, including transfer between biotic and abiotic components below ground that influence soil physical and chemical properties.

9.4.6.1 Litter Carbon Chemistry, Litter Nutrient and Their Ecosystem Budgets

Consistent with previous findings, recent studies show that, although the responses are often species-dependent, O_3 tends to alter litter chemistry (U.S. EPA, 2006b).Alterations

in chemical parameters, such as changes in C chemistry and nutrient concentrations, were observed in both leaf and root litter (9-7).

At the Aspen FACE site, several studies investigated litter chemistry changes (Parsons et al., 2008; Johnson and Pregitzer, 2007; Chapman et al., 2005; Liu et al., 2005). In both aspen and birch leaf litter, elevated O_3 increased the concentrations of soluble sugars, soluble phenolics and condensed tannins (Parsons et al., 2008; Liu et al., 2005). Compared to other treatments, aspen litter under elevated O_3 had the highest fiber concentration, with the lowest concentration associated with the birch litter under the same conditions (Parsons et al., 2008). Chapman et al. (2005) measured chemical changes in fine root litter and found that elevated O_3 decreased lignin concentration. O_3-induced chemistry changes were also reported from other experimental sites. Results from an OTC study in Finland suggested that elevated O_3 increased the concentration of acid-soluble lignin, but had no significant impact on other chemicals such as total sugars, hemicelluloses, cellulose or total lignin in the litter of silver birch (Kasurinen et al., 2006). Results from the free air canopy O_3 exposure experiment at Kranzberg Forest showed that O_3 increased starch concentrations but had no impact on cellulose and lignin in beech and spruce leaf litter (Aneja et al., 2007). The effect of O_3 on three antioxidants (ascorbate, glutathione and α-tocopherol) in fine roots of beech was also assessed at Kranzberg Forest. The results indicated that O_3 had no significant effect on α-tocopherol and ascorbate concentrations, but decreased glutathione concentrations in fine roots (Haberer et al., 2008). In addition to changing C chemistry, O_3 also altered nutrient concentrations in green leaves and litter (Table 9-6).

The combined effects of O_3 on biomass productivity and chemistry changes may alter C chemicals and nutrient contents at the canopy or ecosystem level. For example, although O_3 had different impacts on their concentrations, annual fluxes of C chemicals (soluble sugar, soluble phenolics, condensed tannins, lipid and hemicelluloses), macro nutrients (N, P, K and S) and micro nutrients (Mg, B, Cu and Zn) to soil were all reduced due to lower litter biomass productivity at Aspen FACE (Liu et al., 2007a; Liu et al., 2005). At the Kranzberg Forest, N content of spruce canopy in a mixed culture and Ca^{2+} content of beech canopy in a monoculture increased due to elevated O_3 increased leaf concentrations of those nutrients although leaf production was not significantly altered by O_3 (Rodenkirchen et al., 2009).

Table 9-6 The effect of elevated ozone on leaf/litter nutrient concentrations

Study Site	Species	Ozone Concentration	Response	Reference
Suonenjoki Research Station, Finland	Silver birch	Ambient: 10-60 ppb Elevated: 2×ambient	Decreased the concentration of P, Mn, Zn and B in leaf litter	Kasurinen et al. (2006)
Aspen FACE	Aspen and birch	Ambient: 50-60 ppb Elevated: 1.5×ambient	Decreased the concentrations of P, S, Ca and Zn, but had no impact on the concentrations of N, K, Mg, Mn, B and Cu in leaf litter.	Liu et al. (2007a)
Aspen FACE	Birch	Ambient: 50-60 ppb Elevated: 1.5×ambient	Increase N concentration in birch litter	Parsons et al. (2008)
Kranzberg Forest, Germany	Beech and spruce	Ambient: 9-41 ppb Elevated: 2×ambient	Increased N concentration in beach leaf, but not in spruce needle	Kozovits et al. (2005)
Kranzberg Forest, Germany	Beech and spruce	Ambient: 9-41 ppb Elevated: 2×ambient	1) Had no significant effects on spruce needle chemistry; 2) increased Ca concentration in beech leaves in monoculture, but had no impacts on other nutrients	Rodenkirchen et al. (2009)
Salerno, Italy	Holm oak	Non-filtered OTC: 29 ppb Filtered OTC: 17ppb	Ozone had no significant impacts on litter C, N, lignin and cellulose concentrations	Baldantoni et al. (2011)
Kuopio University Research Garden, Finland	Red Clover	Ambient: 25.7 ppb Elevated: 1.5×ambient	increased the total phenolic content of leaves and had minor effects on the concentrations of individual phenolic compounds	Saviranta et al.(2010)

9.4.6.2 Decomposer Metabolism and Litter Decomposition

The above- and below-ground physiological changes caused by O_3 exposure cascade through the ecosystem and affect soil food webs. In the 2006 O_3 AQCD, there were very few studies on the effect of O_3 on the structure and function of soil food webs, except two studies conducted by Larson et al. (2002) and Phillips et al. (2002). Since the last O_3 AQCD, new studies have provided more information on how O_3 affects the metabolism of soil microbes and soil fauna.

Chung et al.(2006) found that the activity of the cellulose-degrading enzyme 1,4-β-glucosidase was reduced by 25% under elevated O_3 at Aspen FACE. The decrease in cellulose-degrading enzymatic activity was associated with the lower cellulose availability under elevated O_3 (Chung et al., 2006). However, a later study at the same site, which was conducted in the 10th year of the experiment, found that O_3 had no impact on cellulolytic activity in soil (Edwards and Zak, 2011). In a lysimeter study of beech trees (*Fagus sylvatica*) in Germany, soil enzyme activity was found to be suppressed by O_3 exposure (Esperschutz et al., 2009; Pritsch et al., 2009). Except for xylosidase, enzyme activities involved in plant cell wall degradation (cellobiohydrolase, beta-glucosidase and glucuronidase) were decreased in rhizosphere soil samples under elevated O_3 (2 × ambient level) (Pritsch et al., 2009). Similarly, Chen et al. (2009) found

O_3 exposure, with a 3-month AOT40 of 21.4-44.1 ppm-h, decreased the microbial metabolic capability in the rhizosphere and bulk soil of wheat, although the observed reduction in bulk soil was not significant.

Ozone-induced change in soil organisms' activities could affect litter decomposition rates. Results of recent studies indicated that O_3 slightly reduced or have no impacts on litter decomposition (Liu et al., 2009b; Parsons et al., 2008; Kasurinen et al., 2006) (Baldantoni et al., 2011). The responses varied among species, sites and exposure length. Parsons et al. (2008) collected litter from aspen and birch seedlings at Aspen FACE site, and conducted a 23-month field litter incubation starting in 1999. They found that elevated O_3 had different impacts on the decomposition of aspen and birch litter. Elevated O_3 was found to reduce aspen litter decomposition. However, O_3 accelerated birch litter decomposition under ambient CO_2, but reduced it under elevated CO_2 (Parsons et al., 2008). Liu et al. (2009b) conducted another litter decomposition study at Aspen FACE from 2003 to 2006, when stand leaf area index (LAI) reached its maximum. During the 935-day field incubation, elevated O_3 was shown to reduce litter mass loss in the first year, but not in the second year. They suggested that higher initial tannin and phenolic concentrations under elevated O_3 reduced microbial activity in the first year (Liu et al., 2009b). In an OTC experiment, Kasurinen et al. (2006) collected silver birch leaf litter from three consecutive growing seasons and conducted three separate litter-bag incubation experiments. Litter decomposition was not affected by O_3 exposure in the first two incubations, but a slower decomposition rate was found in the third incubation. Their principle component analysis indicated that the litter chemistry changes caused by O_3 (decreased Mn, P, B and increased C:N) might be partially responsible for the decreased mass loss of their third incubation. In another OTC experiment, Baldatoni et al. (2011) found that O_3 significantly reduced leaf litter decomposition of Quercus ilex L, although litter C, N, lignin and cellulose concentrations were not altered by O_3 exposure.

9.4.6.3 Soil respiration and carbon formation

Ozone could reduce the availability of photosynthates for export to roots, and increase root mortality and turnover rates. Ozone has also been shown to reduce above-ground litter productivity and alter litter chemistry, which would affect the quality and quantity of the C supply to soil organisms (Section 9.4.6.1). The complex interactions among those changes make it difficult to predict the response of soil C cycling under elevated O_3. The 2006 O_3 AQCD concluded that O_3 had no consistent impact on soil respiration (U.S. EPA, 2006b). Ozone could increase or decrease soil respiration, depending on the approach and timing of the measurements. Ozone may also alter soil C formation. However, very few experiments directly measured changes in soil organic matter content

under O_3 fumigation (U.S. EPA, 2006b). Recent studies on soil respiration and soil C content also found mixed responses. Most importantly, recent results from long-term fumigation experiments, such as the Aspen FACE experiment, suggest that ecosystem response to O_3 exposure can change over time. Observations made during the late exposure years can be inconsistent with those during the early years, highlighting the need for caution when assessing O_3 effects based on short-term studies (Table 9-7).

Table 9-7 The temporal variation of ecosystem responses to ozone exposure at Aspen FACE site

Endpoint	Period of Measurement	Response	Reference
Litter decomposition	1999-2001	O_3 reduced aspen litter decomposition. However, O_3 accelerated birch litter decomposition under ambient CO_2, but reduced it under elevated CO_2	Parsons et al. (2008)
	2003-2006	O_3 reduced litter mass loss in the first year, but not in the second year.	Liu et al. (2009b)
Fine root production	1999	O_3 had no significant impact on fine root biomass	King et al. (2001)
	2002, 2005	O_3 increased fine root biomass	Pregitzer et al. (2008)
Soil respiration	1998-1999	Soil respiration under $+CO_2+O_3$ treatment was lower than that under $+CO_2$ treatment	King et al. (2001)
	2003-2007	Soil respiration under $+CO_2+O_3$ treatment was 5-25% higher than under elevated CO_2 treatment.	Pregitzer et al. (2006) (2008)
Soil C formation	1998-2001	O_3 reduced the formation rates of total soil C by 51% and acid-insoluble soil C by 48%	Loya et al. (2003)
	2004-2008	No significant effect of O_3 on the new C formed under elevated CO_2	Talhelm et al. (2009)

Soil Respiration

Ozone has shown inconsistent impacts on soil respiration. A sun-lit controlled-environment chamber study found that O_3 had no significant effects on soil respiration, fine root biomass or any of the soil organisms in a reconstructed ponderosa pine/soil-litter system (Tingey et al., 2006). In an adult European beech/Norway spruce forest at Kranzberg Forest, the free air O_3 fumigation (AOT40 of 10.2-117 ppm-h) increased soil respiration under both beech and spruce during a humid year (Nikolova et al., 2010) . The increased soil respiration under beech has been accompanied by the increase in fine root biomass and ectomycorrhizal fungi diversity and turnover (Grebenc and Kraigher, 2007). The stimulating effect on soil respiration disappeared under spruce in a dry year, which was associated with a decrease in fine root production in spruce under drought. This finding suggested that drought was a more dominant stress than O_3 for spruce (Nikolova et al., 2010). Andersen et al. (2010) labeled the canopies of European beech and Norway

spruce with CO_2 depleted in ^{13}C at the same site. They did not observe any significant changes in soil respiration for either species.

The nearly 10 year long studies at Aspen FACE indicated that the response of soil respiration to O_3 interacted with CO_2 exposure and varied temporally (Table 9-7) (Pregitzer et al., 2008; Pregitzer et al., 2006; King et al., 2001). Ozone treatment alone generally had the lowest mean soil respiration rates, although those differences between control and elevated O_3 were usually not significant. However, soil respiration rates were different with O_3 alone and when acting in combination with elevated CO_2. In the first five years (1998-2002), soil respiration under $+CO_2+O_3$ treatment was similar to that under control and lower than that under $+CO_2$ treatment (Pregitzer et al., 2006; King et al., 2001). Since 2003, $+CO_2+O_3$ treatment started to show the greatest impact on soil respiration. Compared to elevated CO_2, soil respiration rate under $+CO_2+O_3$ treatment was 15-25% higher from 2003-2004, and 5-10% higher from 2005-2007 (Pregitzer et al., 2008; Pregitzer et al., 2006). Soil respiration was highly correlated with the biomass of roots with diameters of <2 mm and <1 mm, across plant community and atmospheric treatments. The authors suggested that the increase in soil respiration rate may be due to $+CO_2+O_3$ increased fine root (<1.0 mm) biomass production (Pregitzer et al., 2008).

Changes in leaf chemistry and productivity due to O_3 exposure have been shown to affect herbivore growth and abundance (See Section 9.4.9.1). Canopy insects could affect soil carbon and nutrient cycling through frass deposition, or altering chemistry and quantity of litter input to the forest floor. A study at the Aspen FACE found that although elevated O_3 affected the chemistry of frass and greenfall, these changes had small impact on microbial respiration and no effect on nitrogen leaching (Hillstrom et al., 2010a). However, respiratory carbon loss and nitrate immobilization were nearly double in microcosms receiving herbivore inputs than those receiving no herbivore inputs (Hillstrom et al., 2010a).

Soil Carbon Formation

Ozone-induced reductions in plant growth can result in reduced C input to soil and therefore soil C content (Andersen, 2003). The simulations of most ecosystem models support this prediction (Ren et al., 2007a; Zhang et al., 2007a; Felzer et al., 2004). However, very few studies have directly measured soil C dynamics under elevated O_3. After the first four years of fumigation (from 1998 to 2001) at the Aspen FACE site, Loya et al. (2003) found that forest stands exposed to both elevated O_3 and CO_2 accumulated 51% less total soil C, and 48% less acid-insoluble soil C compared to stands exposed only to elevated CO_2. Soil organic carbon (SOC) was continuously monitored at the Aspen FACE site, and the later data showed that the initial reduction in new

C formation (soil C derived from plant litter since the start of the experiment) by O_3 under elevated CO_2 is only a temporary effect (Table 9-7) (Talhelm et al., 2009). The amount of new soil C in the elevated CO_2 and the combined elevated CO_2 and O_3 treatments has converged since 2002. There was no significant effect of O_3 on the new C formed under elevated CO_2 over the last four years of the study (2004-2008). Talhelm et al. (2009) suggested the observed reduction in the early years of the experiment might be driven by a suppression of C allocated to fine root biomass. During the early exposure years, O_3 had no significant impact on fine root production (King et al., 2001). However, the effect of O_3 on fine root biomass was observed later in the experiment. Ozone increased fine root production and the highest fine root biomass was observed under the combined elevated CO_2 and O_3 treatment in the late exposure years (Table 9-7) (Pregitzer et al., 2006). This increase in fine root production was due to changes in community composition, such as better survival of O_3-tolerant aspen genotype, birch and maple, rather than changes in C allocation at the individual tree level (Pregitzer et al., 2008; Zak et al., 2007).

9.4.6.4 Nutrient cycling

Ozone can affect nutrient cycling by changing nutrient release from litter, nutrient uptake by plants, and soil microbial activity. Nitrogen is the limiting nutrient for most temperate ecosystems, and several studies examined N dynamics under elevated O_3. Nutrient mineralization from decomposing organic matter is important for sustaining ecosystem production. Holmes et al. (2006) found that elevated O_3 decreased gross N mineralization at the Aspen FACE site, indicating that O_3 may reduce N availability. Other N cycling processes, such as NH_4^+ immobilization, gross nitrification, microbial biomass N and soil organic N, were not affected by elevated O_3 (Holmes et al., 2006). Similarly, Kanerva et al. (2006) found total N, NO_3-, microbial biomass N, potential nitrification and denitrification in their meadow mesocosms were not affected by elevated O_3 (40-50 ppb). Ozone was found to decreased soil mineral N content at SoyFACE, which was likely caused by a reduction in plant material input and increased denitrification (Pujol Pereira et al., 2011). Ozone also showed small impact on other micro and macro nutrients. Liu et al. (2007a) assessed N, P, K, S, Ca, Mg, Mn, B, Zn and Cu release dynamics at Aspen FACE, and they found that O_3 had no effects on most nutrients, except to decrease N and Ca release from litter. These studies reviewed above suggested that soil N cycling processes were not affected or slightly reduced by O_3 exposure. However, in a lysimeter study with young beech trees Stoelken et al. (2010) found that elevated O_3 stimulated N release from litter which was largely attributed to an enhanced mobilization of inert nitrogen fraction.

Using the SImple NItrogen Cycle model (SINIC), Hong et al. (2006) evaluated the impacts of O_3 exposure on soil N dynamics and streamflow nitrate flux. The detrimental effect of O_3 on plant growth was found to reduce plant uptake of N and therefore increase nitrate leaching. Their model simulation indicated that ambient O_3 exposure increased the mean annual stream flow nitrate export by 12% (0.042 g N/m^2/year) at the Hubbard Brook Experimental Watershed from 1964-1994 (Hong et al., 2006).

9.4.6.5 Dissolved Organic Carbon and Biogenic Trace Gases Emission

The O_3-induced changes in plant growth, C and N fluxes to soil and microbial metabolism can alter other biogeochemical cycling processes, such as soil dissolved organic carbon (DOC) turnover and trace gases emission.

Jones et al. (2009) collected fen cores from two peatlands in North Wales, UK and exposed them to one of four levels of O_3 (AOT40 of 0, 3.69, 5.87 and 13.80 ppm-h for 41 days). They found the concentration of porewater DOC in fen cores was significantly decreased by increased O_3 exposure. A reduction of the low molecular weight fraction of DOC was concurrent with the observed decrease in DOC concentration. Their results suggested that O_3 damage to overlying vegetation may decrease utilizable C flux to soil. Microbes, therefore, have to use labile C in the soil to maintain their metabolism, which, the authors hypothesized, leads to a decreased DOC concentration with a shift of the DOC composition to more aromatic, higher molecular weight organic compounds.

Several studies since the 2006 O_3 AQCD have examined the impacts of O_3 on nitrous oxide (N_2O) and methane (CH_4) emission. Kanerva et al. (2007) measured the fluxes of N_2O and CH_4 in meadow mesocosms, which were exposed to elevated CO_2 and O_3 in OTCs in south-western Finland. They found that the daily N_2O fluxes were decreased in the NF+O_3 (non-filtered air + elevated O_3, 40-50 ppb) after three seasons of exposure. Elevated O_3 alone or combined with CO_2 did not have any significant effect on the daily fluxes of CH_4 (Kanerva et al., 2007). In another study conducted in central Finland, the 4 year open air O_3 fumigation (AOT40 of 20.8-35.5 ppm-h for growing season) slightly increased potential CH_4 oxidation by 15% in the peatland microcosms, but did not affect the rate of potential CH_4 production or net CH_4 emissions, which is the net result of the potential CH_4 production and oxidation (Morsky et al., 2008). However, several studies found that O_3 could significantly reduce CH_4 emission. Toet et al. (2011) exposed peatland mesocosms to O_3 in OTCs for two years, and found that CH_4 emissions were significantly reduced by about 25% during midsummer periods of both years. In an OTC study of rice paddy, Zheng et al. (2011) found that the daily mean CH_4 emissions were

significantly lower under elevated O_3 treatments than those in charcoal-filtered air and nonfiltered air treatments. They found that the seasonal mean CH_4 emissions were negatively related with AOT40, but positively related to the relative rice yield, aboveground biomass and underground biomass.

9.4.6.6 Summary

Since the 2006 O_3 AQCD, more evidence has shown that although the responses are often site specific, O_3 altered the quality and quantity of litter input to soil, microbial community composition, and C and nutrient cycling. Biogeochemical cycling of below-ground processes is driven by C input from plants. Studies at the leaf and plant level have provided biologically plausible mechanisms, such as reduced photosynthetic rates, increased metabolic cost, and reduced root C allocation for the association of O_3 exposure and the alteration of below-ground processes.

Results from Aspen FACE and other experimental studies consistently found that O_3 reduced litter production and altered C chemistry, such as soluble sugars, soluble phenolics, condensed tannins, lignin, and macro/micro nutrient concentration in litter (Parsons et al., 2008; Kasurinen et al., 2006; Liu et al., 2005). The changes in substrate quality and quantity could alter microbial metabolism under elevated O_3, and therefore soil C and nutrient cycling. Several studies indicated that O_3 suppressed soil enzyme activities (Pritsch et al., 2009; Chung et al., 2006). However, the impact of O_3 on litter decomposition was inconsistent and varied among species, sites and exposure length. Similarly, O_3 had inconsistent impacts on dynamics of micro and macro nutrients.

Studies from the Aspen FACE experiment suggested that the response of below-ground C cycle to O_3 exposure, such as litter decomposition, soil respiration and soil C content, changed over time. For example, in the early part of the experiment (1998-2003), O_3 had no impact on soil respiration but reduced the formation rates of total soil C under elevated CO_2. However, after 10-11 yr of exposure, O_3 was found to increase soil respiration but have no significant impact on soil C formation under elevated CO_2.

The evidence is sufficient to infer that there is a causal relationship between O_3 exposure and the alteration of below-ground biogeochemical cycles.

9.4.7 Community composition

The effects of O_3 on species competition (AX9.3.3.4) and community composition (AX9.6.4) were summarized in the 2006 O_3 AQCD. Plant species differ in their

sensitivity to O_3. Fast growing plants with high stomatal conductance and high specific leaf area (SLA) were more likely to be sensitive to O_3 exposure. Further, different genotypes of a given species also vary in their sensitivity. This differential sensitivity could change the competitive interactions that lead to loss in O_3 sensitive species or genotypes. In addition, O_3 exposure has been found to alter reproductive processes in plants (See Section 9.4.3.3). Changes in reproductive success could lead to changes in species composition. However, since ecosystem-level responses result from the interaction of organisms with one another and with their physical environment, it takes longer for a change to develop to a level of prominence at which it can be identified and measured. A shift in community composition in forest and grassland ecosystems noted in the 2006 O_3 AQCD has continued to be observed from experimental and gradient studies. Additionally, research since the last review has shown that O_3 can alter community composition and diversity of soil microbial communities.

9.4.7.1 Forest

In the San Bernardino Mountains in southern California, O_3 pollution caused a significant decline in ponderosa pine (*Pinus ponderosa*) and Jeffrey pine (*Pinus jeffreyi*) (U.S. EPA, 2006b). Pine trees in the young mature age class group exhibited higher mortality rates compared with mature trees at a site with severe O_3 visible foliar injury. The vulnerability of young mature pines was most likely caused by the fact that trees in this age class were emerging into the canopy, where higher O_3 concentrations were encountered (McBride and Laven, 1999). Because of the loss of O_3-sensitive pines, mixed forests of ponderosa pine, Jeffery Pine and white fir (*Abies concolor*) shifted to predominantly white fir (Miller, 1973). Ozone may have indirectly caused the decline in understory diversity in coniferous forests in the San Bernardino Mountains through an increase in pine litterfall. This increase in litterfall from O_3 exposure results in an understory layer that may prohibit the establishment of native herbs, but not exotic annual *Galium aparine* (Allen et al., 2007).

Ozone damage to conifer forests has also been observed in several other regions. In the Valley of Mexico, a widespread mortality of sacred fir (*Abies religiosa*) was observed in the heavily polluted area of the Desierto de los Leones National Park in the early 1980s (de Lourdes de Bauer and Hernandez-Tejeda, 2007; Fenn et al., 2002). Ozone damage was widely believed to be an important causal factor in the dramatic decline of sacred fir. In alpine regions of southern France and the Carpathians Mountains, O_3 was also considered as the major cause of the observed decline in cembran pine (*Pinus cembra*)(Wieser et al., 2006). However, many environmental factors such as light, temperature, nutrient and soil moisture, and climate extremes such as unusual dry and

wet periods could interact with O_3 and alter the response of forest to O_3 exposure. For those pollution gradient studies, several confounding factors, such as drought, insect outbreak and forest management, may also contribute to or even be the dominant factors causing the mortality of trees (de Lourdes de Bauer and Hernandez-Tejeda, 2007; Wieser et al., 2006).

New evidence from long-term free O_3 fumigation experiments provided additional support for the potential impacts of O_3 on species competition and community composition changes in forest ecosystems. At the Aspen FACE site, community composition at both the genetic and species levels was altered after seven years of fumigation with O_3 (Kubiske et al., 2007). In the pure aspen community, O_3 fumigation reduced growth and increased mortality of sensitive clone 259, while the O_3 tolerant clone 8L emerged as the dominant clone. Growth of clone 8L was even greater under elevated O_3 compared to controls, probably due to O_3 alleviated competitive pressure on clone 8L by reducing growth of other clones. In the mixed aspen-birch and aspen-maple communities, O_3 reduced the competitive capacity of aspen compared to birch and maple (Kubiske et al., 2007). In a phytotron study, O_3 fumigation reduced growth of beech but not spruce in mixed culture, suggesting a higher susceptibility of beech to O_3 under interspecific competition (Kozovits et al., 2005).

9.4.7.2 Grassland and Agricultural Land

The response of managed pasture, often cultivated as a mixture of grasses and clover, to O_3 pollution has been studied for many years. The tendency for O_3-exposure to shift the biomass of grass-legume mixtures in favor of grass species, reported in the previous O_3 AQCD has been generally confirmed by recent studies. In a mesocosm study, *Trifolium repens* and *Lolium perenne* mixtures were exposed to an episodic rural O_3 regime within solardomes for 12 weeks. *T. repens* showed significant changes in biomass but not *L. perenne*, and the proportion of *T. repens* decreased in O_3-exposed mixtures compared to the control (Hayes et al., 2009). The changes in community composition of grass-legume-forb mixtures were also observed at the Le Mouret FACE experiment, Switzerland. During the 5-year O_3 fumigation (AOT40 of 13.3-59.5 ppm-h), the dominance of legumes in fumigated plots declined more quickly than those in the control plots (Volk et al., 2006). However, Stampfli and Fuhrer (2010) re-analyzed the species and soil data and suggested that Volk et al. (2006) overestimated the O_3 effect. Stampfli and Fuhrer (2010) found that the difference in the species dynamics between control and O_3 treatment was more caused by heterogeneous initial conditions than O_3 exposure. Several studies also suggested the mature/species-rich ecosystems were more resilient to O_3 exposure. At another FACE experiment, located at Alp Flix, Switzerland, O_3 fumigation (AOT40 of

15.2-64.9 ppm-h) showed no significant impact on community composition of this species-rich pasture (Bassin et al., 2007b). Although most studies demonstrated an increase in grass:forb ration with O_3 exposure (Hayes et al., 2009; U.S. EPA, 2006b), a study on a simulated upland grassland community O_3 reduce grass:forb ratio (Felicity et al., 2010), which may be due to grass species in this community, such as Anthoxanthum odoratum, was more sensitive to O_3 than other most studied grass species such as L. perenne (Hayes et al., 2009). Pfleeger et al. (2010) collected seed bank soil from an agricultural field and examined how the plant community responded over several generations to elevated O_3 exposures. Sixty plant species from 22 families emerged in the chambers over their four year study. Overall, they found that O_3 appeared to have small impacts on seed germination and only a minor effect on species richness of pioneer plant communities.

Several review papers have discussed the physiological and ecological characteristics of O_3-sensitive herbaceous plants. Hayes et al. (2007) assessed species traits associated with O_3 sensitivity by the changes in biomass caused by O_3 exposure. Plants of the therophyte (e.g., annual) life form were particularly sensitive to O_3. Species with higher mature leaf N concentration tended to be more sensitive than those with lower leaf N concentration. Plants growing under high oxidative stress environments, such as high light or high saline, were more sensitive to O_3. Using the same dataset from Hayes et al. (2007), Mills et al. (2007a) identified the O_3 sensitive communities. They found that the largest number of these O_3 sensitive communities were associated with grassland ecosystems. Among grassland ecosystems, alpine grassland, sub-alpine grassland, woodland fringe, and dry grassland were identified as the most sensitive communities.

9.4.7.3 Microbes

Several methods have been used to study microbial composition changes associated with elevated O_3. Phospholipid fatty acid (PLFA) analysis is widely used to determine whether O_3 elicits an overall effect on microbial community composition. However, since PLFA markers cover a broad range of different fungi, resolution of this method may be not fine enough to detect small changes in the composition of fungal communities. Methods, such as microscopic analyses and polymerase chain reaction–denaturing gradient gel electrophoresis (PCR–DGGE), have better resolution to specifically analyze the fungal community composition. The resolution differences among those methods needs to be considered when assessing the O_3 impact on microbial community composition.

Kanerva et al. (2008) found that elevated O_3 (40-50 ppb) decreased total, bacterial, actinobacterial and fungal PLFA biomass values as well as fungal:bacterial PLFA biomass ratio in their meadow mesocosms in south-western Finland. The relative proportions of individual PLFAs between the control and elevated O_3 treatments were significantly different, suggesting that O_3 modified the structure of the microbial community. Morsky et al. (2008) exposed boreal peatland microcosms to elevated O_3, with growing season AOT40 of 20.8-35.3 ppm-h, in an open-air O_3 exposure field in Central Finland. They also found that microbial composition was altered after three growing seasons with O_3 fumigation, as measured by PLFA. Ozone tended to increase the presence of Gram-positive bacteria and the biomass of fungi in the peatland microcosms. Ozone also resulted in higher microbial biomass, which co-occurred with the increases in concentrations of organic acids and leaf density of sedges (Morsky et al., 2008). In a lysimeter experiment in Germany, O_3 was found to alter the PLFA profiles in the upper 0-20 cm rhizosphere soil of European beech. Elevated O_3 reduced bacterial abundance but had no detectable effect on fungal abundance (Pritsch et al., 2009). Using microscopic analyses, Kasurinen et al. (2005) found that elevated O_3, with 5 or 6 months of AOT40 of 20.6-30.9 ppm-h, decreased the proportions of black and liver-brown mycorrhizas and increased that of light brown/orange mycorrhizas. In an herbaceous plant study, SSCP (single-strand conformation polymorphism) profiles indicated that O_3 stress (about 75 ppb) had a very small effect on the structural diversity of the bacterial community in rhizospheres (Dohrmann and Tebbe, 2005). At the Aspen FACE site, O_3 had no significant effect on fungal relative abundance, as indicated by PLFA profile. However, elevated O_3 altered fungal community composition, according to the identification of 39 fungal taxonomic units from soil using polymerase chain reaction–denaturing gradient gel electrophoresis (PCR-DGGE) (Chung et al., 2006). In another study at Aspen FACE, phylogenetic analysis suggested that O_3 exposure altered agaricomycete community. The ectomycorrhizal communities developing under elevated O_3 had higher proportions of Cortinarius and Inocybe species, and lower proportions of Laccaria and Tomentella (Edwards and Zak, 2011). Ozone was found to change microbial community composition in an agricultural system. Chen et al. (2010b) found elevated O_3 (100-150 ppb) had significant effects on soil microbial composition expressed as PLFA percentage in a rice paddy in China.

9.4.7.4 Summary

In the 2006 O_3 AQCD, the impact of O_3 exposure on species competition and community composition was assessed. Ozone was found to cause a significant decline in ponderosa and Jeffrey pine in the San Bernardino Mountains in southern California. Ozone exposure

also tended to shift the grass-legume mixtures in favor of grass species (U.S. EPA, 2006b). Since the 2006 O_3 AQCD, more evidence has shown that O_3 exposure changed the competitive interactions and could lead to loss of O_3 sensitive species or genotypes. Studies at plant level found that the severity of O_3 damage on growth, reproduction and foliar injury varied among species, which provided the biological plausibility for the alteration of community composition. Additionally, research since the last review has shown that O_3 can alter community composition and diversity of soil microbial communities.

The decline of conifer forests under O_3 exposure was continually observed in several regions. Ozone damage was believed to be an important causal factor in the dramatic decline of sacred fir in the valley of Mexico (de Lourdes de Bauer and Hernandez-Tejeda, 2007), as well as cembran pine in southern France and Carpathian Mountains (Wieser et al., 2006). Results from the Aspen FACE site indicated that O_3 could alter community composition of broadleaf forests as well. At the Aspen FACE site, O_3 reduced growth and increased mortality of a sensitive aspen clone, while the O_3 tolerant clone emerged as the dominant clone in the pure aspen community. In the mixed aspen-birch and aspen-maple communities, O_3 reduced the competitive capacity of aspen compared to birch and maple (Kubiske et al., 2007).

The tendency for O_3-exposure to shift the biomass of grass-legume mixtures in favor of grass species, was reported in the 2006 O_3 AQCD and has been generally confirmed by recent studies. However, in a high elevation mature/species-rich grass-legume pasture, O_3 fumigation showed no significant impact on community composition (Bassin et al., 2007b).

Ozone exposure not only altered community composition of plant species, but also microorganisms. The shift in community composition of bacteria and fungi has been observed in both natural and agricultural ecosystems, although no general patterns could be identified (Kanerva et al., 2008; Morsky et al., 2008; Kasurinen et al., 2005).

The evidence is sufficient to conclude that there is likely a causal relationship between O_3 exposure and the alteration of community composition.

9.4.8 Factors that Modify Functional and Growth Response

Many biotic and abiotic factors, including insects, pathogens, root microbes and fungi, temperature, water and nutrient availability, and other air pollutants, as well as elevated CO_2, influence or alter plant response to O_3. These modifying factors were comprehensively reviewed in AX9.3 of the 2006 O_3 AQCD and thus, this section serves

mainly as a brief summary of the previous findings. A limited number of new studies published since the 2006 O_3 AQCD add to our understanding of the role of these interactions in modifying O_3-induced plant responses. Many of these modifying factors and interactions are integrated into discussions elsewhere in this chapter and the reader is directed to those sections.

9.4.8.1 Genetics

It is well known that species vary greatly in their responsiveness to O_3. Even within a given species, individual genotypes or populations can also vary significantly with respect to O_3 sensitivity (U.S. EPA, 2006b). Therefore, caution should be taken when considering a species' degree of sensitivity to O_3. Plant response to O_3 is determined by genes that are directly related to oxidant stress and to an unknown number of genes that are not specifically related to oxidants, but instead control leaf and cell wall thickness, stomatal conductance, and the internal architecture of the air spaces. It is rarely the case that single genes are responsible for O_3 tolerance. Studies using molecular biological tools and transgenic plants have positively verified the role of various genes and gene products in O_3 tolerance and are continuing to increase the understanding of O_3 toxicity and differences in O_3 sensitivity. See Section 9.3.3.2 of this document for a discussion of recent studies related to gene expression changes in response to O_3.

9.4.8.2 Environmental Biological Factors

As stated in the 2006 O_3 AQCD, the biological factors within the plant's environment that may influence its response to O_3 encompass insects and other animal pests, diseases, weeds, and other competing plant species. Ozone may influence the severity of a disease or infestation by a pest or weed, either by direct effects on the causal species, or indirectly by affecting the host, or both. In addition, the interaction between O_3, a plant, and a pest, pathogen, or weed may influence the response of the target host species to O_3 (U.S. EPA, 2006b). Several recent studies on the effects of O_3 on insects via their interactions with plants are discussed in Section 9.4.9.1. In addition, O_3 has also been shown to alter soil fauna communities (Section 9.4.9.2).

In contrast to detrimental biological interactions, there are mutually beneficial relationships or symbioses involving higher plants and bacteria or fungi. These include (1) the nitrogen-fixing species *Rhizobium* and *Frankia* that nodulate the roots of legumes and alder and (2) the mycorrhizae that infect the roots of many crop and tree species, all

of which may be affected by exposure of the host plants to O_3. Some discussion of mycorrhizae can be found in Section 9.4.6.

In addition to the interactions involving animal pests, O_3 also has indirect effects on higher herbivorous animals, e.g., livestock, due to O_3-induced changes in feed quality. Recent studies on the effects of O_3 on nutritive quality of plants are discussed in Sections 9.4.4.2.

Intra- and interspecific competition are also important factors in determining vegetation response to O_3. Plant competition involves the ability of individual plants to acquire the environmental resources needed for growth and development: light, water, nutrients, and space. Intraspecific competition involves individuals of the same species, typically in monoculture crop situations, while interspecific competition refers to the interference exerted by individuals of different species on each other when they are in a mixed culture. This topic was previously reviewed in AX9.3.3.4 of the 2006 O_3 AQCD. Recent studies on competition and its implications for community composition are discussed in Section 9.4.7.

9.4.8.3 Physical Factors

Physical or abiotic factors play a large role in modifying plant response to O_3, and have been extensively discussed in previous O_3 AQCDs. This section summarizes those findings as well as recent studies published since the last review.

Although some studies have indicated that O_3 impact significantly increases with increased ambient temperature (Ball et al., 2000; Mills et al., 2000), other studies have indicated that temperature has little effect (Balls et al., 1996; Fredericksen et al., 1996). A recent study by Riikonen et al. (2009) at the Ruohoniemi open air exposure field in Kuopio, Finland found that the effects of temperature and O_3 on total leaf area and photosynthesis of *Betula pendula* were counteractive. Elevated O_3 reduced the saplings' ability to utilize the warmer growth environment by increasing the stomatal limitation for photosynthesis and by reducing the redox state of ascorbate in the apoplast in the combination treatment as compared to temperature alone (Riikonen et al., 2009).

Temperature affects the rates of all physiological processes based on enzyme catalysis and diffusion; each process and overall growth (the integral of all processes) has a distinct optimal temperature range. It is important to note that a plant's response to changes in temperature will depend on whether it is growing near its optimum temperature for growth or near its maximum temperature (Rowland-Bamford, 2000). However, temperature is very likely an important variable affecting plant O_3 response in

the presence of the elevated CO_2 levels contributing to global climate change. In contrast, some evidence suggests that O_3 exposure sensitizes plants to low temperature stress (Colls and Unsworth, 1992) and, also, that O_3 decreases below-ground carbohydrate reserves, which may lead to responses in perennial species ranging from rapid demise to impaired growth in subsequent seasons (i.e., carry-over effects) (Andersen et al., 1997).

Light, a component of the plant's physical environment, is an essential "resource" of energy content that drives photosynthesis and C assimilation. It has been suggested that increased light intensity may increase the O_3 sensitivity of light-tolerant species while decreasing that of shade-tolerant species, but this appears to be an oversimplification with many exceptions. Several studies suggest that the interaction between O_3 sensitivity and light environment is complicated by the developmental stage as well as the light environment of individual leaves in the canopy (Kitao et al., 2009; Topa et al., 2001; Chappelka and Samuelson, 1998).

Although the relative humidity of the ambient air has generally been found to increase the effects of O_3 by increasing stomatal conductance (thereby increasing O_3 flux into the leaves), abundant evidence also indicates that the ready availability of soil moisture results in greater O_3 sensitivity (Mills, 2002). The partial "protection" against the effects of O_3 afforded by drought has been observed in field experiments (Low et al., 2006) and modeled in computer simulations (Broadmeadow and Jackson, 2000). Conversely, drought may exacerbate the effects of O_3 on plants (Pollastrini et al., 2010; Grulke et al., 2003b). There is also some evidence that O_3 can predispose plants to drought stress (Maier-Maercker, 1998). Hence, the nature of the response is largely species-specific and will depend to some extent upon the sequence in which the stressors occur.

9.4.8.4 Interactions with other Pollutants

Ozone-Nitrogen Interactions

Elevated O_3 exposure and N deposition often co-occur. However, the interactions of O_3 exposure and N deposition on vegetation are complex and less well understood compared to their independent effects. Consistent with the conclusion of the 2006 O_3 AQCD, the limited number of studies published since the last review indicated that the interactive effects of N and O_3 varied among species and ecosystems (Table 9-8). To better understand these interactions in ecosystems across the U.S., more information is needed considering combined O_3 exposure and N deposition related effects.

Nitrogen deposition could stimulate relative growth rate (RGR), and lead to increased stomatal conductance. Therefore, plants might become more susceptible to O_3 exposure.

Alternatively, N deposition may increase the availability of photosynthates for use in detoxification and plants could become more tolerant to O_3 (Bassin et al., 2007a). Only a few recent studies have investigated the interactive effects of O_3 and N in the U.S. Grulke et al. (2005) measured stomatal conductance of California black oak (*Quercus kelloggii*) at a long-term N-enrichment site located in the San Bernardino Mountains, which is accompanied by high O_3 exposure (80 ppb, 24-h avg. over a six month growing season). The authors found that N amendment led to poor stomatal control in full sun in midsummer of the average precipitation years, but enhanced stomatal control in shade leaves of California black oak. In an OTC study, Handley and Grulke (2008) found that O_3 lowered photosynthetic ability and water-use efficiency, and increased leaf chlorosis and necrosis of California black oak. Nitrogen fertilization tended to reduce plant sensitivity to O_3 exposure; however, the interaction was not statistically significant.

Studies conducted outside the U.S. are also summarized in Table 9-8. Generally, the responses were species specific. The O_3-induced reduction in photosynthetic rate and biomass loss were greater in the relatively high N treatment for watermelon (*Citrillus lanants*) (Calatayud et al., 2006) and Japanese beech (*Fagus crenata*) seedlings (Yamaguchi et al., 2007). However, there was no significant interactive effect of O_3 and N on biomass production for *Quercus serrata* seedlings (Watanabe et al., 2007), young Norway spruce (*Picea abies*) trees (Thomas et al., 2005), and young European beech (*Fagus sylvatica*) trees (Thomas et al., 2006).

Table 9-8 Response of plants to the interactive effects of elevated ozone exposure and N enrichment

Site	Species	Ozone exposure	N addition	Responses	References
San Bernardino Mountains, U.S.	California black oak (*Quercus kelloggii*)	80 ppb	0, and 50 kg N/ ha/yr	N-amended trees had lower late summer C gain and greater foliar chlorosis in the drought year, and poor stomatal control and lower leaf water use efficiency and in midsummer of the average precipitation year.	Grulke et al. (2005)
San Bernardino Mountains, U.S.	California black oak (*Quercus kelloggii*)	0, 75, and 150 ppb	0, and 50 kg N/ ha/yr	N fertilization tended to reduce plant sensitivity to O_3 exposure; however the interaction was not statistically significant.	Handley and Grulke (2008)
Switzerland	Spruce trees (*Picea abies*)	Filtered (19.4-28.1 ppb); ambient (37.6-47.4 ppb)	0, 20, 40 and 80 kg N/ ha/yr	Higher N levels alleviated the negative impact of O_3 on root starch concentrations	Thomas et al. (2005)
Switzerland	Beech trees (*Fagus sylvatica*)	Filtered (19.4-28.1 ppb); ambient (37.6-47.4 ppb)	0, 20, 40 and 80 kg N/ ha/yr	N addition amplified the negative effects of O_3 on leaf area and shoot elongation.	Thomas et al. (2006)
Switzerland	Alpine pasture	Ambient (AOT40 of 11.1-12.6 ppm-h); 1.2 ambient (AOT40 of 15.2-29.5 ppm-h) and 1.6 ambient (28.4-64.9 ppm-h)	0, 5, 10' 25, 50 kg N/ ha/yr	The positive effects of N addition on canopy greenness were counteracted by accelerated leaf senescence in the highest O_3 treatment.	Bassin et al. (2007b)
Switzerland	Alpine pasture	Ambient (AOT40 of 11.1-12.6 ppm-h); 1.2 ambient (AOT40 of 15.2-29.5 ppm-h) and 1.6 ambient (28.4-64.9 ppm-h)	0, 5, 10, 25, 50 kg N/ha/yr	Only a small number of species showed significant O_3 and N interactive effects on leaf chlorophyll concentration, leaf weight and change in 18O, and the patterns were not consistent.	Bassin et al. (2009)
Switzerland	Alpine pasture	Ambient (AOT40 of 11.1-12.6 ppm-h); 1.2 ambient (AOT40 of 15.2-29.5 ppm-h) and 1.6 ambient (28.4-64.9 ppm-h)	0, 5, 10' 25, 50 kg N/ ha/yr	The positive effects of N addition on canopy greenness were counteracted by accelerated leaf senescence in the highest O_3 treatment.	Bassin et al. (2007b)
Switzerland	Alpine pasture	Ambient (AOT40 of 11.1-12.6 ppm-h); 1.2 ambient (AOT40 of 15.2-29.5 ppm-h) and 1.6 ambient (28.4-64.9 ppm-h)	0, 5, 10' 25, 50 kg N/ ha/yr	Highest N addition resulted in carbon loss, but there was no interaction between O_3 and N treatments.	Volk et al. (2011)
Spain	Watermelon (*Citrillus lanants*)	O_3 free (AOT40 of 0 ppm-h), ambient (AOT40 of 5.1-6.3 ppm-h) and elevated O_3 (AOT40 of 32.5-35.6 ppm-h)	140, 280, and 436 kg N/ ha/yr	High N concentration enhanced the detrimental effects of O_3 on Chlorophyll a fluorescence parameters, lipid peroxidation, and the total yield.	Calatayud et al. (2006)
Spain	Trifolium striatum	Filtered (24-h avg. of 8-22 ppb); ambient (29-34 ppb), elevated O_3 (35-56 ppb)	10, 30, and 60 kg N/ ha/yr	O_3 reduced total aerial biomass. N fertilization counterbalanced O_3-induced effects only when plants were exposed to moderate O_3 levels (ambient) but not under elevated O_3 concentrations.	Sanz et al. (2007)
Japan	Japanese beech seedlings (*Fagus crenata*)	Filtered (24-h avg. of 10.3-13.2 ppb); ambient (42.0-43.3 ppb), 1.5 ambient (62.6-63.9 ppb) and 2.0 ambient (82.7-84.7 ppb)	0, 20 and 50 kg N/ ha/yr	The O_3-induced reduction in net photosynthesis and whole-plant dry mass were greater in the relatively high N treatment than that in the low N treatment.	Yamaguchi et al. (2007)
Japan	*Quercus serrata* seedlings	Filtered (24-h avg. of 10.3-13.2 ppb); ambient (42.0-43.3 ppb), 1.5 ambient (62.6-63.9 ppb) and 2.0 ambient (82.7-84.7 ppb)	0, 20 and 50 kg N/ ha/yr	No significant interactive effects of O_3 and N load on the growth and net photosynthetic rate were detected.	Watanabe et al. (2007)

Ozone-Carbon Dioxide Interactions

Several decades of research has shown that exposure to elevated CO_2 increases photosynthetic rates (Bernacchi et al., 2006; Bernacchi et al., 2005; Tissue et al., 1999;

Tissue et al., 1997; Will and Ceulemans, 1997), decreases stomatal conductance (Ainsworth and Rogers, 2007; Paoletti et al., 2007; Bernacchi et al., 2006; Leakey et al., 2006; Medlyn et al., 2001) and generally increases the growth of plants(McCarthy et al., 2009; Norby et al., 2005). This is in contrast to the decrease in photosynthesis and growth in many plants that are exposed to elevated O_3. The interactive effects on vegetation have been the subject of research in the past two decades due to the implications on productivity and water use of ecosystems. This area of research was discussed in detail in AX9.3.8.1 of the 2006 O_3 AQCD and the conclusions made then are still relevant (U.S. EPA, 2006b).

The bulk of the available evidence shows that, under the various experimental conditions used (which almost exclusively employed abrupt or "step" increases in CO_2 concentration, as discussed below), increased CO_2 levels (ambient + 200 to 400 ppm) may protect plants from the adverse effects of O_3 on growth. This protection may be afforded in part by CO_2 acting together with O_3 in inducing stomatal closure, thereby reducing O_3 uptake, and in part by CO_2 reducing the negative effects of O_3 on Rubisco and its activity in CO_2-fixation. Although both CO_2-induced and O_3-induced decreases in stomatal conductance have been observed primarily in short-term studies, recent data show a long-term and sustained reduction in stomatal conductance under elevated CO_2 for a number of species (Ainsworth and Long, 2005; Ellsworth et al., 2004; Gunderson et al., 2002). Instances of increased stomatal conductance have also been observed in response to O_3 exposure, suggesting partial stomatal dysfunction after extended periods of exposure (Paoletti and Grulke, 2010; Grulke et al., 2007a; Maier-Maercker, 1998).

Important caveats must be raised with regard to the findings presented in published research. The first caveat concerns the distinctly different natures of the exposures to O_3 and CO_2 experienced by plants in the field. Changes in the ambient concentrations of these gases have very different dynamics. In the context of climate change, CO_2 levels increase relatively slowly (globally 2 ppm/year) and may change little over several seasons of growth. On the other hand, O_3 presents a fluctuating stressor with considerable hour-to-hour, day-to-day and regional variability (Polle and Pell, 1999). Almost all of the evidence presented comes from experimentation involving plants subjected to an abrupt step increase to a higher, steady CO_2 concentration. In contrast, the O_3 exposure concentrations usually varied from day to day. Luo and Reynolds (1999), Hui et al. (2002), and Luo (2001) noted the difficulties in predicting the likely effects of a gradual CO_2 increase from experiments involving a step increase or those using a range of CO_2 concentrations. It is also important to note that the levels of elevated CO_2 in many of the studies will not be experienced in the field for 30 or 40 years, but elevated levels of O_3 can occur presently in several areas of the U.S. Therefore, the $CO_2 \times O_3$ interaction studies may be less relevant for current ambient conditions.

Another caveat concerns the interactions of O_3 and CO_2 with other climatic variables, such as temperature and precipitation. In light of the key role played by temperature in regulating physiological processes and modifying plant response to increased CO_2 levels (Morison and Lawlor, 1999; Long, 1991) and the knowledge that relatively modest increases in temperature may lead to dramatic consequences in terms of plant development (Lawlor, 1998), it is important to consider that studying CO_2 and O_3 interactions alone may not create a complete understanding of effects on plants under future climate change.

9.4.9 Insects and Other Wildlife

9.4.9.1 Insects

Insects may respond indirectly to changes to plants (i.e., increased reactive oxygen species, altered phytochemistry, altered nutrient content) that occur under elevated O_3 conditions, or O_3 can have a direct effect on insect performance (Menendez et al., 2009). Effects of O_3 on insects occur at the species level (i.e., growth, survival, reproduction, development, feeding behavior) and at the population and community-level (i.e., population growth rate, community composition). In general, effects of O_3 on insects are highly context- and species-specific (Lindroth, 2010; Bidart-Bouzat and Imeh-Nathaniel, 2008). Furthermore, plant responses to O_3 exposure and herbivore attack have been demonstrated to share signaling pathways, complicating characterization of these stressors (Lindroth, 2010; Menendez et al., 2010, 2009). Although both species-level and population and community-level responses to elevated O_3 are observed in field and laboratory studies discussed below, there is no consensus on how insects respond to feeding on O_3–exposed plants.

Species-Level Responses

In considering insect growth, survival and reproduction in elevated O_3 conditions, several studies have indicated an effect while others have found no correlation. The performance of five herbivore species (three moths and two weevils) was assessed in an OTC experiment at 2 × ambient concentration (Peltonen et al., 2010). Growth of larvae of the Autumnal moth, *Epirrita autumna*, was significantly decreased in the O_3 treatment while no effects were observed in the other species. In an aphid oviposition preference study using birch buds grown in a three year OTC experiment, O_3 had neither a stimulatory or deterring effect on egg-laying (Peltonen et al., 2006). Furthermore, changes in birch bud phenolic compounds associated with the doubled ambient concentrations of O_3 did not

correlate with changes in aphid oviposition (Peltonen et al., 2006). Reproduction in *Popillia japonica*, that were fed soybeans and grown under elevated O_3 appeared to be unaffected (O'Neill et al., 2008). In a meta-analysis of effects of elevated O_3 on 22 species of trees and 10 species of insects, the rates of survival, reproduction and food consumption were typically unaffected while development times were reduced and pupal masses were increased (Valkama et al., 2007).

At the Aspen FACE site insect performance under elevated (50-60 ppb) O_3 conditions (approximately 1.5 × background ambient levels of 30-40 ppb O_3) have been considered for several species. Cumulative fecundity of aphids (*Cepegillettea betulaefoliae)*, that were reared on O_3-exposed paper birch (*Betula papyrifera*) trees, was lower than aphids from control plots (Awmack et al., 2004). No effects on growth, development, adult weight, embryo number and birth weight of newborn nymphs were observed. In a study conducted using three aspen genotypes, performance of the aspen beetle (*Chrysomela crochi*) decreased across all parameters measured (development time, adult mass and survivorship) under elevated O_3 (Vigue and Lindroth, 2010). There was an increase in the development time of male and female aspen beetle larvae although the percentages varied across genotypes. Decreased beetle adult mass and survivorship was observed across all genotypes under elevated O_3 conditions. Another study from the Aspen FACE site, did not find any significant effects of elevated O_3 on performance (longevity, fecundity, abundance) of the invasive weevil (*Polydrusus sericeus*) (Hillstrom et al., 2010b).

Since the 2006 O_3 AQCD, several studies have considered the effect of elevated O_3 on feeding behavior of insects. In a feeding preference study, the common leaf weevil (*Phyllobius pyri*) consumed significantly more leaf discs from one aspen clone when compared to a second clone under ambient air conditions (Freiwald et al., 2008). In a moderately elevated O_3 environment (1.5 × ambient), this preference for a certain aspen clone was less evident, however, leaves from O_3-exposed trees were significantly preferred to leaves grown under ambient conditions. Soybeans grown under enriched O_3 had significantly less loss of leaf tissue to herbivory in August compared to earlier in the growing season (July) when herbivory was not affected (Hamilton et al., 2005). Other plant-herbivore interactions have shown no effects of elevated O_3 on feeding. Feeding behavior of Japanese beetles (*P. japonica*) appeared to be unchanged when beetles were fed soybean leaves grown under elevated O_3 conditions (O'Neill et al., 2008). At the Aspen FACE site, feeding by the invasive weevil (*Polydrusus sericeus*), as measured by leaf area consumption, was not significantly different between foliage that was grown under elevated O_3 versus ambient conditions (Hillstrom et al., 2010b).

Population-Level and Community-Level Responses

Recent data on insects provide evidence of population-level and community-level responses to O_3. Elevated levels of O_3 can affect plant phytochemistry and nutrient content which in turn can alter population density and structure of the associated herbivorous insect communities and impact ecosystem processes (Cornelissen, 2011; Lindroth, 2010). In 72-hour exposures to elevated O_3, mean relative growth rate of the aphid *Diuraphis noxia* increased with ozone concentration suggesting that more rapid population growth may occur when atmospheric O_3 is elevated (Summers et al., 1994, 735955). In a long-term study of elevated O_3 on herbivore performance at the Aspen FACE site, individual performance and population-level effects of the aphid *C. betulaefoliae* were assessed. Elevated O_3 levels had a strong positive effect on the population growth rates of the aphids; although effects were not detected by measuring growth, development, adult weight, embryo number or birth weight of newborn nymphs (Awmack et al., 2004). Conversely, a lower rate of population growth was observed in aphids previously exposed to O_3 in an OTC (Menendez et al., 2010). No direct effects of O_3 were observed; however, nymphs born from adults exposed to and feeding on O_3 exposed plants were less capable of infesting new plants when compared to nymphs in the control plots (Menendez et al., 2010). Elevated O_3 reduced total arthropod abundance by 17% at Aspen FACE, largely as a result of the negative effects on parasitoids, although phloem-feeding insects may benefit (Hillstrom and Lindroth, 2008). Herbivore communities affected by O_3 and N were sampled along an air pollution gradient in the Los Angeles basin (Jones and Paine, 2006). Abundance, diversity, and richness of herbivores were not affected. However, a shift in community structure, from phloem-feeding to chewing dominated communities, was observed along the gradient. No consistent effect of elevated O_3 on herbivory or insect population size was detected at SoyFACE (O'Neill et al., 2010; Dermody et al., 2008).

Evidence of modification of insect populations and communities in response to elevated O_3 includes genotypic and phenotypic changes. In a study conducted at the Aspen FACE site, elevated O_3 altered the genotype frequencies of the pea aphid (*Acyrthosiphon pisum*) grown on red clover (*Trifolium pratense*) over multiple generations (Mondor et al., 2005). Aphid color was used to distinguish between the two genotypes. Ozone increased the genotypic frequencies of pink-morph:green-morph aphids from 2:1 to 9:1, and depressed wing-induction responses more strongly in the pink than the green genotype (Mondor et al., 2005). Growth and development of individual green and pink aphids reared as a single genotype or mixed genotypes were unaffected by elevated O_3 (Mondor et al., 2010). However, growth of pea aphid populations is not readily predictable using individual growth rates.

9.4.9.2 Wildlife

Herpetofauna

Since the 2006 O_3 AQCD, direct effects of O_3 exposure including physiological changes and alterations of ecologically important behaviors such as feeding and thermoregulation have been observed in wildlife. These studies have been conducted in limited laboratory exposures, and the levels of O_3 treatment (e.g. 0.2-0.8 ppm) were often unrealistically higher than the ambient levels. Amphibians may be especially vulnerable to airborne oxidants due to the significant gas exchange that occurs across the skin (Andrews et al., 2008; Dohm et al., 2008). Exposure to 0.2 ppm to 0.8 ppm O_3 for 4 hours resulted in a decrease of oxygen consumption and depressed lung ventilation in the California tree frog *Pseudacris cadaverina* (Mautz and Dohm, 2004). Following a single 4-h exposure to O_3, reduced pulmonary macrophage phagocytosis was observed at 1 and 24 hours post exposure in the marine toad (*Bufo marinus*) indicating an effect on immune system function (Dohm et al., 2005). There was no difference in macrophage function at 48 hours post exposure in exposed and control individuals.

Behavioral effects of O_3 observed in amphibians include responses to minimize the surface area of the body exposed to the air and a decrease in feeding rates (Dohm et al., 2008; Mautz and Dohm, 2004). The adoption of a low-profile "water conservation posture" during O_3 exposure was observed in experiments with the California tree frog (Mautz and Dohm, 2004). Marine toads, *Bufo marinus*, exposed to 0.06 µL/L O_3 for 4 hours ate significantly fewer mealworms at 1 hour and 48 hours post exposure than control toads (Dohm et al., 2008). In the same study, escape/exploratory behavior as measured by total distance moved was not adversely affected in the O_3-exposed individuals as compared to the controls (Dohm et al., 2008).

Water balance and thermal preference in herpetofauna are altered with elevated O_3. Marine toads exposed to 0.8 ppm O_3 for 4 hours exhibited behavioral hypothermia when temperature selection in the toads was assessed at 1, 24 and 48 hours post exposure (Dohm et al., 2001). Ozone-exposed individuals lost almost 5g more body mass on average than controls due to evaporative water loss. At 24 hours after exposure, the individuals that had lost significant body mass selected lower body temperatures(Dohm et al., 2001). Behavioral hypothermia was also observed in reptiles following 4-h exposures to 0.6 ppm O_3. Exposure of the Western Fence Lizard (*Sceloporus occidentalis*) at 25°C induced behavioral hypothermia that recovered to control temperatures by 24 hours (Mautz and Dohm, 2004). The behavioral hypothermic response persisted in lizards exposed to O_3 at 35°C at 24 hours post exposure resulting in a mean body temperature of 3.3°C over controls.

Soil Fauna Communities

Ozone has also been shown to alter soil fauna communities (Meehan et al., 2010; Kasurinen et al., 2007; Loranger et al., 2004). Abundance of Acari (mites and ticks) decreased by 47% under elevated O_3 at Aspen FACE site, probably due to the higher secondary metabolites and lower N concentrations in litter and foliage under elevated O_3 (Loranger et al., 2004). In another study from the Aspen FACE site, leaf litter collected from aspen grown under elevated O_3 conditions were higher in fiber and lignin concentrations than trees grown under ambient conditions. These chemical characteristics of the leaves were associated with increased springtail population growth following 10 weeks in a laboratory microcosm (Meehan et al., 2010). Consumption rates of earthworms fed on leaf litter for 6 weeks from trees grown under elevated O_3 conditions and ambient air did not vary significantly between treatments (Meehan et al., 2010). In another study on juvenile earthworms *Lumbricus terrestris*, individual growth was reduced when worms were fed high-O_3 birch litter from trees exposed for three years to elevated O_3 in an OTC system (Kasurinen et al., 2007). In the same study no significant growth or mortality effects were observed in isopods.

9.4.9.3 Indirect Effects on Wildlife

In addition to the direct effects of O_3 exposure on physiological and behavioral endpoints observed in the laboratory, there are indirect effects to wildlife. These effects include changes in biomass and nutritive quality of O_3-exposed plants (reviewed in Section 9.4.4) that are consumed by wildlife. Reduced digestibility of O_3-exposed plants may alter dietary intake and foraging strategies in herbivores. In a study using native highbush blackberry (*Rubus argutus*) relative feed value of the plants decreased in bushes exposed to double ambient concentrations of O_3 (Ditchkoff et al., 2009). Indirect effects of elevated O_3 on wildlife include changes in chemical signaling important in ecological interactions reviewed below.

Chemical Signaling in Ecological Interactions

Ozone has been shown to degrade or alter biogenic VOC signals important to ecological interactions including; (1) attraction of pollinators and seed dispersers; (2) defense against herbivory; and (3) predator-prey interactions (Pinto et al., 2010; McFrederick et al., 2009; Yuan et al., 2009; Pinto et al., 2007a; Pinto et al., 2007b). Each signal released by emitters has an atmospheric lifetime and a unique chemical signature comprised of different ratios of individual hydrocarbons that is susceptible to atmospheric oxidants such as O_3 (Yuan et al., 2009; Wright et al., 2005). Under elevated O_3 conditions, these

olfactory cues may travel shorter distances before losing their specificity (McFrederick et al., 2009; McFrederick et al., 2008). Additional non-phytogenic VOC-mediated interrelationships with the potential to be modified by O_3 include territorial marking, pheromones for attraction of mates and various social interactions including scent trails, nestmate recognition and signals involved in aggregation behaviors (McFrederick et al., 2009). For example, the alcohols, ketones and aldehydes comprising sex pheromones in moths could be especially vulnerable to degradation by O_3, since some males travel >100 m to find mates (Carde and Haynes, 2004). In general, effects of O_3 on scent-mediated ecological interactions are highly context- and species-specific (Lindroth, 2010; Bidart-Bouzat and Imeh-Nathaniel, 2008).

Pollination and Seed Dispersal

Phytogenic VOC's attract pollinators and seed dispersers to flowers and fruits (Dudareva et al., 2006; Theis and Raguso, 2005). These floral scent trails in plant-insect interactions may be destroyed or transformed by O_3 (McFrederick et al., 2008). Using a Lagrangian model, the rate of destruction of phytogenic VOC's was estimated in air parcels at increasing distance from a source in response to increased regional levels of O_3, hydroxyl and nitrate radicals (McFrederick et al., 2008). Based on the model, the ability of pollinators to locate highly reactive VOCs from emitting flowers may have decreased from kilometers during pre-industrial times to <200 m at current ambient conditions (McFrederick et al., 2008). Scents that travel shorter distances (0-10 m) are less susceptible to air pollutants, while highly reactive scents that travel longer distances (10 to 100's of meters), are at a higher risk for degradation (McFrederick et al., 2009). For example, male euglossine bees can detect bait stations from a distance of at least one kilometer (Dobson, 1994).

Defense Against Herbivory

Ozone can alter the chemical signature of VOCs emitted by plants and these VOCs are subsequently detected by herbivores (Blande et al., 2010; Iriti and Faoro, 2009; Pinto et al., 2007a; Vuorinen et al., 2004; Jackson et al., 1999; Cannon, 1990). These modifications can make the plant either more attractive or repellant to phytophagous insects (Pinto et al., 2010). For example, under elevated O_3, the host plant preference by forest tent caterpillars increased for birch compared to aspen (Agrell et al., 2005). Ozone-induced emissions from red spruce needles were found to repel spruce budworm larvae (Cannon, 1990). Transcriptional profiles of field grown soybean (*Glycine max*) grown in elevated O_3 conditions were altered due to herbivory by Japanese beetles. The herbivory

resulted in a higher number of transcripts in the leaves of O_3-exposed plants and up-regulation of antioxidant metabolism associated with plant defense (Casteel et al., 2008).

Ozone may modify signals involved in plant-to-plant interactions and plant defense against pathogens (Blande et al., 2010; Pinto et al., 2010; McFrederick et al., 2009; Yuan et al., 2009). In a recent study with lima beans, 80 ppb O_3 degraded several herbivore-induced VOCs, reducing the distance over which plant-to-plant signaling occurred (Blande et al., 2010).

Predator-Prey Interactions

Elevated O_3 conditions are associated with disruption of pheromone-mediated interactions at higher trophic levels (e.g., predators and parasitoids of herbivores). In a study from the Aspen FACE site, predator escape behaviors of the aphid (*Chatophorus stevensis*) were enhanced on O_3-fumigated aspen trees although the mechanism of this response remains unknown (Mondor et al., 2004). The predatory mite *Phytoseiulus persimilis* can distinguish between the VOC signature of ozonated lima bean plants and ozonated lima bean plants simultaneously damaged by *T. urticae* (Vuorinen et al., 2004) however, other tritrophic interactions have shown no effect (Pinto et al., 2007b).

There are few studies that consider host location behaviors of parasites under elevated O_3. In closed chambers fumigated with O_3, the searching efficiency and proportion of the host larval fruit flies parasitized by *Asobara tabida*, declined when compared to filtered air controls (Gate et al., 1995). The host location behavior and rate of parasitism of the wasp (*Coesia plutellae*) on *Plutella xylostella*-infested potted cabbage plants was tested under ambient and doubled O_3 conditions in an open-air fumigation system (Pinto et al., 2008). The number of wasps found in the field and the percentages of parasitized larvae were not significantly different from controls under elevated O_3.

Elevated O_3 has the potential to perturb specialized food-web communication in transgenic crops. In insect-resistant oilseed rape *Brassica napus* grown under 100 ppb O_3 in a growth chamber, reduced feeding damage by *Putella xylostella* led to deceased attraction of the endoparasitoid (*Costesia vestalis*), however this tritrophic interaction was influenced by the degree of herbivore feeding (Himanen et al., 2009a; Himanen et al., 2009b). Under chronic O_3-exposure, the insect resistance trait BT cry1Ac in transgenic *B. napus* was higher than the control (Himanen et al., 2009c). There was a negative relative growth rate of the Bt target herbivore, *P. xylostella*, in all O_3 treatments.

9.4.9.4 Summary

New information on O_3 effects on insects and other wildlife is limited to a few species and there is no consensus on how these organisms respond to elevated O_3. Studies published since the last review show impacts of elevated O_3 on both species-level responses (reproduction, growth, feeding behavior) and community and ecosystem-level responses (population growth, abundance, shift in community structure) in some insects and soil fauna. Changes in ecologically important behaviors such as feeding and thermoregulation have recently been observed with O_3 exposure in amphibians and reptiles, however, these responses occur at concentrations of O_3 much higher that ambient levels.

New information available since the last review considers the effects of O_3 on chemical signaling in insect and wildlife interactions. Specifically, studies on O_3 effects on pollination and seed dispersal, defenses against herbivory and predator-prey interactions all consider the ability of O_3 to alter the chemical signature of VOCs emitted during these pheromone-mediated events. The effects of O_3 on chemical signaling between plants, herbivores and pollinators as well as interactions between multiple trophic levels is an emerging area of study that may result in further elucidation of O_3 effects at the species, community and ecosystem-level.

9.5 Effects-Based Air Quality Exposure Indices and Dose Modeling

9.5.1 Introduction

Exposure indices are metrics that quantify exposure as it relates to measured plant damage (e.g., reduced growth). They are summary measures of monitored ambient O_3 concentrations over time, intended to provide a consistent metric for reviewing and comparing exposure-response effects obtained from various studies. Such indices may also provide a basis for developing a biologically-relevant air quality standard for protecting vegetation and ecosystems. Effects on plant growth and/or yield have been a major focus of the characterization of O_3 impacts on plants for purposes of the air quality standard setting process (U.S. EPA, 2007b, 1996e, 1986). The relationship of O_3 and plant responses can be characterized quantitatively as “dose-response” or “exposure-response.” The distinction is in how the pollutant concentration is expressed: “dose” is the pollutant concentration absorbed by the leaf over some time period, and is very difficult to measure directly, whereas “exposure” is the ambient air concentration

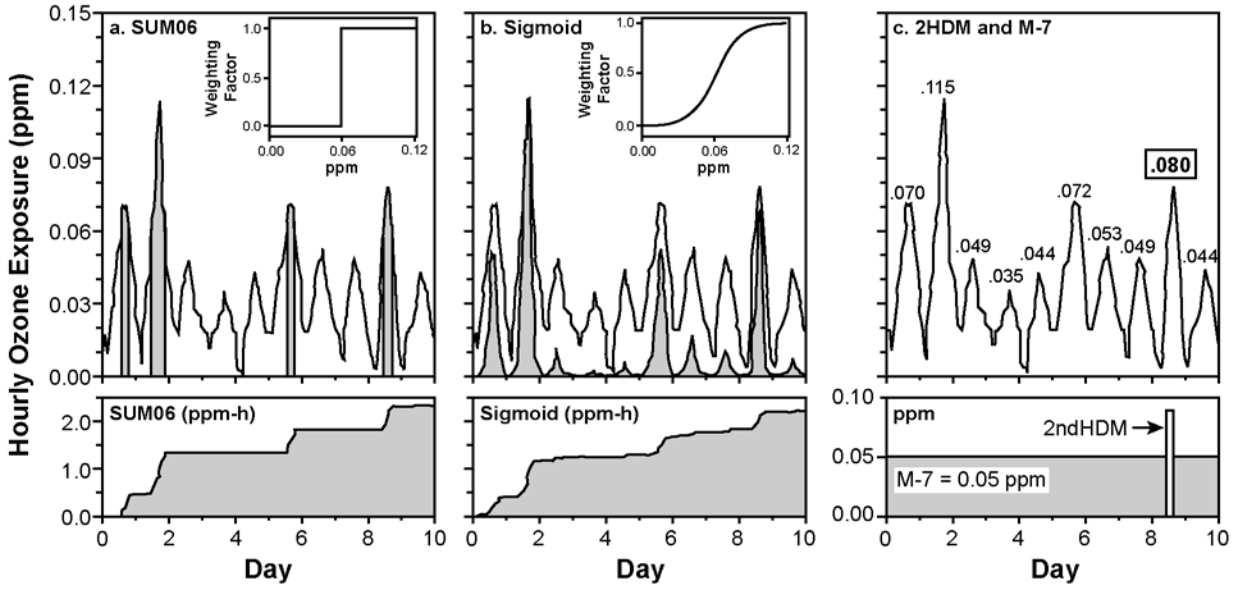
measured near the plant over some time period, and summarized for that period using an index. Exposure indices have been most useful in considering the form of secondary O_3 NAAQS, in large part because they only require ambient air quality data rather than more complex indirect calculations of dose to the plant. The attributes of exposure indices that are most relevant to plant damage are the weighting of O_3 concentrations and the daily and seasonal time-periods. Several different types of exposure indices are discussed in Section 9.5.2.

Form a theoretical perspective, a measure of plant O_3 uptake or dose from ambient air (either rate of uptake or cumulative seasonal uptake) might be a better predictor of O_3 damage to plants than an exposure index and may be useful in improving risk assessment. An uptake estimate would have to integrate all those environmental factors that influence stomatal conductance, including but not limited to temperature, humidity, and soil water status (Section 9.5.4). Therefore, uptake values are generally obtained with simulation models that require knowledge of species- and site-specific values for the variables mentioned. However, a limitation of modeling dose is that environmental variables are poorly characterized. In addition, it has also been recognized that O_3 detoxification processes and the temporal dynamics of detoxification must be taken into account in dose modeling (Heath et al., 2009) (Section 9.5.4). Because of this, research has focused historically on predictors of O_3 damage to plants based only on exposure as a summary measure of monitored ambient pollutant concentration over some integral of time, rather than dose (U.S. EPA, 1996c; Costa et al., 1992; Lee et al., 1988b; U.S. EPA, 1986; Lefohn and Benedict, 1982; O'Gara, 1922).

9.5.2 Description of Exposure Indices Available in the Literature

Mathematical approaches for summarizing ambient air quality information in biologically meaningful forms for O_3 vegetation effects assessment purposes have been explored for more than 80 years (U.S. EPA, 1996b; O'Gara, 1922). In the context of national standards that protect for "known or anticipated" effects on many plant species in a variety of habitats, exposure indices provide a numerical summary of very large numbers of ambient observations of concentration over extended periods. Like any summary statistic, exposure indices retain information on some, but not all, characteristics of the original observations. Several indices have been developed to attempt to incorporate some of the biological, environmental, and exposure factors that influence the magnitude of the biological response and contribute to observed variability (Hogsett et al., 1988). In the 1996 O_3 AQCD, the exposure indices were arranged into five categories; (1) One event, (2) Mean, (3) Cumulative, (4) Concentration weighted, and (5) Multicomponent, and were discussed in detail (Lee et al., 1989). Figure 9-9 illustrates how several of the

indices weight concentration and accumulate exposure. For example, the SUM06 index (panel a) is a threshold-based approach wherein concentrations below 0.06 ppm are given a weight of zero and concentrations above 0.06 ppm are given a weight of 1.0 that is summed usually over 3 to 6 months . The Sigmoid approach (panel b), which is similar to the W126 index, is a non-threshold approach wherein all concentrations are given a weight that increases from zero to 1.0 with increasing concentration and summed.



Source: Used with permission from Air and Waste Management Association (Tingey et al., 1991)

(a) SUM06: the upper graphic illustrates an episodic exposure profile; the shaded area under some of the peaks illustrates the concentrations greater than or equal to 0.06 ppm that are accumulated in the index. The insert shows the concentration weighting (0 to 1) function. The lower portion of the graphic illustrates how concentration is accumulated over the exposure period. (b) SIGMOID: the upper graphic illustrates an episodic exposure profile; the variable shaded area under the peaks illustrates the concentration-dependent weights that are accumulated in the index. The insert shows the sigmoid concentration weighting function. This is similar to the W126 function. The lower portion of the graphic illustrates how concentration is accumulated over the exposure period. (c) second HDM and M-7: the upper graphic illustrates an episodic exposure profile. The lower portion of the graphic illustrates that the second HDM considers only a single exposure peak, while the M-7 (average of 7-h daily means) applies a constant exposure value over the exposure period.

Figure 9-9 Diagrammatic representation of several exposure indices illustrating how they weight concentration and accumulate exposure.

Various factors with known or suspected bearing on the exposure-response relationship, including concentration, time of day, respite time, frequency of peak occurrence, plant

phenology, predisposition, etc., have been weighted with various functions in a large set of indices. The resulting indices were evaluated by ranking them according to the goodness-of-fit of a regression model of growth or yield response (Lee et al., 1989). The statistical evaluations for each of these indices were completed using growth or yield response data from many earlier exposure studies (e.g., NCLAN). This retrospective approach was necessary because there were no studies specifically designed to test the goodness of fit of the various indices. The goodness of fit of a set of linear and nonlinear models for exposure-response was ranked as various proposed indices were used in turn to quantify exposure. This approach provided evidence for the best indices. The results of retrospective analyses are described below.

Most of the early retrospective studies reporting regression approaches used data from the NCLAN program or data from Corvallis, Oregon or California (Costa et al., 1992; Lee et al., 1988b; Lefohn et al., 1988; Musselman et al., 1988; Lee et al., 1987; U.S. EPA, 1986). These studies were previously reviewed by the EPA (U.S. EPA, 1996c; Costa et al., 1992) and were in general agreement that the best fit to the data resulted from using cumulative concentration-weighted exposure indices (e.g. W126, SUM06). Lee et al. (1987) suggested that exposure indices that included all the 24-h data performed better than those that used only 7 hours of data; this was consistent with the conclusions of Heagle et al. (1987) that plants receiving exposures for an additional 5-h/day showed 10% greater yield loss than those exposed for 7-h/day. In an analysis using the National Crop Loss Assessment Network (NCLAN) data, Lee et al. (1988) found several indices which only cumulated and weighted higher concentrations (e.g., W126, SUM06, SUM08, and AOT40) performed very well. Amongst this group no index had consistently better fits than the other indices across all studies and species (Heagle et al., 1994b; Lefohn et al., 1988; Musselman et al., 1988). Lee et al. (1988) found that adding phenology weighting to the index somewhat improved the performance of the indices. The "best" exposure index was a phenologically weighted cumulative index, with sigmoid weighting on concentration and a gamma weighting function as a surrogate for plant growth stage. This index provided the best statistical fit when used in the models under consideration, but it required data on species and site conditions, making specification of weighting functions difficult for general use.

Other factors, including predisposition time (Hogsett et al., 1988; McCool et al., 1988) and crop development stage (Tingey et al., 2002; Heagle et al., 1991) contributed to variation in the biological response and suggested the need for weighting O_3 concentrations to account for predisposition time and phenology. However, the roles of predisposition and phenology in plant response vary considerably with species and environmental conditions; therefore, specification of a weighting function for general use in characterizing plant exposure has not been possible.

European scientists took a similar approach in developing indices describing growth and yield loss in crops and tree seedlings, using OTCs with modified ambient exposures, but many fewer species and study locations were employed in the European studies. There is evidence from some European studies that a lower (Pleijel et al., 1997) or higher (Finnan et al., 1997; Finnan et al., 1996) cutoff value in indices with a threshold may provide a better statistical fit to the experimental data. Finnan et al. (1997) used seven exposure studies of spring wheat to confirm that cumulative exposure indices emphasizing higher O_3 concentrations were best related to plant response and that cumulative exposure indices using weighting functions, including cutoff concentrations, allometric and sigmoidal, provided a better fit and that the ranking of these indices differed depending on the exposure-response model used. Weighting those concentrations associated with sunshine hours in an attempt to incorporate an element of plant uptake did not improve the index performance (Finnan et al., 1997). A more recent study using data from several European studies of Norway spruce, analyzed the relationship between relative biomass accumulation and several cumulative, weighted indices, including the AOT40 (area over a threshold of 40ppb) and the SUM06 (Skarby et al., 2004). All the indices performed relatively well in regressing biomass and exposure index, with the AOT20 and AOT30 doing slightly better than others (r^2 = 0.46-0.47). In another comparative study of four independent data sets of potato yield and different cumulative uptake indices with different cutoff values, a similarly narrow range of r^2 was observed (r^2 = 0.3-0.4) (Pleijel et al., 2004b).

In Europe, the cutoff concentration-weighted index AOT40 was selected in developing exposure-response relationships based on OTC studies of a limited number of crops and trees (Grunhage and Jager, 2003). The United Nations Economic Commission for Europe (UNECE, 1988) adopted the critical levels approach for assessment of O_3 risk to vegetation across Europe. As used by the UNECE, the critical levels are not like the air quality regulatory standards used in the U.S., but rather function as planning targets for reductions in pollutant emissions to protect ecological resources. Critical levels for O_3 are intended to prevent long-term deleterious effects on the most sensitive plant species under the most sensitive environmental conditions, but not intended to quantify O_3 effects. A critical level was defined as "the concentration of pollutant in the atmosphere above which direct adverse effects on receptors, such as plants, ecosystems, or materials may occur according to present knowledge" (UNECE, 1988). The nature of the "adverse effects" was not specified in the original definition, which provided for different levels for different types of harmful effect (e.g., visible injury or loss of crop yield). There are also different critical levels for crops, forests, and semi-natural vegetation. The caveat, "according to present knowledge" is important because critical levels are not rigid; they are revised periodically as new scientific information becomes available. For example, the original critical level for O_3 specified concentrations for three averaging times, but

further research and debate led to the current critical level being stated as the cumulative exposure (concentration × hours) over a cutoff concentration of 40 ppb (AOT40) (Fuhrer et al., 1997).

More recently in Europe, a decision was made to work towards a flux-based approach (see section 9.5.4) for the critical levels ("Level II"), with the goal of modeling O_3 flux-effect relationships for three vegetation types: crops, forests, and semi-natural vegetation (Grunhage and Jager, 2003). Progress has been made in modeling flux (U.S. EPA, 2006b) and the Mapping Manual is being revised (Ashmore et al., 2004a, b; Grennfelt, 2004; Karlsson et al., 2003). The revisions may include a flux-based approach for three crops: wheat, potatoes, and cotton. However, because of a lack of flux-response data, a cumulative, cutoff concentration-based (AOTx) exposure index will remain in use for the near future for most crops and for forests and semi-natural herbaceous vegetation (Ashmore et al., 2004b)

In both the U.S. and Europe, the adequacy of these numerical summaries of exposure in relating biomass and yield changes have, for the most part, all been evaluated using data from studies not necessarily designed to compare one index to another (Skarby et al., 2004; Lee et al., 1989; Lefohn et al., 1988). Very few studies in the U.S. have addressed this issue since the 2006 O_3 AQCD. McLaughlin et al. (2007a) reported that the cumulative exposure index of AOT60 related well to reductions in growth rates at forest sites in the southern Appalachian Mountains. However, the authors did not report an analysis to compare multiple indices. Overall, given the available data from previous O_3 AQCDs and the few recent studies, the cumulative, concentration-weighted indices perform better than the peak or mean indices. It is still not possible, however, to distinguish the differences in performance among the cumulative, concentration-weighted indices.

The main conclusions from the 1996 and 2006 O_3 AQCDs regarding an index based on ambient exposure are still valid. No information has come forth since the 2006 O_3 AQCD to alter those conclusions significantly. These key conclusions can be restated as follows:

- O_3 effects in plants are cumulative;
- higher O_3 concentrations appear to be more important than lower concentrations in eliciting a response;
- plant sensitivity to O_3 varies with time of day and plant development stage; and
- exposure indices that accumulate the O_3 hourly concentrations and preferentially weight the higher concentrations have better statistical fits to growth/yield response than do the mean and peak indices.

Following the 2006 criteria review process (U.S. EPA, 2006b), the EPA proposed an alternative form of the secondary NAAQS for O_3 using a cumulative, concentration-weighted exposure index to protect vegetation from damage (72 FR 37818). The EPA considered two specific concentration-weighted indices: the cutoff concentration weighted SUM06 and the sigmoid-weighted W126 exposure index (U.S. EPA, 2007b). These two indices performed equally well in predicting the exposure-response relationships observed in the crop and tree seedlings studies (Lee et al., 1989). At a workshop convened to consider the science supporting these indices (Heck and Cowling, 1997) there was a consensus that these cumulative concentration-weighted indices being considered were equally capable of predicting plant response. Below are the definitions of the two cumulative index forms considered in the previous staff paper review (U.S. EPA, 2007b):

- **SUM06:** Sum of all hourly O_3 concentrations greater than or equal to 0.06 ppm observed during a specified daily and seasonal time window (Figure 9-9a).
- **W126:** Sigmoidally weighted sum of all hourly O_3 concentrations observed during a specified daily and seasonal time window (Similar to Figure 9-9b). The sigmoidal weighting of hourly O_3 concentration is given in the equation below, where C is the hourly O_3 concentration in ppm:

$$w_c = \frac{1}{1 + 4403e^{-126C}}$$

Equation 9-1

The SUM06 and W126 indices have a variety of relevant time windows that may be applied and are discussed in Section 9.5.3.

It should be noted that there are some important differences between the SUM06 and W126. When considering the response of vegetation to ozone exposures represented by the threshold (e.g., SUM06) and non-threshold (e.g., W126) indices, the W126 metric does not have a cut-off in the weighting scheme as does SUM06 and thus it includes consideration of potentially damaging exposures below 60 ppb. The W126 metric also adds increasing weight to hourly concentrations from about 40 ppb to about 100 ppb. This is unlike cut-off metrics such as the SUM06 where all concentrations above 60 ppb are treated equally. This is an important feature of the W126 since as hourly concentrations become higher, they become increasingly likely to overwhelm plant defenses and are known to be more detrimental to vegetation (See Section 9.5.3.1).

9.5.3 Important Components of Exposure Indices

In the previous O_3 AQCDs it was established that higher hourly concentrations have greater effects on vegetation than lower concentrations (U.S. EPA, 2006b, 1996c). Further, it was determined that the diurnal and seasonal duration of exposure is important for plant response. Weighting of hourly concentrations and the diurnal and seasonal time window of exposure are the most important variables in a cumulative exposure index and will be discussed below. However, these variables must be taken in the context of plant phenology, diurnal conductance rates, plant canopy structure, and detoxification mechanisms of vegetation as well as the climate and meteorology, all of which are determinants of plant response. These more specific factors will be discussed in the uptake and dose modeling section 9.5.4.

9.5.3.1 Role of Concentration

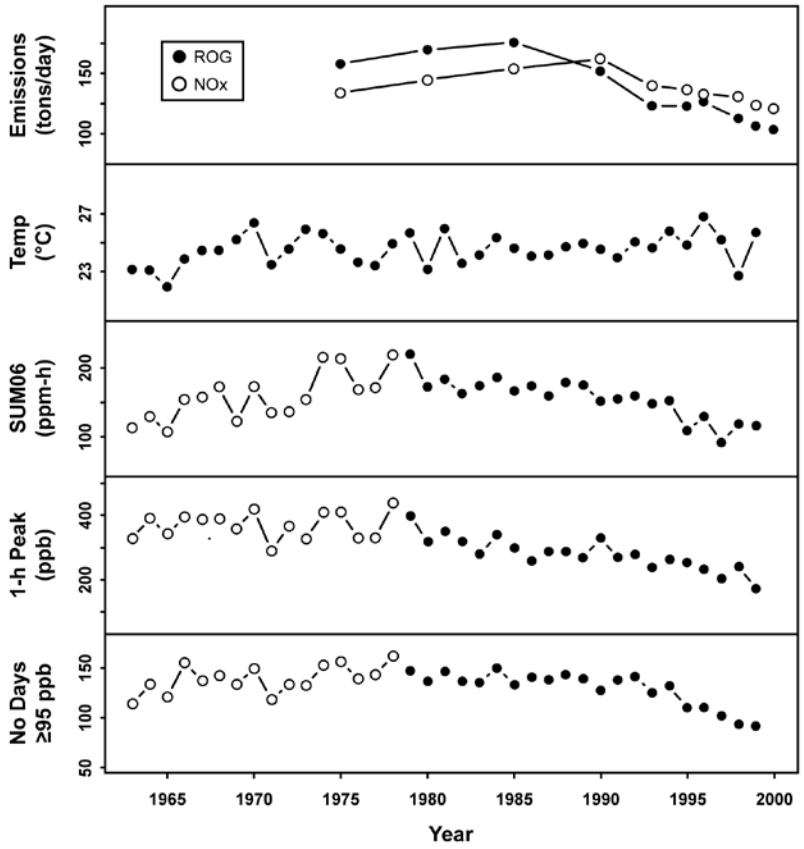
The significant role of peak O_3 concentrations was established based on several experimental studies (U.S. EPA, 1996c). Several studies (Oksanen and Holopainen, 2001; Yun and Laurence, 1999; Nussbaum et al., 1995) have added support for the important role that peak concentrations, as well as the pattern of occurrence, plays in plant response to O_3. Oksanen and Holopainen (2001) found that the peak concentrations and the shape of the O_3 exposure (i.e., duration of the event) were important determinants of foliar injury in European white birch saplings, but growth reductions were found to be more related to total cumulative exposure. Based on air quality data from 10 U.S. cities, three 4-week exposure treatments having the same SUM06 value were constructed by Yun and Laurence (1999). The authors used different exposure regimes to explore effects of treatments with variable versus uniform peak occurrence during the exposure period. The authors reported that the variable peak exposures were important in causing injury, and that the different exposure treatments, although having the same SUM06, resulted in very different patterns of foliar injury. Nussbaum et al. (1995) also found peak concentrations and the pattern of occurrence to be critical in determining the measured response. The authors recommended that to describe the effect on total forage yield, peak concentrations >0.11 ppm must be emphasized by using an AOT with higher threshold concentrations.

A greater role for peak concentrations in effects on plant growth might be inferred based on air quality analyses for the southern California area (Tingey et al., 2004; Lee et al., 2003a). In the late 1960s and 1970s, extremely high O_3 concentrations had impacted the San Bernardino National Forest. However, over the past 20+ years, significant reductions in O_3 exposure have occurred (Bytnerowicz et al., 2008; Lee et al., 2003a; Lefohn and

Shadwick, 2000; Davidson, 1993). An illustration of this improvement in air quality is shown by the 37-year history of O_3 air quality at the Crestline site in the San Bernardino Mountains (Figure 9-10) (Lee et al., 2003a). Ozone exposure increased from 1963 to 1979 concurrent with increased population and vehicular miles, followed by a decline to the present mirroring decreases in precursor emissions. The pattern in exposure was evident in various exposure indices including the cumulative concentration weighted (SUM06), as well as maximum peak event (1-h peak), and the number of days having hourly averaged O_3 concentrations greater than or equal to 95 ppb. The number of days having hourly averaged O_3 concentrations greater than or equal to 95 ppb declined significantly from 163 days in 1978 to 103 days in 1997. The changes in ambient O_3 air quality for the Crestline site were reflected in the changes in frequency and magnitude of the peak hourly concentration and the duration of exposure (Figure 9-10). Considering the role of exposure patterns in determining response, the seasonal and diurnal patterns in hourly O_3 concentration did not vary appreciably from year to year over the 37-year period (Lee et al., 2003a).

The potential importance of exposure to peak concentrations comes both from results of measures of tree conditions on established plots and from results of model simulations. Across a broad area of the San Bernardino National Forest, the Forest Pest Management (FPM) method of injury assessment indicated an improvement in crown condition from 1974 to 1988; and the area of improvement in injury assessment is coincident with an improvement in O_3 air quality (Miller and Rechel, 1999). A more recent analysis of forest changes in the San Bernardino National Forest, using an expanded network of monitoring sites, has verified significant changes in growth, mortality rates, basal area, and species composition throughout the area since 1974 (Arbaugh et al., 2003). A model simulation of ponderosa pine growth over the 40-year period in the San Bernardino National Forest showed a significant impact of O_3 exposure on tree growth and indicates improved growth with reduced O_3 concentrations. This area has also experienced elevated N deposition and based on a number of environmental indicators, it appears that this area is experiencing N saturation (Fenn et al., 1996). To account for this potential interaction, the model simulations were conducted under conditions of unlimited soil N. The actual interactions are not known. The improvement in growth over the years was attributed to improved air quality, but no distinction was made regarding the relative role of mid-range and higher hourly concentrations, only that improved growth tracked decreasing SUM06, maximum peak concentration, and number of days of hourly O_3 >95 ppb (Tingey et al., 2004). A summary of air quality data from 1980 to 2000 for the San Bernardino National Forest area of the number of “mid-range” hourly concentrations indicated no dramatic changes over this 20-year period, ranging from about 1,500 to 2,000 hours per year (Figure 9-11). There was a slow increase in the number of mid-range concentrations from 1980 to 1986, which corresponds to the period after

implementation of the air quality standard. Another sharper increase was observed in the late 1990s. This pattern of occurrence of mid-range hourly concentrations suggests a lesser role for these concentration ranges compared to the higher values in either of the ground-level tree injury observations of the model simulation of growth over the 40-year period.



Source: Used with permission from Elsevier Science Ltd. (Lee et al., 2003a).

Annual ROG and NO_X emissions data for San Bernardino County were obtained from Alexis et al. (2001a) and the California Air Resource Board's emission inventory available at http://www.arb.ca.gov/aqd/aqdpage.htm (Cal/EPA, 2010).

Figure 9-10 Trends in May to September 12-h SUM06, peak 1-h ozone concentration and number of daily exceedances of 95 ppb for the Crestline site in 1963 to 1999 in relation to trends in mean daily maximum temperature for Crestline and daily reactive organic gases (ROG) and oxides of nitrogen (NO_X) for San Bernardino County.

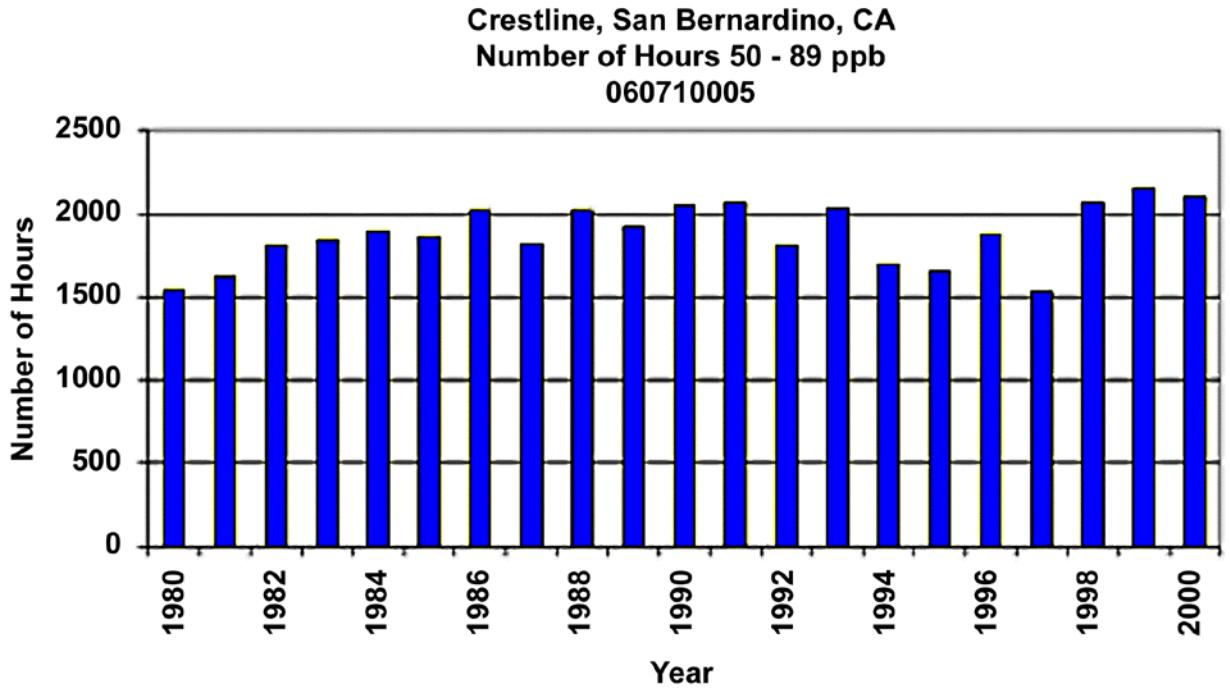


Figure 9-11 The number of hourly average concentrations between 50 and 89 ppb for the period 1980-2000 for the Crestline, San Bernardino County, CA, monitoring site.

9.5.3.2 Diurnal and Seasonal Exposure

Diurnal Exposure

The diurnal patterns of maximal leaf/needle conductance and occurrence of higher ambient concentrations can help determine which hours during the day over a season should be included in an exposure index. Stomatal conductance is species and phenology dependent and is linked to both diurnal and seasonal meteorological activity as well as to soil/site conditions (e.g., VPD, soil moisture). Daily patterns of leaf/needle conductance are often highest in midmorning, whereas higher ambient O_3 concentrations generally occurred in early to late afternoon when stomata were often partially closed and conductances were lower. Total O_3 flux depends on atmospheric and boundary layer resistances, both of which exhibit variability throughout the day. Experimental studies with tree species demonstrated the decoupling of ambient O_3 exposure, peak occurrence,

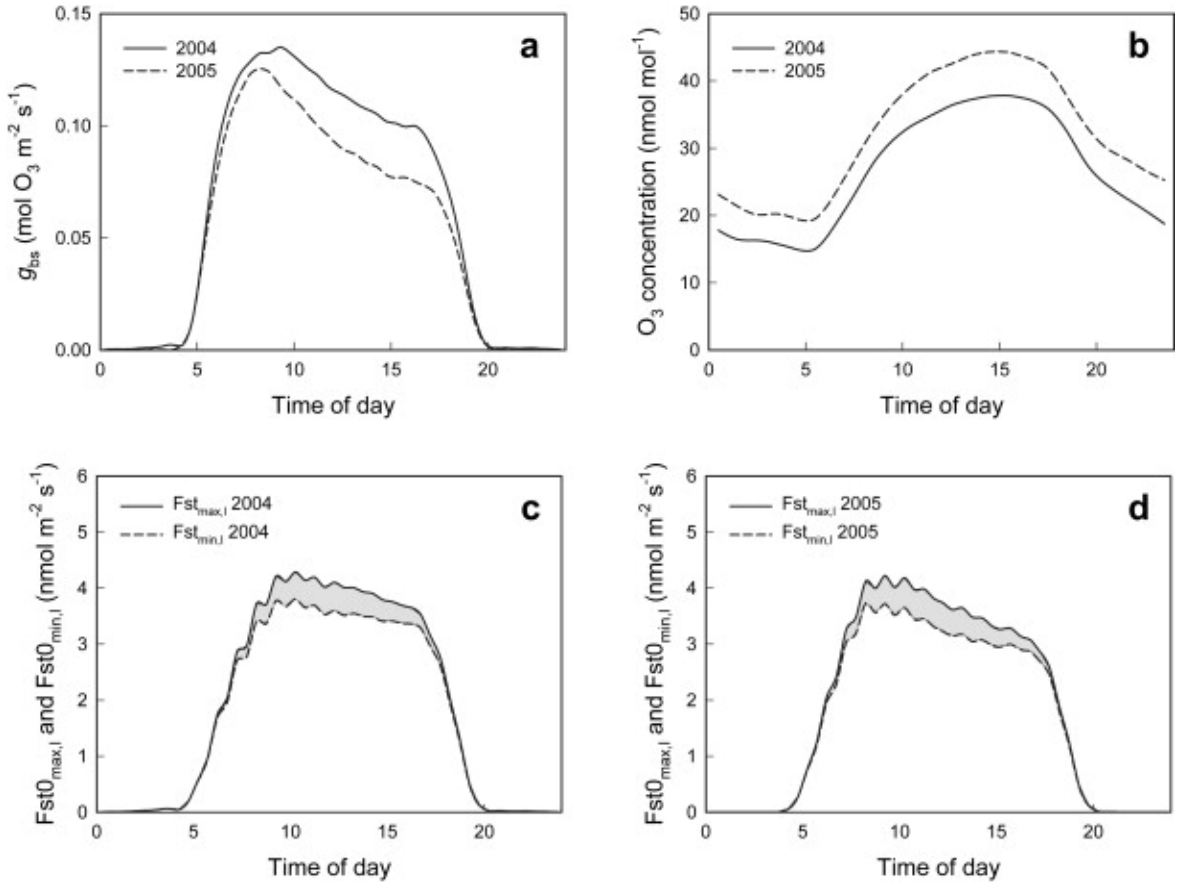
and gas exchange, particularly in areas of drought (Panek, 2004). Several studies have suggested that ponderosa pine trees in the southern and northern Sierra Nevada Mountains may not be as susceptible to high O_3 concentrations as to lower concentrations, due to reduced needle conductance and O_3 uptake during the period when the highest concentrations occur (Panek et al., 2002; Panek and Goldstein, 2001; Bauer et al., 2000; Arbaugh et al., 1998). Panek et al. (2002) compared direct O_3 flux measurements into a canopy of ponderosa pine and demonstrated a lack of correlation of daily patterns of conductance and O_3 occurrence, especially in the late season drought period; the authors concluded that a consideration of climate or season was essential, especially considering the role of soil moisture and conductance/uptake. In contrast, Grulke et al. (2002) reported high conductance when O_3 concentrations were high in the same species, but under different growing site conditions. The longer-term biological responses reported by Miller and Rechel (1999) for ponderosa pine in the same region, and the general reduction in recent years in ambient O_3 concentrations, suggest that stomatal conductance alone may not be a sufficient indicator of potential vegetation injury or damage. Another consideration for the effect of O_3 uptake is the diurnal pattern of detoxification capacity of the plant. The detoxification capacity may not follow the same pattern as stomatal conductance (Heath et al., 2009).

The use of a 12-h (8:00 a.m. to 8:00 p.m.) daylight period for a W126 cumulating exposure was based primarily on evidence that the conditions for uptake of O_3 into the plant occur mainly during the daytime hours. In general, plants have the highest stomatal conductance during the daytime and in many areas atmospheric turbulent mixing is greatest during the day as well (Uddling et al., 2010; U.S. EPA, 2006b). However, notable exceptions to maximum daytime conductance are cacti and other plants with crassulacean acid metabolism (CAM photosynthesis) which only open their stomata at night. This section will focus on plants with C3 and C4 photosynthesis, which generally have maximum stomatal conductance during the daytime.

Recent reviews of the literature reported that a large number of species had varying degrees of nocturnal stomatal conductance (Caird et al., 2007; Dawson et al., 2007; Musselman and Minnick, 2000). The reason for night-time water loss through stomata is not well understood and is an area of active research (e.g. (Christman et al., 2009; Howard et al., 2009) Night-time stomata opening may be enhanced by O_3 damage that could result in loss of stomatal control, and less complete closure of stomata, than under low O_3 conditions (Caird et al., 2007; Grulke et al., 2007b). In general, the rate of stomatal conductance at night is much lower than during the day (Caird et al., 2007). Atmospheric turbulence at night is also often low, which results in stable boundary layers and unfavorable conditions for O_3 uptake into vegetation (Finkelstein et al., 2000). Nevertheless, nocturnal turbulence does intermittently occur and may result in

nonnegligible O_3 flux into the plants. In addition, plants might be more susceptible to O_3 exposure at night than during the daytime, because of potentially lower plant defenses (Heath et al., 2009; Loreto and Fares, 2007; Musselman et al., 2006; Musselman and Minnick, 2000). For significant nocturnal stomatal flux and O_3 effects to occur, specific conditions must exist. A susceptible plant with nocturnal stomatal conductance and low defenses must be growing in an area with relatively high night-time O_3 concentrations and appreciable nocturnal atmospheric turbulence. It is unclear how many areas there are in the U.S. where these conditions occur. It may be possible that these conditions exist in mountainous areas of southern California, front-range of Colorado (Turnipseed et al., 2009) and the Great Smoky Mountains of North Carolina and Tennessee. Tobiessen et al. (1982) found that shade intolerant tree species showed opening of stomata in the dark and did not find this in shade tolerant species. This may indicate shade intolerant trees may be more likely to be susceptible to O_3 exposure at night. More information is needed in locations with high night-time O_3 to assess the local O_3 patterns, micrometeorology and responses of potentially vulnerable plant species.

Several field studies have attempted to quantify night-time O_3 uptake with a variety of methods. However, many of these studies have not linked the night-time flux to measured effects on plants. Grulke et al. (2004) showed that the stomatal conductance at night for ponderosa pine in the San Bernardino National Forest (CA) ranged from one tenth to one fourth that of maximum daytime stomatal conductance. In June, at a high-elevation site, it was calculated that 11% of the total daily O_3 uptake of pole-sized trees occurred at night. In late summer, however, O_3 uptake at night was negligible. However, this study did not consider the turbulent conditions at night. Finklestein et al. (2000) investigated O_3 deposition velocity to forest canopies at three different sites. The authors found the total flux (stomatal and non-stomatal) to the canopy to be very low during night-time hours as compared to day-time hours. However, the authors did note that higher nocturnal deposition velocities at conifer sites may be due to some degree of stomatal opening at night (Finkelstein et al., 2000). Work by Mereu et al. (2009) in Italy on Mediterranean species indicated that nocturnal uptake was from 10 to 18% of total daily uptake during a weak drought and up to 24% as the drought became more pronounced. The proportion of night-time uptake was greater during the drought due to decreases in daytime stomatal conductance (Mereu et al., 2009). In a study conducted in California, Fares et al. (Fares et al., 2011) reported that calculated mean percentages of nocturnal uptake were 5%, 12.5%, 6.9% of total O_3 uptake for lemon, mandarin, and orange, respectively. In another recent study at the Aspen FACE site in Wisconsin, calculated leaf-level stomatal O_3 flux was near zero from the night-time hours of 8:00 p.m. to 5:00 a.m. (Uddling et al., 2010). This was likely due to low horizontal wind speed (>1 m/s) and low O_3 concentrations (<25 ppb) during those same night-time hours (Figure 9-12).



Source: Used with permission from Elsevier Ltd (Uddling et al., 2010).

Figure 9-12 Mean diurnal. (a) conductance through boundary layer and stomata (g_{bs}), (b) Ozone concentration, and leaf-level stomatal ozone flux without flux cut-off threshold ($Fst0_l$) in control plots from mid-June through August in (c) 2004 and (d) 2005 in the Aspen FACE experiment. Subscripts "max" and "min" refer to stomatal fluxes calculated neglecting and accounting for potential non-stomatal ozone flux, respectively.

A few studies have tested the biological effects of night-time O_3 exposure on vegetation in controlled chambers. Biomass of ponderosa pine seedlings was significantly reduced when seedlings were exposed to either daytime or nighttime episodic profiles (Lee and Hogsett, 1999). However, the biomass reductions were much greater with daytime peak concentrations than with nighttime peak concentrations. Similarly, birch cuttings grown in field chambers that were exposed to O_3 at night only, daytime only, and 24 hours showed similar reductions in biomass in night only and day only treatments. Birch seedling showed greater reductions in growth in 24-h exposures than those exposed to O_3 at night or day only (Matyssek et al., 1995). Field mustard (*Brassica rapa*) plants

exposed to O_3 during the day or night showed little significant difference in the amounts of injury or reduced growth response to O_3 treatment, although the stomatal conductance was 70-80% lower at night (Winner et al., 1989). These studies show that effects can be seen with night-time exposures to O_3 but when atmospheric conditions are stable at night, it is uncertain how these exposures may affect plants and trees with complex canopies in the field.

Seasonal Exposure

Vegetation across the U.S. has widely varying periods of physiological activity during the year due to variability in climate and phenology. In order for a particular plant to be vulnerable to O_3 pollution, it must have foliage and be physiologically active. Annual crops are typically grown for periods of two to three months. In contrast, perennial species may be photosynthetically active longer (up to 12 months each year for some species) depending on the species and where it is grown. In general, the period of maximum physiological activity and thus, potential O_3 uptake for vegetation coincides with some or all of the intra-annual period defined as the O_3 season, which varies on a state-by-state basis (Figure 3-19). This is because the high temperature and high light conditions that typically promote the formation of tropospheric O_3 also promote physiological activity in vegetation. There are very limited exceptions to this pattern where O_3 can form in the winter in areas in the western U.S. with intense natural gas exploration (Pinto, 2009), but this is typically when plants are dormant and there is little chance of O_3 uptake. The selection of any single window of time for a national standard to consider hourly O_3 concentrations represents a compromise, given the significant variability in growth patterns and lengths of growing season among the wide range of vegetation species that may experience adverse effects associated with O_3 exposure.

Various intra-annual averaging and accumulation time periods have been considered for the protection of vegetation. The 2010 proposal for secondary O_3 standard (75 FR 2938, p. 3003) proposed to use the maximum consecutive 3-month period within the O_3 season. The U.S. Forest Service and federal land managers have used a 24-h W126 accumulated for 6 months from April through September (2000). However, some monitors in the U.S. are operational for as little as four months and would not have enough data for a 6-month seasonal window. The exposure period in the vast majority of O_3 exposure studies conducted in the U.S. has been much shorter than 6 months. Most of the crop studies done through NCLAN had exposures less than three months with an average of 77 days. Open-top chamber studies of tree seedlings, compiled by the EPA, had an average exposure of just over three months or 99 days. In more recent FACE experiments, SoyFACE exposed soybeans for an average of approximately 120 days per year and the Aspen FACE experiment exposed trees to an average of approximately 145 days per year

of elevated O_3, which included the entire growing season at those particular sites. Despite the possibility that plants may be exposed to ambient O_3 longer than 3 months in some locations, there is a lack of exposure experiments conducted for longer than 3 months.

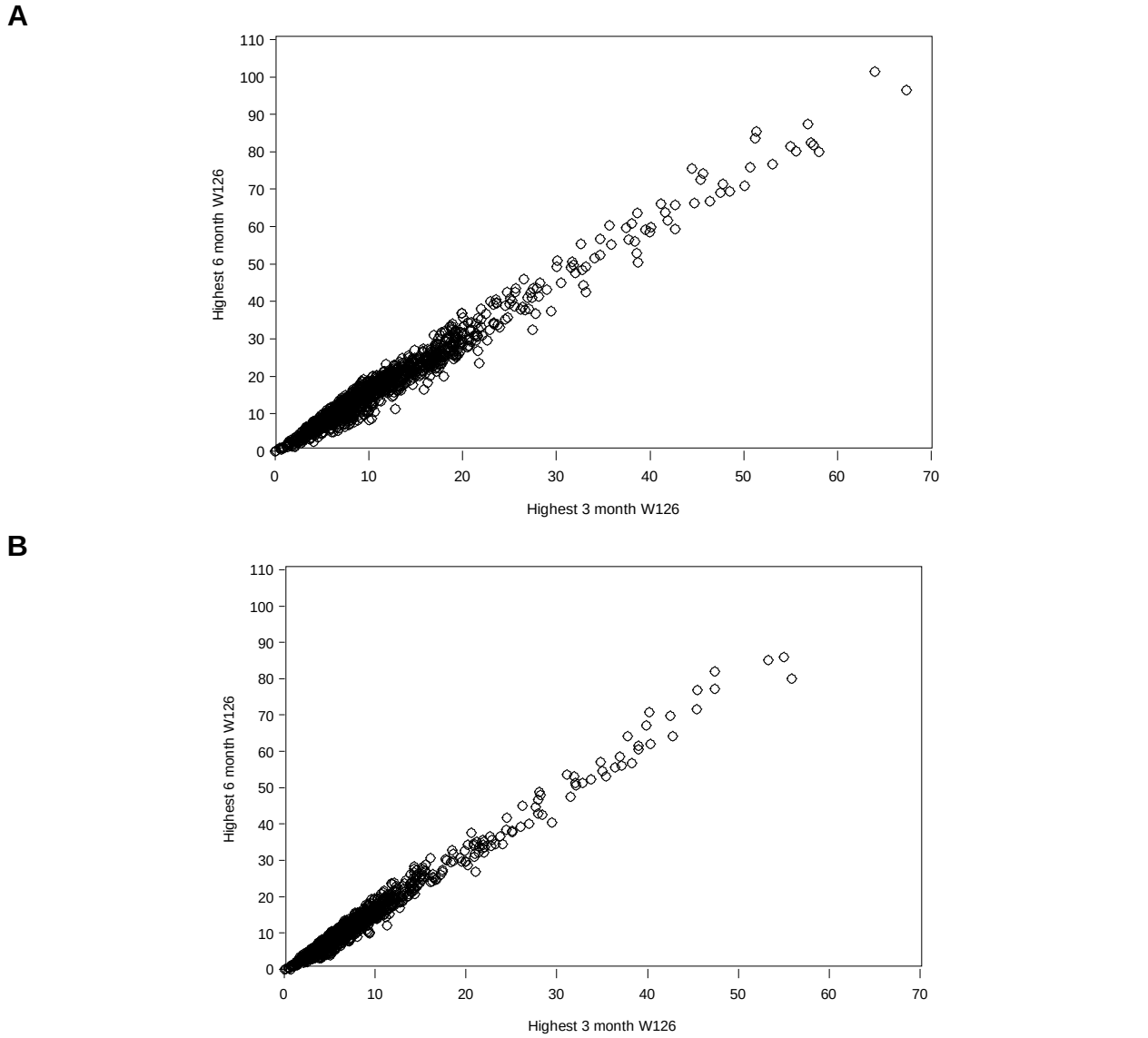


Figure 9-13 Maximum 3-month, 12-h W126 plotted against maximum 6-month, 12-h W126. Data are from the AQS and CASTNET monitors for the years 2008 and 2009. (A) W126, 3 month versus 6 month, 2008 (Pearson correlation = 0.99); (B) W126, 3 month versus 6 month, 2009 (Pearson correlation = 0.99).

In an analysis of the 3- and 6-month maximum W126 values calculated for over 1,200 AQS (Air Quality System) and CASTNET (Clean Air Status and Trend Network) EPA monitoring sites for the years 2008-2009, it was found that these 2 accumulation periods resulted in highly correlated metrics (Figure 9-13). The two accumulation periods were centered on the yearly maximum for each monitoring site, and it is possible that this correlation would be weaker if the two periods were not temporally aligned. In the U.S., W126 cumulated over 3 months, and W126 cumulated over 6 months are proxies of one another, as long as the period in which daily W126 is accumulated corresponds to the seasonal maximum. Therefore, it is expected that either statistic will predict vegetation response equally well. In other words, the strength of the correlation between maximum 3-month W126 and maximum 6-month W126 is such that there is no material difference in their predictive value for vegetation response.

9.5.4 Ozone Uptake/Dose Modeling for Vegetation

Another approach for improving risk assessment of vegetation response to ambient O_3 is based on estimating the O_3 concentration from the atmosphere that enters the leaf (i.e., flux or deposition). Interest has been increasing in recent years, particularly in Europe, in using mathematically tractable flux models for O_3 assessments at the regional, national, and European scale (Matyssek et al., 2008; Paoletti and Manning, 2007; M and M, 2004; Emberson et al., 2000b; Emberson et al., 2000a). Some researchers have claimed that using flux models can be used to better predict vegetation responses to O_3 than exposure-based approaches (Matyssek et al., 2008). However, other research has suggested that flux models do not predict vegetation responses to O_3 better than exposure-based models, such as AOT40 (Gonzalez-Fernandez et al., 2010). While some efforts have been made in the U.S. to calculate O_3 flux into leaves and canopies (Fares et al., 2010a; Turnipseed et al., 2009; Uddling et al., 2009; Bergweiler et al., 2008; Hogg et al., 2007; Grulke et al., 2004; Grantz et al., 1997; Grantz et al., 1995), little information has been published relating these fluxes to effects on vegetation. The lack of flux data in the U.S. and the lack of understanding of detoxification processes have made this technique less viable for vulnerability and risk assessments in the U.S.

Flux calculations are data intensive and must be carefully implemented. Reducing uncertainties in flux estimates for areas with diverse surface or terrain conditions to within ±50% requires “very careful application of dry deposition models, some model development, and support by experimental observations” (Wesely and Hicks, 2000). As an example, the annual average deposition velocity of O_3 among three nearby sites in similar vegetation was found to vary by ±10%, presumably due to terrain (Brook et al., 1997). Moreover, the authors stated that the actual variation was even greater, because

stomatal uptake was unrealistically assumed to be the same among all sites, and flux is strongly influenced by stomatal conductance (Brook et al., 1997; Massman and Grantz, 1995; Fuentes et al., 1992; Reich, 1987; Leuning et al., 1979). This uptake-based approach to quantify the vegetation impact of O_3 requires inclusion of those factors that control the diurnal and seasonal O_3 flux to vegetation (e.g., climate patterns, species and/or vegetation-type factors and site-specific factors). The models have to distinguish between stomatal and non-stomatal components of O_3 deposition to adequately estimate actual concentration reaching the target tissue of a plant to elicit a response (Uddling et al., 2009). Determining this O_3 uptake via canopy and stomatal conductance relies on models to predict flux and ultimately the "effective" flux (Grunhage et al., 2004; Massman, 2004; Massman et al., 2000). "Effective flux" has been defined as the balance between O_3 flux and detoxification processes (Heath et al., 2009; Musselman and Massman, 1999; Grunhage and Haenel, 1997; Dammgen et al., 1993). The time-integrated "effective flux" is termed "effective dose." The uptake mechanisms and the resistances in this process, including stomatal conductance and biochemical defense mechanisms, are discussed below. The flux-based index is the goal for the "Level II" critical level for assessment of O_3 risk to vegetation and ecosystems across Europe (Ashmore et al., 2004a).

An important consideration in both O_3 exposure and uptake is how the O_3 concentration at the top of low vegetation such as, crops and tree seedlings may be lower than the height at which the measurement is taken. Ambient monitor inlets in the U.S. are typically at heights of 3 to 5 meters. During daytime hours, the vertical O_3 gradient can be relatively small because turbulent mixing maintains the downward flux of O_3. For example, Horvath et al. (1995) calculated a 7% decrease in O_3 going from a height of 4 meters down to 0.5 meters above the surface during unstable (or turbulent) conditions in a study over low vegetation in Hungary [see section AX3.3.2. of the 2006 O_3 AQCD (U.S. EPA, 2006b)]. There have been several studies indicating decreased O_3 concentrations under tree canopies (Kolb et al., 1997; Samuelson and Kelly, 1997; Joss and Graber, 1996; Fredericksen et al., 1995; Lorenzini and Nali, 1995; Enders, 1992; Fontan et al., 1992; Neufeld et al., 1992). In contrast, for forests, measured data may underestimate O_3 concentration at the top of the canopy. The difference between measurement height and canopy height is a function of several factors, the intensity of turbulent mixing in the surface layer and other meteorological factors, canopy height and total deposition to the canopy. Some researchers have used deposition models to estimate O_3 concentration at canopy-top height based on concentrations at measurement height (Emberson et al., 2000a). However, deposition models usually require meteorological data inputs that are not always available or well characterized across large spatial scales.

Soil moisture is a critical factor in controlling O_3 uptake through its effect on plant water status and stomatal conductance. In an attempt to relate uptake, soil moisture, and ambient air quality to identify areas of potential risk, available O_3 monitoring data for 1983 to 1990 were used along with literature-based seedling exposure-response data from regions within the southern Appalachian Mountains that might have experienced O_3 exposures sufficient to inhibit growth (Lefohn et al., 1997). In a small number of areas within the region, O_3 exposures and soil moisture availability were sufficient to possibly cause growth reductions in some O_3 sensitive species (e.g., black cherry). The conclusions were limited, however, because of the uncertainty in interpolating O_3 exposures in many of the areas and because the hydrologic index used might not reflect actual water stress.

The non-stomatal component of plant defenses are the most difficult to quantify, but some studies are available (Heath et al., 2009; Barnes et al., 2002; Plochl et al., 2000; Chen et al., 1998; Massman and Grantz, 1995). Massman et al. (2000) developed a conceptual model of a dose-based index to determine how plant injury response to O_3 relates to the traditional exposure-based parameters. The index used time-varying-weighted fluxes to account for the fact that flux was not necessarily correlated with plant injury or damage. The model applied only to plant foliar injury and suggested that application of flux-based models for determining plant damage (yield or biomass) would require a better understanding and quantification of the relationship between injury and damage.

9.5.5 Summary

Exposure indices are metrics that quantify exposure as it relates to measured plant damage (i.e., reduced growth). They are summary measures of monitored ambient O_3 concentrations over time intended to provide a consistent metric for reviewing and comparing exposure-response effects obtained from various studies. No new information is available since 2006 that alters the basic conclusions put forth in the 2006 and 1996 O_3 AQCDs. These AQCDs focused on the research used to develop various exposure indices to help quantify effects on growth and yield in crops, perennials, and trees (primarily seedlings). The performance of indices was compared through regression analyses of earlier studies designed to support the estimation of predictive O_3 exposure-response models for growth and/or yield of crops and tree (seedling) species.

Another approach for improving risk assessment of vegetation response to ambient O_3 is based on determining the O_3 concentration from the atmosphere that enters the leaf (i.e., flux or deposition). Interest has been increasing in recent years, particularly in Europe, in

using mathematically tractable flux models for O_3 assessments at the regional, national, and European scale (Matyssek et al., 2008; Paoletti and Manning, 2007; M and M, 2004; Emberson et al., 2000b; Emberson et al., 2000a). While some efforts have been made in the U.S. to calculate O_3 flux into leaves and canopies (Turnipseed et al., 2009; Uddling et al., 2009; Bergweiler et al., 2008; Hogg et al., 2007; Grulke et al., 2004; Grantz et al., 1997; Grantz et al., 1995), little information has been published relating these fluxes to effects on vegetation. There is also concern that not all O_3 stomatal uptake results in a yield reduction, which depends to some degree on the amount of internal detoxification occurring with each particular species. Those species having high amounts of detoxification potential may, in fact, show little relationship between O_3 stomatal uptake and plant response (Musselman and Massman, 1999). The lack of data in the U.S. and the lack of understanding of detoxification processes have made this technique less viable for vulnerability and risk assessments in the U.S.

The main conclusions from the 1996 and 2006 O_3 AQCDs regarding indices based on ambient exposure are still valid. These key conclusions can be restated as follows:

- O_3 effects in plants are cumulative;
- higher O_3 concentrations appear to be more important than lower concentrations in eliciting a response;
- plant sensitivity to O_3 varies with time of day and plant development stage; and
- exposure indices that cumulate hourly O_3 concentrations and preferentially weight the higher concentrations have better statistical fits to growth/yield response data than do the mean and peak indices.

Various weighting functions have been used, including threshold-weighted (e.g., SUM06) and continuous sigmoid-weighted (e.g., W126) functions. Based on statistical goodness-of-fit tests, these cumulative, concentration-weighted indices could not be differentiated from one another using data from previous exposure studies. Additional statistical forms for O_3 exposure indices have been discussed in Lee et al. (1988b). The majority of studies published since the 2006 O_3 AQCD do not change earlier conclusions, including the importance of peak concentrations, and the duration and occurrence of O_3 exposures in altering plant growth and yield.

Given the current state of knowledge and the best available data, exposure indices that cumulate and differentially weight the higher hourly average concentrations and also include the mid-level values continue to offer the most defensible approach for use in developing response functions and comparing studies, as well as for defining future indices for vegetation protection.

9.6 Ozone Exposure-Plant Response Relationships

9.6.1 Introduction

The adequate characterization of the effects of O_3 on plants for the purpose of setting air quality standards is contingent not only on the choice of the index used (i.e. SUM06, W126) to summarize O_3 concentrations (Section 9.5), but also on quantifying the response of the plant variables of interest at specific values of the selected index. The many factors that determine the response of plants to O_3 exposure have been discussed in previous sections. They include species, genotype and other genetic characteristics (Section 9.3), biochemical and physiological status (Section 9.3), previous and current exposure to other stressors (Section 9.4.8), and characteristics of the exposure itself (Section 9.5). Establishing a secondary air quality standard requires the capability to generalize those observations, in order to obtain predictions that are reliable enough under a broad variety of conditions, taking into account these factors. This section reviews results that have related specific quantitative observations of O_3 exposure with quantitative observations of plant responses, and the predictions of responses that have been derived from those observations through empirical models.

For four decades, exposure to O_3 at ambient concentrations found in many areas of the U.S. has been known to cause detrimental effects in plants (U.S. EPA, 2006b, 1996b, 1984, 1978a). Results published after the 2006 O_3 AQCD continue to support this finding, and the following sections deal with the quantitative characterizations of the relationship, and what new insights may have appeared since 2006. Detrimental effects on plants include visible injury, decreases in the rate of photosynthesis, reduced growth, and reduced yield of marketable plant parts. Most published exposure-response data have reported O_3 effects on the yield of crops and the growth of tree seedlings, and those two variables have been the focus of the characterization of ecological impacts of O_3 for the purpose of setting secondary air quality standards. In order to support quantitative modeling of exposure-response relationships, data should preferably include more than three levels of exposure, and some control of potential confounding or interacting factors should be present in order to model the relationship with sufficient accuracy. Letting potential confounders, such as other stressors, vary freely when generating O_3 exposure-response data might improve the 'realism' of the data, but it also greatly increases the amount of data necessary to extract a clear quantitative description of the relationship. Conversely however, experimental settings should not be so exhaustively restrictive as to make generalization outside of them problematic. During the last four decades, many of the studies of the effects of O_3 on growth and yield of plants have not included enough levels of O_3 to parameterize more than the simplest linear model. The majority of these

studies have only contrasted two levels, ambient and elevated, or sometimes three by adding carbon filtration in OTC studies, with little or no consideration of quantitatively relating specific values of exposure to specific values of growth or yield. This is not to say that studies that did not include more than two or three levels of O_3 exposure, or studies that were conducted in uncontrolled environments, do not provide exposure-response information that is highly relevant to reviewing air quality standards. In fact, they can be essential in verifying the agreement between predictions obtained through the empirical models derived from experiments such as NCLAN, and observations. The consensus of model predictions and observations from a variety of studies conducted in other locations, at other times, and using different exposure methods, greatly increases confidence in the reliability of both. Furthermore, if they are considered in the aggregate, studies with few levels of exposure or high unaccounted variability can provide additional independent estimates of decrements in plant growth and yield, at least within a few broad categories of exposure.

Extensive exposure-response information on a wide variety of plant species has been produced by two long-term projects that were designed with the explicit aim of obtaining quantitative characterizations of the response of such an assortment of crop plants and tree seedlings to O_3 under North American conditions: the NCLAN project for crops, and the EPA National Health and Environmental Effects Research Laboratory, Western Ecology Division tree seedling project (NHEERL/WED). The NCLAN project was initiated by the EPA in 1980 primarily to improve estimates of yield loss under field conditions and to estimate the magnitude of crop losses caused by O_3 throughout the U.S. (Heck et al., 1991; Heck et al., 1982). The cultural conditions used in the NCLAN studies approximated typical agronomic practices, and the primary objectives were: (1) to define relationships between yields of major agricultural crops and O_3 exposure as required to provide data necessary for economic assessments and development of O_3 NAAQS; (2) to assess the national economic consequences resulting from O_3 exposure of major agricultural crops; and (3) to advance understanding of cause-and-effect relationships that determine crop responses to pollutant exposures.

NCLAN experiments yielded 54 exposure-response curves for 12 crop species, some of which were represented by multiple cultivars at several of 6 locations throughout the U.S. The NHEERL/WED project was initiated by EPA in 1988 with the same objectives for tree species, and yielded 49 exposure-responses curves for multiple genotypes of 11 tree species grown for up to three years in Oregon, Michigan, and the Great Smoky Mountains National Park. Both projects used OTCs to expose plants to three to five levels of O_3. Eight of the 54 crop datasets were from plants grown under a combination of O_3 exposure and experimental drought conditions. Figure 9-14 through 9-17 summarize some of the NCLAN and NHEERL/WED results.

It should be noted that data from FACE experiments might also be used for modeling exposure-response. They only use two levels of O_3 (ambient concentration at the site and a multiple of it), but given that the value of both levels of exposure changes every year, and that they are typically run for many consecutive years, aggregating data over time produces twice as many levels of O_3 as there are years. As described in Section 9.2.4, FACE experiments seek to impose fewer constraints on the growth environment then OTCs. As a consequence, FACE studies have to contend with larger variability, especially year-to-year variability, but the difference in experimental conditions between the two methodologies makes comparisons between their results especially useful.

Growth and yield of at least one crop (soybean) has been investigated in yearly experiments since 2001 at a FACE facility in Illinois (University of Illinois, 2010; Morgan et al., 2006), however almost all analyses of SoyFACE published so far have been based on subsets of one or two years, and have only contrasted ambient versus elevated O_3 as categorical variables. They have not modeled the response of growth and yield to O_3 exposure continuously over the range of exposure values that have occurred over time. The only exception is a study by Betzelberger et al. (2010), who used a linear regression model on data pooled over 2 years. Likewise, trees of three species (trembling aspen, paper birch, and sugar maple) were grown between 1998 and 2009 in a FACE experiment located in Rhinelander, Wisconsin (Pregitzer et al., 2008; Dickson et al., 2000). The Aspen FACE experiment has provided extensive data on responses of trees beyond the seedling stage under long-term exposure, and also on ecosystem-level responses (Section 9.4), but the only attempt to use those data in a continuous model of the response of tree growth to O_3 exposure (Percy et al., 2007) suffered severe methodological problems, some of which are discussed in Section 9.6.3. Finally, one experiment was able to exploit a naturally occurring gradient of O_3 concentrations to fit a linear regression model to the growth of cottonwood (Gregg et al., 2006, 2003). Factors such as genotype, soil type and soil moisture were under experimental control, and the authors were able to partition out the effects of potential confounders such as temperature, atmospheric N deposition, and ambient CO_2.

A serious difficulty in assessing results of exposure-response research is the multiplicity of O_3 metrics that have been used in reporting. As described in Section 9.5, metrics that entail either weighting or thresholding of hourly values cannot be converted into one another, or into unweighted metrics such as hourly average. When computing O_3 exposure using weighted or thresholded metrics, the computation of each metric has to start with the original hourly data. Comparisons of exposure-response models can only be made between studies that used the same metric, and the value of exposure at which a given plant response is expected using one metric of exposure cannot be exactly converted to another metric. Determining the exposure value at which an effect would be

observed in a different metric can only be accomplished by first computing the experimental exposures in this metric from the hourly data, then estimating (fitting) model coefficients again. This problem is irremediable, although useful comparisons might be made using categorical exposures such as 'current ambient exposure' or '2050 projected exposure', which can serve as a common reference for quantitative values expressed in various metrics. Studies that contained growth or yield exposure-response data at few levels of exposure, and/or using metrics other than W126 are summarized in Tables 9-18 and 9-19.

9.6.2 Estimates of Crop Yield Loss and Tree Seedling Biomass Loss in the 1996 and 2006 Ozone AQCDs

The 1996 and 2006 O_3 AQCDs relied extensively on analyses of NCLAN and NHEERL/WED by Lee et al. (1994; 1989, 1988b, 1987), Hogsett et al. (1997), Lee and Hogsett (1999), Heck et al. (1984), Rawlings and Cure (1985), Lesser et al. (1990), and Gumpertz and Rawlings (1992). Those analyses concluded that a three-parameter Weibull model –

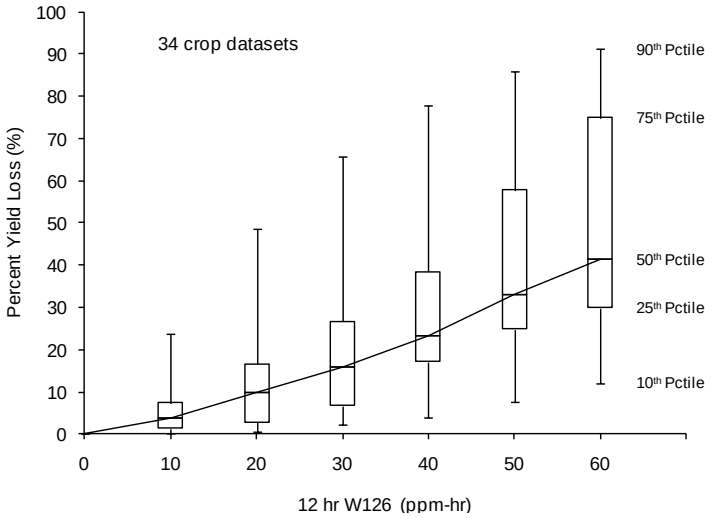
$$Y = \alpha e^{-\left(\frac{W126}{\eta}\right)^{\beta}}$$

Equation 9-2

is the most appropriate model for the response of absolute yield and growth to O_3 exposure, because of the interpretability of its parameters, its flexibility (given the small number of parameters), and its tractability for estimation. In addition, removing the intercept $\boldsymbol{\alpha}$ results in a model of relative yield (yield relative to [yield at exposure=0]) without any further reparameterization. Formulating the model in terms of relative yield or relative yield loss (yield loss=[1 − relative yield]) is essential in comparing exposure-response across species, genotypes, or experiments for which absolute values of the response may vary greatly. In the 1996 and 2006 O_3 AQCDs, the two-parameter model of relative yield was used in deriving common models for multiple species, multiple genotypes within species, and multiple locations.

Given the disparate species, genotypes, and locations that were included in the NCLAN and NHEERL/WED projects, and in the absence of plausible distributional assumptions with respect to those variables, a three step process using robust methods was used to obtain parameter estimates that could be generalized. The models that were derived for each species or group of species were referred to as median composite functions. In the first step, the three parameters of the Weibull model were computed for absolute yield or

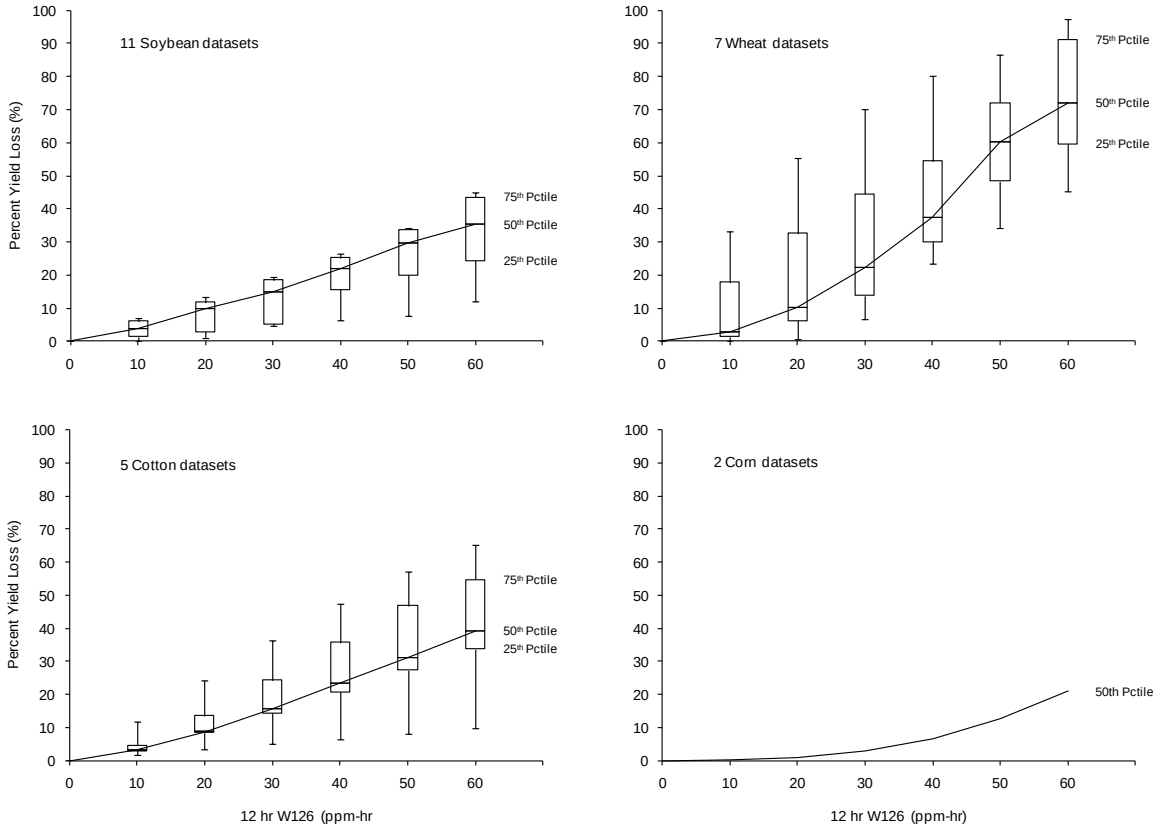
biomass data from each NCLAN and NHEERL/WED experiment (54 crop datasets and 49 tree seedling datasets), using nonlinear regression. When data were only available for three levels of exposure because of experimental problems, the shape parameter β was constrained to 1, reducing the model to an exponential decay model. In the second step, α was dropped, and predicted values of relative yield or biomass were then computed for 12-hr W126 exposures between 0 and 60 ppm-h. At each of these W126 exposure values, the 25th, 50th, and 75th percentiles of the response were identified among the predicted curves of relative response. For example, for the 34 NCLAN studies of 12 crop species grown under non-droughted conditions for a complete cropping cycle (Figure 9-14), the 3 quartiles of the response were identified at every integer value of W126 between 0 and 60. The third step fitted a two-parameter Weibull model to those percentiles, yielding the median composite function for the relative yield or biomass response to O_3 exposure for each grouping of interest (e.g., all crops, all trees, all datasets for one species), as well as composite functions for the other quartiles. In the 1996 and 2006 O_3 AQCDs this modeling of crop yield loss and tree seedling biomass loss was conducted using the SUM06 metric for exposure. This section updates those results by using the 12-hr W126 as proposed in 2007 (72 FR 37818) and 2010 (75 FR 2938, p. 3003). Figures 9-14 through 9-17 present quantiles of predicted relative yield or biomass loss at seven values of the 12-h W126 for some representative groupings of NCLAN and NHEERL/WED results. Tables 9-10 through 9-12 give the 90-day 12-h W126 O_3 exposure values at which 10 and 20% yield or biomass losses are predicted in 50 and 75% of crop or tree species using the composite functions.



Source of Weibull parameters: Lee and Hogsett (1996).

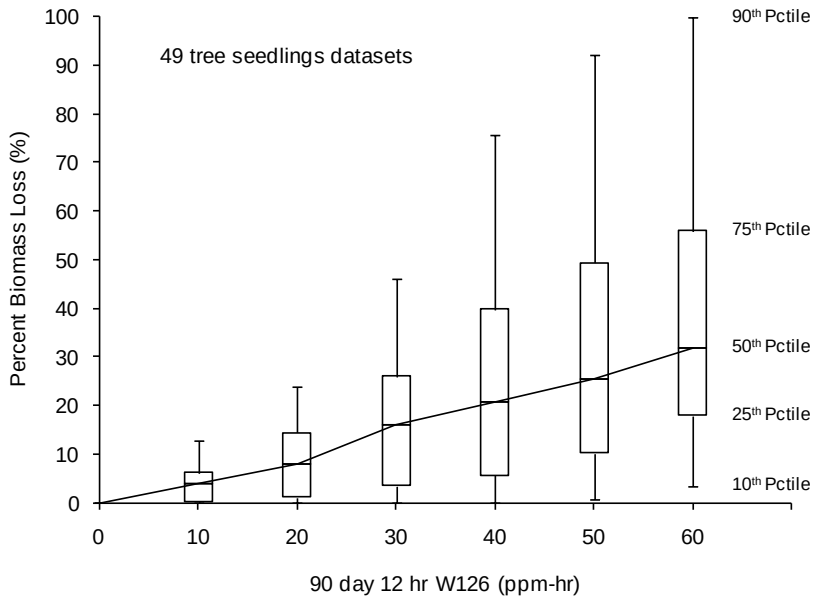
Quantiles of the predicted relative yield loss at 7 values of 12-hour W126 for 34 Weibull curves estimated using nonlinear regression on data from 34 studies of 12 crop species grown under well-watered conditions for the full duration of 1 cropping cycle.

Figure 9-14 Quantiles of predicted relative yield loss for 34 NCLAN crop experiments.



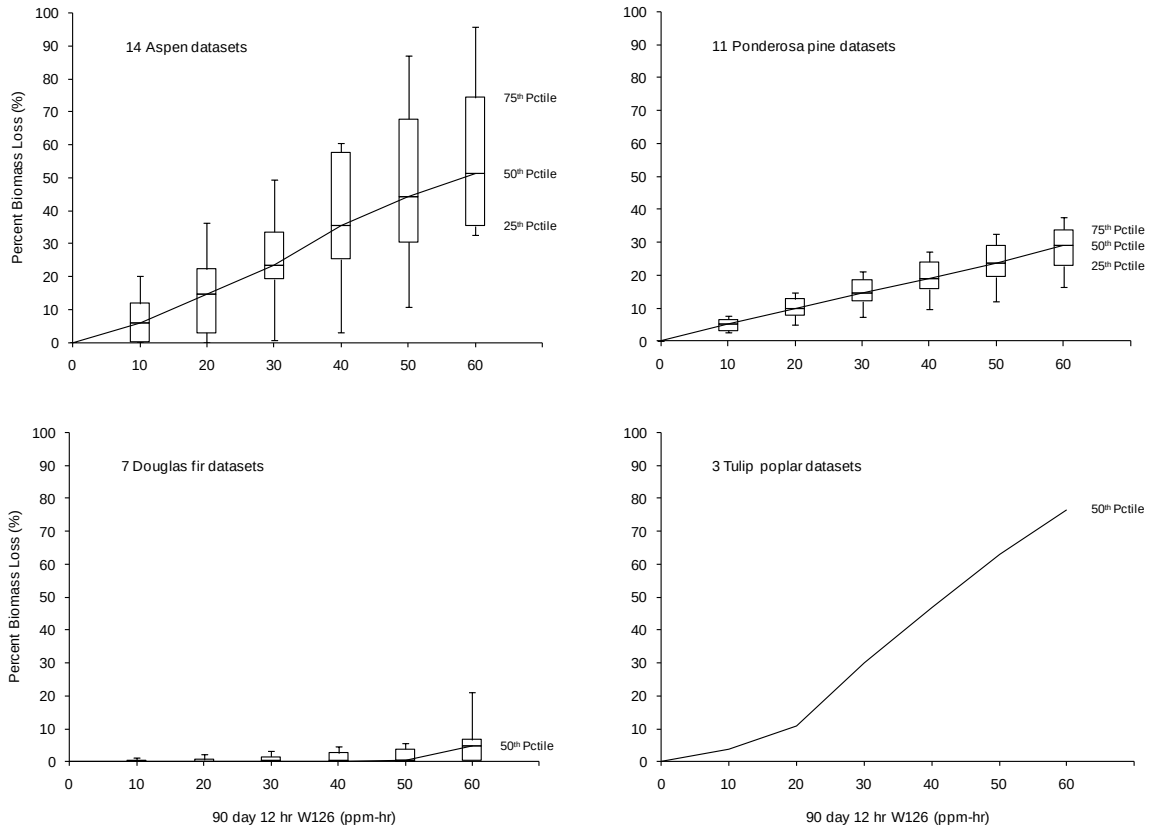
Source of Weibull parameters: Lee and Hogsett (1996).

Figure 9-15 Quantiles of predicted relative yield loss for 4 crop species in NCLAN experiments. Quantiles of the predicted relative yield loss at 7 values of 12-h W126 for Weibull curves estimated using nonlinear regression for 4 species grown under well-watered conditions for the full duration of 1 cropping cycle. The number of studies available for each species is indicated on each plot.



Source of Weibull parameters: Lee and Hogsett (1996).

Figure 9-16 Quantiles of predicted relative biomass loss for 49 tree species in NHEERL/WED experiments. Quantiles of the predicted relative above-ground biomass loss at 7 values of 12-h W126 for 49 Weibull curves estimated using nonlinear regression on data from 49 studies of 11 tree species grown under well-watered conditions for 1 or 2 years. Curves were standardized to 90-day W126.



Source of Weibull parameters: Lee and Hogsett (1996).

Figure 9-17 Quantiles of predicted relative biomass loss for 4 tree species in NHEERL/WED experiments. Quantiles of the predicted relative above-ground biomass loss at 7 exposure values of 12-h W126 for Weibull curves estimated using nonlinear regression on data for 4 tree species grown under well-watered conditions for 1 or 2 year. Curves were standardized to 90-day W126. The number of studies available for each species is indicated on each plot.

Table 9-9 Ozone exposures at which 10 and 20% yield loss is predicted for 50 and 75% of crop species, based on composite functions for the 50th and 75th percentiles of 34 Weibull curves for relative yield loss data from 34 non-droughted NCLAN studies of 12 crop species; curves were standardized to 90-day W126

	90-day 12-h W126 for 10% yield loss (ppm-h)	90-day 12-h W126 for 20% yield loss (ppm-h)
Model for the 50th Percentile of 34 curves		
Relative yield=exp(-(W126/104.82)**1.424)	22	37
Model for the 75th Percentile of 34 curves		
Relative yield=exp(-(W126/78.12)**1.415)	16	27

Source of parameters for the 34 curves: Lee and Hogsett (1996)

Table 9-10 Ozone exposures at which 10 and 20% yield loss is predicted for 50 and 75% of crop species under drought conditions and adequate moisture, based on composite functions for the 50th and 75th percentiles of 16 Weibull curves for relative yield loss data from 8 NCLAN studies that paired droughted and watered conditions for the same genotype; curves were standardized to 90-day W126

		90 day 12-h W126 for 10% yield loss (ppm-h)	90 day 12-h W126 for 20% yield loss (ppm-h)
Model for the 50th Percentile of 2×8 curves			
Watered	Relative yield=exp(-(W126/132.86)**1.170)	19	37
Droughted	Relative yield=exp(-(W126/179.84)**1.713)	48	75
Model for the 75th Percentile of 2×8 curves			
Watered	Relative yield=exp(-(W126/90.43)**1.310)	16	29
Droughted	Relative yield=exp(-(W126/105.16)**1.833)	31	46

Source of parameters for the 16 curves: Lee and Hogsett (1996)

Table 9-11 Ozone exposures at which 10 and 20% biomass loss is predicted for 50 and 75 %of tree species, based on composite functions for the 50th and 75th percentiles of 49 Weibull curves for relative above-ground biomass loss data from 49 studies of 11 tree species grown under well-watered conditions for 1 or 2 year; curves were standardized to 90-day W126

	90 day 12 h W126 for 10% yield loss (ppm-h)	90 day 12 h W126 for 20% yield loss (ppm-h)
Model for the 50th Percentile of 49 curves		
Relative yield=exp(-(W126/131.57)**1.242)	21	39
Model for the 75th Percentile of 49 curves		
Relative yield=exp(-(W126/65.49)**1.500)	15	24

Source of parameters for the 49 curves: Lee and Hogsett (1996)

9.6.3 Validation of 1996 and 2006 Ozone AQCD Models and Methodology Using the 90 day 12-h W126 and Current FACE Data

Since the completion of the NCLAN and NHEERL/WED projects, almost no studies have been published that could provide a basis for estimates of exposure-response that can be compared to those of the 1996 and 2006 O_3 AQCDs. Most experiments, regardless of exposure methodology, include only two levels of exposure. In addition, very few studies have included measurements of exposure using the W126 metric, or the hourly O_3 concentration data that would allow computing exposure using the W126. Two FACE projects, however, were conducted over multiple years, and by adding to the number of exposure levels over time, may support independent model estimation and prediction using the same model and the same robust process as summarized in Section 9.6.2. Hourly O_3 data were available from both FACE projects.

The SoyFACE project is situated near Champaign, IL, and comprises 32 octagonal rings (20m-diameter), 4 of which in a given year are exposed to ambient conditions, and 4 of which are exposed to elevated O_3 as a fixed proportion of the instantaneous ambient concentration (Betzelberger et al., 2010; University of Illinois, 2010; Morgan et al., 2006; Morgan et al., 2004). Since 2002, yield data have been collected for up to 8 genotypes of soybean grown in subplots within each ring. The Aspen FACE project is situated in Rhinelander, WI, and comprises 12 rings (30m-diameter), 3 of which are exposed to ambient conditions, and 3 of which are exposed to O_3 as a fixed proportion of the instantaneous ambient concentration (Pregitzer et al., 2008; Karnosky et al., 2005; Dickson et al., 2000). In the summer of 1997, half the area of each ring was planted with small (five to seven leaf sized) clonally propagated plants of five genotypes of trembling

aspen, which were left to grow in those environments until 2009. Biomass data are currently available for the years 1997-2005 (King et al., 2005). Ozone exposure in these two FACE projects can be viewed as a categorical variable with two levels: ambient, and elevated. However, this overlooks the facts that yearly ambient and elevated exposure both vary with every year, and that the proportionality between them also changes. This change has two sources: first, the dispensing of O_3 into the elevated exposure rings varies from the proportionality set point to some extent, and for SoyFACE, the set point changed between years. Second, the proportionality does not propagate predictably from the hourly data to the yearly value when using threshold or concentration-weighted cumulative metrics (such as AOT40, SUM06 or W126). Hourly average elevated exposures that are, for example, a constant 1.5 times greater than ambient do not result in AOT40, SUM06 or W126 values that are some constant multiple of the ambient values of those indices. The greater the fraction of elevated hourly values that are above the threshold or heavily weighted, compared to the fraction of hourly ambient values that are, the greater the difference between ambient and elevated yearly exposure, as measured using weighted cumulative indices. When elevated exposure is a multiple of ambient hourly intervals, the number of hours for which elevated exposure meets the threshold for inclusion can vary widely, even though the hourly mean for the year retains the proportionality. As a consequence, the number of exposure levels in multi-year experiments is twice the number of years. In the case of SoyFACE for the period between 2002 and 2008, ambient exposure in the highest year was approximately equal to elevated exposure in the lowest year, with 14 levels of O_3 exposure evenly distributed from lowest to highest. The particular conditions of the Aspen FACE experiment resulted in 12 exposure levels between 1998 and 2003, but they were not as evenly distributed between minimum and maximum over the 6-year period.

There are necessary differences in the modeling of exposure-response in annual plants such as soybean, and in perennial plants such as aspen trees, when exposure takes place over multiple years. In annual plants, responses recorded at the end of the life cycle, i.e., yearly, are analyzed in relationship to that year's exposure. Yield of soybeans is affected by exposure during the year the crop was growing, and a new crop is planted every year. Thus an exposure-response relationship can be modeled from yearly responses matched to yearly exposures, with those exposure-response data points having been generated in separate years. For perennial organisms, which are not harvested yearly and continue to grow from year to year, such pairing of exposure and response cannot be done without accounting for time. Not only does the size of the organism at the beginning of each year of exposure increase, but size is also dependent on the exposure from previous years. Therefore the relationship of response and exposure must be analyzed either one year at a time, or by standardizing the response as a yearly increment relative to size at the beginning of each year. Furthermore, the relevant measurement of exposure is

cumulative, or cumulative yearly average exposure, starting in the year exposure was initiated, up to the end of the year of interest. When analyzing the growth of trees over several years, it would be evidently incorrect to pair the exposure level in every discrete year with absolute size of the trees that year, and posit a direct relationship between them, without taking increasing age into consideration. In the Aspen FACE experiment, for example, one could not establish an exposure-response relationship by matching 12 yearly exposures and 12 yearly tree sizes, while disregarding age as if size did not also depend on it. This is the basis of the 2007 study of Aspen FACE data by Percy et al. (2007), which compares the size of trees of various ages as if they were all the same age, and was therefore not informative.

9.6.3.1 Comparison of NCLAN-Based Prediction and SoyFACE Data

For this ISA, EPA conducted a comparison between yield of soybean as predicted by the composite function three-step process (Section 9.6.2) using NCLAN data, and observations of yield in SoyFACE. The median composite function for relative yield was derived for the 11 NCLAN soybean Weibull functions for non-droughted studies, and comparisons between the predictions of the median composite and SoyFACE observations were conducted as follows.

For the years 2007 and 2008, SoyFACE yield data were available for 7 and 6 genotypes, respectively. The EPA used those data to compare the relative change in yield observed in SoyFACE in a given year between ambient O_3 and elevated O_3, versus the relative change in yield predicted by the NCLAN-based median composite function between those same two values of O_3 exposure. The two parameter median composite function for relative yield of soybean based on NCLAN data was used to predict yield response at the two values of exposure observed in SoyFACE in each year, and the change between yield under ambient and elevated was compared to the change observed in SoyFACE for the relevant year (Table 9-12). This approach results in a direct comparison of predicted versus observed change in yield. Because the value of relative response between any two values of O_3 exposure is independent of the intercept α, this comparison does not require prediction of the absolute values of the responses.

Since comparisons of absolute values might be of interest, the predictive functions were also scaled to the observed data: SoyFACE data were used to compute an intercept α while the shape and scale parameters (β and η) were held at their value in the NCLAN predictive model. This method gives a comparison of prediction and observation that takes all the observed information into account to provide the best possible estimate of

the intercept, and thus the best possible scaling (Table 9-13 and Figure 9-18). For the comparison of NCLAN and SoyFACE, this validation was possible for 2007 and 2008, where data for 7 and 6 soybean genotypes, respectively, were available. The median composite function for relative yield was derived for the 11 NCLAN soybean Weibull functions for nondroughted studies, and the values of median yield under ambient exposure at SoyFACE in 2007 and 2008 were used to obtain an estimate of the intercept α for the NCLAN median function in each of the two years.

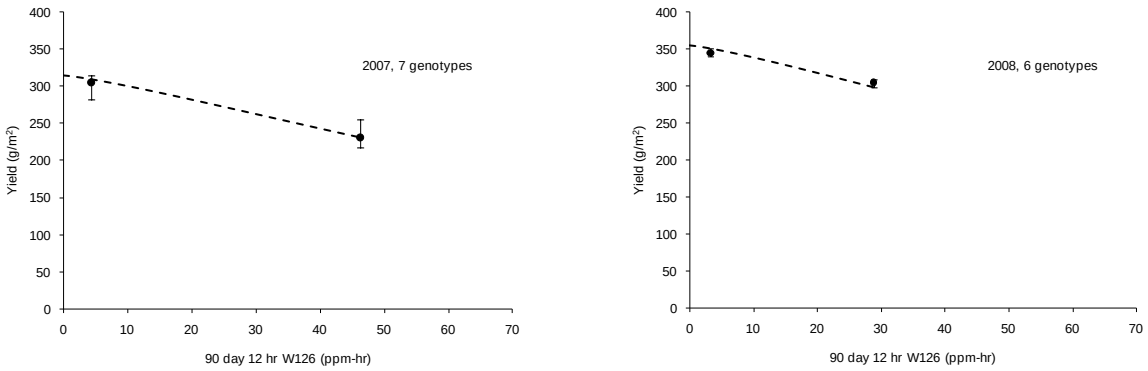
Table 9-12 presents the results of ambient/elevated relative yield comparisons between the NCLAN-derived predictions and SoyFACE observations. Table 9-13 and figure 9-18 present the results of comparisons between NCLAN-derived predictions and SoyFACE observations of yield, with the predictive function scaled to provide absolute yield values.

Table 9-12 Comparison between change in yield observed in the SoyFACE experiment between elevated and ambient ozone, and change predicted at the same values of ozone by the median composite function for NCLAN (two-parameter relative yield model)

Year	90-day 12-h W126 (ppm-h) observed at SoyFACE		Yield in Elevated O_3 Relative to Ambient O_3 (%)	
	Ambient	Elevated	Predicted by NCLAN	Observed at SoyFACE
2007	4.39	46.23	75	76
2008	3.23	28.79	85	88

Table 9-13 Comparison between yield observed in the SoyFACE experiment and yield predicted at the same values of ozone by the median composite function for NCLAN (three-parameter absolute yield model with intercept scaled to SoyFACE data)

Year	90-day 12-h W126 (ppm-h) observed at SoyFACE		Yield predicted by NCLAN (g/m^2)		Yield observed at SoyFACE (g/m^2)	
	Ambient	Elevated	Ambient	Elevated	Ambient	Elevated
2007	4.39	46.23	309.2	230.6	305.2	230.6
2008	3.23	28.79	350.3	298.2	344.8	304.4

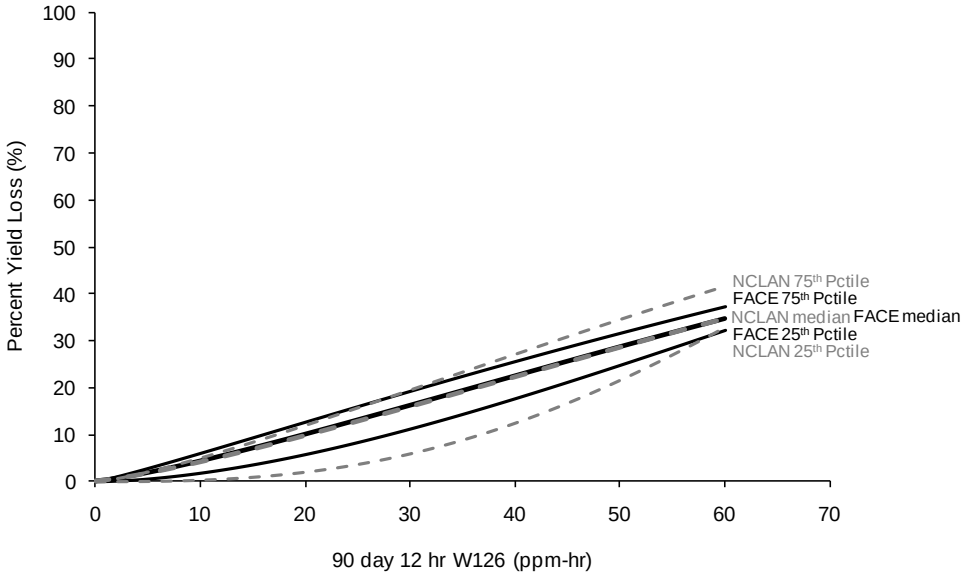


Source of data: Betzelberger et al. (2010); Morgan et al. (2006); Lee and Hogsett (1996).

Note: Black dots are the median of 7 or 6 soybean genotypes in SoyFACE (2007, 2008); bars are IQR for genotypes; dashed line is median composite model for 11 studies in NCLAN.

Figure 9-18 Comparison of yield observed in SoyFACE experiment in a given year with yield predicted by the median composite function based on NCLAN.

Finally, a composite function for the 25th, 50th, and 75th percentiles was developed from SoyFACE annual yield data, and compared to the NCLAN-based function. The process described in Section 9.6.2 was applied to SoyFACE data for individual genotypes, aggregated over the years during which each was grown; one genotype from 2003 to 2007, and six genotypes in 2007 and 2008. First, the three parameter Weibull model described in Section 9.6.2 was estimated using nonlinear regression on exposure-yield data for each genotype separately, over the years for which data were available, totaling seven curves. The 25th, 50th, and 75th percentiles of the predicted values for the two parameter relative yield curves were then identified at every integer of W126 between 0 and 60, and a two-parameter Weibull model estimated by regression for the three quartiles. The comparison between these composite functions for the quartiles of relative yield loss in SoyFACE and the corresponding composite functions for NCLAN is presented in Figure 9-19.



Source of data: Betzelberger et al. (2010);Morgan et al. (2006); Lee and Hogsett (1996).

Figure 9-19 Comparison of composite functions for the quartiles of 7 curves for 7 genotypes of soybean grown in the SoyFACE experiment, and for the quartiles of 11 curves for 5 genotypes of soybean grown in the NCLAN project.

As seen in Tables 9-13 and 9-14, and in Figure 9-18, the agreement between predictions based on NCLAN data and SoyFACE observations was notably close in single-year comparisons. Together with the very high agreement between median composite models for NCLAN and SoyFACE (Figure 9-19), it provides very strong mutual confirmation of those two projects' results with respect to the response of yield of soybeans to O_3 exposure. It is readily apparent from these results that the methodology described in Section 9.6.2 for obtaining predictions of yield or yield loss from NCLAN data is strongly validated by SoyFACE results. As described in Section 9.2, the exposure technologies used in the two projects were in sharp contrast, specifically with respect to the balance each achieved between control of potential interacting factors or confounders, and fidelity to natural conditions. The comparisons that EPA conducted therefore demonstrate that the methodology used in developing the composite functions is resistant to the influence of nuisance variables and that predictions are reliable. They may also suggest that the aspects in which the two exposure technologies differ have less influence on exposure-response than initially supposed. These results are also in agreement with comparative studies reviewed in 9.2.6.

9.6.3.2 Comparison of NHEERL/WED-Based Prediction of Tree Biomass Response and Aspen FACE Data

EPA also conducted two comparisons between prediction of above-ground biomass loss based on NHEERL/WED results and observations from Aspen FACE. The median composite function was developed from NHEERL/WED data for 11 studies that used wild-type seedlings of aspen as well as four clonally propagated genotypes. All plants were grown in OTCs for one growing season before being destructively harvested. Aspen FACE data were from clonally propagated trees of five genotypes grown from 1998 to 2003, with above-ground biomass calculated using allometric equations derived from data for trees harvested destructively in 2000 and 2002 (King et al., 2005).

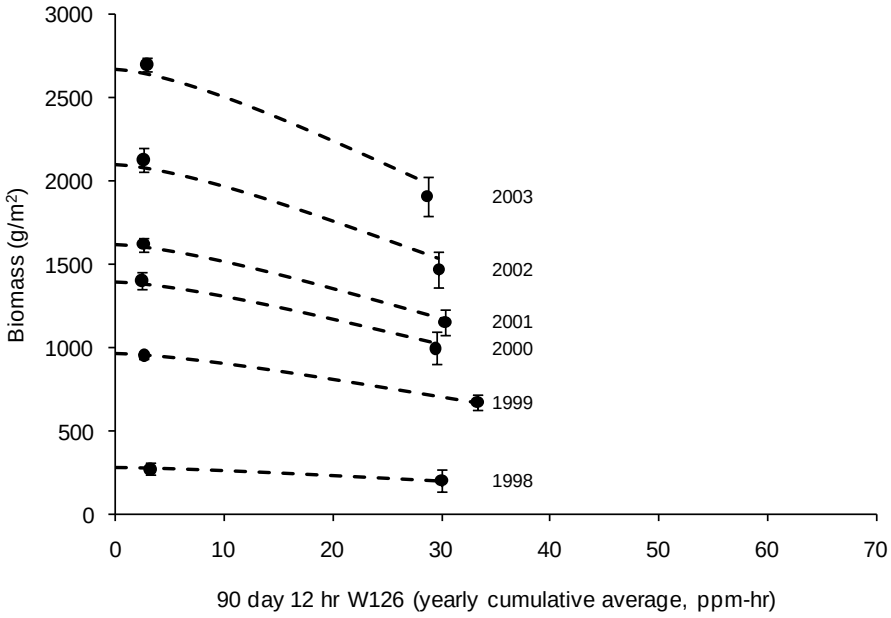
The two parameter median composite function for relative biomass was used to predict biomass response under the observed elevated exposure, relative to its value under observed ambient exposure, for each separate year of Aspen FACE. EPA first compared Aspen FACE observations of the change in biomass between ambient and elevated exposure with the corresponding prediction at the same values of exposure. Comparisons between observed and predicted absolute biomass values were then conducted for each year by scaling the predictive function to yearly Aspen FACE data as described for soybean data in Section 9.6.3.1. In all cases, yearly 90 day 12-hour W126 values for Aspen FACE were computed as the cumulative average from the year of planting up to the year of interest. A comparison of composite functions between NHEERL/WED and Aspen FACE, similar to the one performed for NCLAN and SoyFACE, was not possible: as discussed in the introduction to Section 9.6, the pairing of 12 exposure values from separate years and 12 values of biomass cannot be the basis for a model of exposure-response, because the trees continued growing for the six-year period of exposure. Because the same trees were used for the entire duration, and continued to grow, data could not be aggregated over years. Table 9-14 presents the results of ambient/elevated relative biomass comparisons between the NHEERL/WED-derived predictions and Aspen FACE observations. Table 9-15 and Figure 9-20 present the results of the comparison between NHEERL/WED-derived predictions and Aspen FACE observations for absolute biomass, using Aspen FACE data to scale the NHEERL/WED-derived composite function.

Table 9-14 Comparison between change in above-ground biomass elevated and ambient ozone in Aspen FACE experiment in 6 year, and change predicted at the same values of ozone by the median composite function for NHEERL/WED (two-parameter relative biomass model)

Year	90-day 12-h W126 (ppm-h) Cumulative Average observed at Aspen FACE		Above-Ground Biomass in Elevated O_3 relative To Ambient O_3 (%)	
	Ambient	Elevated	Predicted by NHEERL/WED	Observed at Aspen FACE
1998	3.19	30.08	74	75
1999	2.61	33.85	70	70
2000	2.43	30.16	74	71
2001	2.55	31.00	73	71
2002	2.51	30.27	74	69
2003	2.86	29.12	75	71

Table 9-15 Comparison between above-ground biomass observed in Aspen FACE experiment in 6 year and biomass predicted by the median composite function based on NHEERL/WED (three-parameter absolute biomass model with intercept scaled to Aspen FACE data)

Year	90 day 12-h W126 (ppm-h) Cumulative Average observed at Aspen FACE		Biomass Predicted by NHEERL/WED (g/m^2)		Biomass Observed at Aspen FACE (g/m^2)	
	Ambient	Elevated	Ambient	Elevated	Ambient	Elevated
1998	3.19	30.08	276.0	203.2	274.7	204.9
1999	2.61	33.85	958.7	668.3	955.3	673.3
2000	2.43	30.16	1382.4	1022.8	1400.3	998.6
2001	2.55	31.00	1607.0	1173.7	1620.7	1154.9
2002	2.51	30.27	2079.0	1532.1	2125.9	1468.41
2003	2.86	29.12	2640.1	1981.2	2695.2	1907.8



Source of data: King et al. (2005), Lee and Hogsett (1996).

Note: Black dots are aspen biomass/m^2 for 3 FACE rings filled with an assemblage of 5 clonal genotypes of aspen at Aspen FACE; bars are SE for 3 rings; dashed line is median composite model for 4 clonal genotypes and wild-type seedlings in 11 NHEERL/WED 1-year OTC studies.

Figure 9-20 Comparison between above-ground biomass observed in Aspen FACE experiment in 6 year and biomass predicted by the median composite function based on NHEERL/WED.

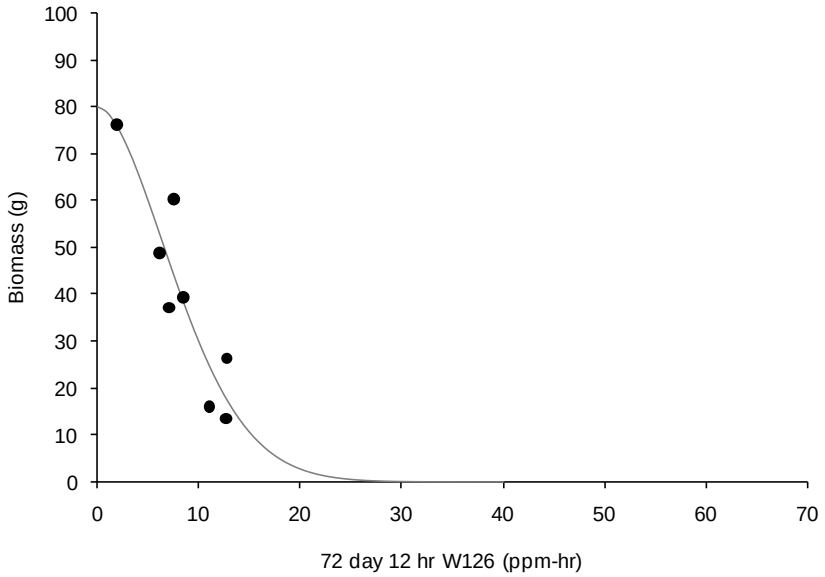
As in the comparisons between NCLAN and SoyFACE, the agreement between predictions based on NHEERL/WED data and Aspen FACE observations was very close. The results of the two projects strongly reinforce each other with respect to the response of aspen biomass to O_3 exposure. The methodology used for obtaining the median composite function is shown to be capable of deriving a predictive model despite potential confounders, and despite the added measurement error that is expected from calculating biomass using allometric equations. In addition, the function based on one year of growth was shown to be applicable to subsequent years.

The results of experiments that used different exposure methodologies, different genotypes, locations, and durations converged to the same values of response to O_3 exposure for each of two very dissimilar plant species, and predictions based on the earlier experiments were validated by the data from current ones. However, in these comparisons, the process used in establishing predictive functions involved aggregating data over variables such as time, locations, and genotypes, and the use of a robust statistic

(quartiles) for that aggregation. The validating data, from SoyFACE and Aspen FACE, were in turn aggregated over the same variables. The accuracy of predictions is not expected to be conserved for individual values of those variables over which aggregation occurred. For example, the predicted values for soybean, based on data for five genotypes, are not expected to be valid for each genotype separately. As shown in the validation, however, aggregation that occurred over different values of the same variable did not affect accuracy: composite functions based on one set of genotypes were predictive for another set, as long as medians were used for both sets. A study of cottonwood (*Populus deltoides*) conducted using a naturally occurring gradient of O_3 exposure (Gregg et al., 2006, 2003) may provide an illustration of the response of an individual species whose response is far from the median response for an aggregation of species.

9.6.3.3 Exposure-Response in a Gradient Study

Gregg et al. (2003) grew saplings of one clonally propagated genotype of cottonwood (*Populus deltoides*) in seven locations within New York City and in the surrounding region between July and September in 1992, 1993 and 1994, and harvested them 72 days after planting. Owing to regional gradients of atmospheric O_3 concentration, the experiment yielded eight levels of exposure (Figure 9-21), and the authors were able to rule out environmental variables other than O_3 to account for the large differences in biomass observed after one season of growth. The deficit in growth increased substantially faster with increasing O_3 exposure than has been observed in aspen, another species of the same genus (*Populus tremuloides*, Section 9.6.3.2). Using a three parameter Weibull model (Figure 9-21), the biomass of cottonwood at a W126 exposure of 15 ppm-h, relative to biomass at 5 ppm-h, is estimated to be 0.18 (18% of growth at 5 ppm-h). The relative biomass of trembling aspen within the same 5-15 ppm-h range of exposure is estimated to be 0.92, using the median composite model for aspen whose very close agreement with Aspen FACE data was shown in Section 9.6.3.2. Using a median composite function for all deciduous trees in the NHEERL/WED project (6 species in 21 studies) also gives predictions that are very distant from the cottonwood response observed in this experiment. For all deciduous tree species in NHEERL/WED, biomass at a W126 exposure of 15 ppm-h, relative to biomass at 5 ppm-h, was estimated to be 0.87.



Source: Modified with permission from Nature Publishing Group (Gregg et al., 2003).

Figure 9-21 Above-ground biomass for one genotype of cottonwood grown in seven locations for one season in 3 years. Line represents the three-parameter Weibull model.

These cottonwood data confirm that, as should be expected, some individual tree species are substantially more sensitive than the median of NHEERL/WED (Figure 9-16). As shown in Section 9.6.2, the median models available for trembling aspen and soybean have verifiable predictive ability for those particular species. This suggests that the corresponding NCLAN- and NHEERL/WED-based models for multiple crop and tree species can provide reliable estimates of losses for similar assortments of species. However, their predictive ability would likely be poor for individual species not tested.

An alternative hypothesis for the difference between the response of cottonwood in this experiment and deciduous tree species in NHEERL/WED, or the difference between the response of cottonwood and aspen in NHEERL/WED and Aspen FACE, could be the presence of confounding factors in the environments where the experiment was conducted. However, variability in temperature, moisture, soil fertility, and atmospheric deposition of N were all ruled out by Gregg et al. (2003) as contributing to the observed response to O_3. In addition, this hypothesis would imply that the unrecognized confounder(s) were either absent from *both* OTC and FACE studies, or had the same value in both. This is not impossible, but the hypothesis that cottonwood is very sensitive to O_3 exposure is more parsimonious, and sufficient.

9.6.3.4 Meta-analyses of growth and yield studies

Since the 2006 O_3 AQCD, five studies have used meta-analytic methods to integrate results from experimental studies of crops or tree species relevant to the U.S. It is possible to obtain exposure-response data for growth and yield from those meta-analyses, but because all of them provided summary measurements of O_3 exposure as hourly averages of various lengths of exposures, comparisons with exposure-response results where exposure is expressed as W126 are problematic. Table 9-16 summarizes the characteristics of the five meta-analyses. They all included studies conducted in the U.S. and other locations worldwide, and all of them expressed responses as comparative change between levels of exposure to O_3, with carbon filtered air (CF) among those levels. Using hourly average concentration to summarize exposure, CF rarely equates absence of O_3, although it almost always near zero when exposure is summarized as W126, SUM06, or AOT40.

Table 9-16 Meta-analyses of growth or yield studies published since 2005

Study	Number of articles included	Years of publication surveyed	Crop, species or genera	Response	Number of O_3 levels	Duration of exposure
Ainsworth (2008)	12	1980-2007	rice	Yield	2	unreported
Feng et al. (2008b)	53	1980-2007	wheat	Yield	5	> 10 days
Feng and Kobayashi (2009)	All crops together : 81	1980-2007	Potato, barley, wheat, rice, bean, soybean	Yield	3	> 10 days
Grantz et al. (2006)	16	1992-2004	34 herbaceous dicots 21 herbaceous monocots 5 tree species	Relative Growth Rate	2	2-24 weeks
Wittig et al. (2009)	All responses:263 Articles that included biomass:unreported	1970-2006	4 gymnosperm tree genera 11 angiosperm tree genera	Total biomass	4	> 7 days

The only effect of O_3 exposure on yield of rice reported in Ainsworth (2008) was a decrease of 14% with exposure increasing from CF to 62 ppb average concentration. Feng et al. (2008b) were able to separate exposure of wheat into four classes with average concentrations of 42, 69, 97, and 153 ppb, in data where O_3 was the only treatment. Mean responses relative to CF were yield decreases of 17, 25, 49, and 61% respectively. Feng et al. (2008b) observed that wheat yield losses were smaller under conditions of drought, and that Spring wheat and Winter wheat appeared similarly affected. However, mean exposure in studies of Winter wheat was substantially higher than in studies of Spring wheat (86 versus 64 ppb), which suggests that the yield of Spring wheat was in fact more severely affected, since yield was approximately the same, even though Spring wheat was exposed to lower concentrations. Exposures of the six crops considered in Feng and Kobayashi (2009) were classified into two ranges, each compared to CF air. In the lower

range of exposure (41-49 ppb), potato studies had the highest average exposure (45 ppb) and wheat and rice the lowest (41 ppb). In the higher range (51-75 ppb), wheat studies had the highest average exposure (65 ppb), and potato, barley and rice the lowest (63 ppb). In other words, across the studies included, all crops were exposed to very similar levels of O_3. At approximately 42 ppb, the yield of potato, barley, wheat, rice, bean, and soybean declined by 5.3, 8.9, 9.7, 17.5, 19, and 7.7% respectively, relative to CF air. At approximately 64 ppb O_3, declines were 11.9, 12.5, 21.1, 37.5, 41.4, and 21.6%. Grantz et al. (2006) reported Relative Growth Rate (RGR) rather than growth, and did not report O_3 exposure values in a way that would allow calculation of mean exposure for each of the three categories of plants for which RGR changes are reported. All studies used only two levels of exposure, with CF air as the lower one, and most used elevated exposure in the range of 40 to 70 ppb. Decline in RGR was 8.2% for the 34 herbaceous dicots, 4.5% for the 21 herbaceous monocots, and 17.9% for the 5 tree species. Finally, Wittig et al. (2009) divided the studies analyzed into three classes of comparisons: CF versus ambient, CF versus elevated, and ambient versus elevated, but reported comparisons between three average levels of exposure besides CF: 40 ppb, 64 ppb, and 97 ppb. Corresponding decreases in total biomass relative to CF were 7, 17, and 17%.

These meta-analyses provide very strong confirmation of EPA's conclusions from previous O_3 AQCDs: compared to lower levels of ambient O_3, current levels in many locations are having a substantial detrimental effect on the growth and yield of a wide variety of crops and natural vegetation. They also confirm strongly that decreases in growth and yield continue at exposure levels higher than current ambient levels. However, direct comparisons with the predictions of exposure-response models that use concentration-weighted cumulative metrics are difficult.

9.6.3.5 Additional exposure-response data

The studies summarized in Tables 9-18 and 9-19 contain growth or yield exposure-response data at too few levels of exposure for exposure-response models, and/or used metrics other than W126. These tables update Tables AX9-16 through AX9-19 of the 2006 O_3 AQCD.

9.6.4 Summary

None of the information on effects of O_3 on vegetation published since the 2006 O_3 AQCD has modified the assessment of quantitative exposure-response relationships that was presented in that document. This assessment updates the 2006 exposure-response

models by computing them using the W126 metric, cumulated over 90 days. Almost all of the experimental research on the effects of O_3 on growth or yield of plants published since 2006 used only two levels of exposure. In addition, hourly O_3 concentration data that would allow calculations of exposure using the W126 metric are generally unavailable. However, two long-term experiments, one with a crop species (soybean), one with a tree species (aspen), have produced data that can be used to validate the exposure-response models presented in the 2006 O_3 AQCD, and methodology used to derive them.

Quantitative characterization of exposure-response in the 2006 O_3 AQCD was based on experimental data generated for that purpose by the National Crop Loss Assessment Network (NCLAN) and EPA National Health and Environmental Effects Research Laboratory, Western Ecology Division (NHEERL-WED) projects, using OTCs to expose crops and trees seedling to O_3. In recent years, yield and growth results for two of the species that had provided extensive exposure-response information in those projects have become available from studies that used FACE technology, which is intended to provide conditions much closer to natural environments (Pregitzer et al., 2008; Morgan et al., 2006; Morgan et al., 2004; Dickson et al., 2000). The robust methods that were used previously with exposure measured as SUM06 were applied to the NCLAN and NHEERL-WED data with exposure measured as W126, in order to derive single-species median models for soybean and aspen from studies involving different genotypes, years, and locations. The resulting models were used to predict the change in yield of soybean and biomass of aspen between the two levels of exposure reported in current FACE experiments. Results from these new experiments were exceptionally close to predictions from the models. The accuracy of model predictions for two widely different plant species provides support for the validity of the corresponding multiple-species models for crops and trees in the NCLAN and NHEERL-WED projects. However, variability among species in those projects indicates that the range of sensitivity is likely quite wide. This was confirmed by a recent experiment with cottonwood in a naturally occurring gradient of exposure (Gregg et al., 2006), which established the occurrence of species with responses substantially more severe under currently existing conditions than are predicted by the median model for multiple species.

Results from several meta-analyses have provided approximate values for responses of yield of soybean, wheat, rice and other crops under broad categories of exposure, relative to charcoal-filtered air (Ainsworth, 2008; Feng et al., 2008b; Morgan et al., 2003). Likewise, Feng and Kobayashi (2009) have summarized yield data for six crop species under various broad comparative exposure categories, while Wittig et al. (2009) reviewed 263 studies that reported effects on tree biomass. However, these analyses have proved

difficult to compare with exposure-response models, especially given that exposure was not expressed in the same W126 metric.

Table 9-17 Summary of studies of effects of ozone exposure on growth and yield of agricultural crops

Species Facility Location	Exposure Duration	O_3 Exposure (Additional Treatment)	Response Measured	percent change from CF (percent change from ambient)	Reference
Alfalfa (*Medicago sativa*) OTC; 0.27m^3 pots Federico, Italy	2 yr, 2005, 2006	AOT40: CF 0 ppm-h 13.9 ppm-h (2005), 10.1 ppm-h (2006) (NaCl: 0.29, 0.65, 0.83, 1.06 deciSiemens/meter)	Total shoot yield	n.s. (N/A)	Maggio et al. (2009)
Bean (*Phaseolus vulgaris* I. cv Borlotto) OTC; ground-planted Curno, Italy	3 months, 2006	Seasonal AOT40: CF (0.5 ppm-h); ambient (4.6 ppm-h) (N/A)	# Seeds per plant; 100-seed weight	-33 (N/A) n.s. (N/A)	Gerosa et al. (2009)
Big Blue Stem (*Andropogon gerardii*) OTC Alabama	4 months, 2003	12-h avg: CF (14 ppb), Ambient (29 ppb), Elevated (71 ppb) (N/A)	Final harvest biomass; RVF	n.s. (n.s.) -7 (-7)	Lewis et al. (2006)
Brassica napus cv. Westar Growth chambers Finland	17-26 days	8-h avg: CF (0 ppb), 100 ppb (Bt/non-Bt; herbivory)	Shoot biomass	-30.70 (N/A)	Himanen et al. (2009b)
Corn (*Zea mays* cv. Chambord) OTC France	33 days	AOT40 ppm-h: 1.1; 1.3; 4.9; 7.2; 9.3; 12.8 (N/A)	Total above-ground biomass	N/A (Highest treatment caused -26% change)	Leitao et al. (2007c)
Cotton cv. Pima OTC; 9-L pots France	8 wk	12-h avg: 12.8 ± 0.6; 79.9 ± 6.3; 122.7 ± 9.7 (N/A)	Above-ground biomass	-76 (n.s.)	Grantz and Shrestha (2006)
Eastern Gamagrass (*Tripsacum dactyloides*) OTC Alabama	4 months, 2003	12-h avg: CF (14ppb), Ambient (29 ppb), Elevated (71 ppb) (N/A)	Final harvest biomass; RVF	+68 (+42); -17 (-12)	Lewis et al. (2006)
Grapevine (*Vitis vinivera*) OTC Austria	3 yr, May-Oct	AOT40 ppm-h: CF (0), Ambient (7-20), Elevated. 1 (20-30), Elevated. 2 (38-48)	Total fruit yield/ Sugar yield	-20 to -80 in different yr (-20 to -90 in different yr)	Soja et al. (2004)
Mustard (*Brassica campestris*) Chambers; 7.5-cm pots	10 days	CF & 67.8 ppb for 7 h (N/A)	Seeds/plant	n.s. (N/A)	Black et al. (2007)
Oilseed Rape (*Brassica napus*) OTC Yangtze Delta, China	39 days	Daily avg: 100 ppb, one with diurnal variation and one with constant concentration (N/A)	Biomass and pods per plant	Diurnal variability reduced both biomass and pod number more than constant fumigation (N/A)	Wang et al. (2008)
Peanut (*Arachis hypogaea*) OTC Raleigh, NC	3 yr	12-h avg: CF (22 ppb), Ambient (46 ppb), Elevated (75ppb) (CO_2: 375 ppm; 548 ppm; 730 ppm)	Yield (seed weight, g/m)	-33 (-8)	Burkey et al. (2007)
Poa pratensis OTC Braunschweig, Germany	2000-2002: 4-5 wk in the Spring	8-h avg: CF+25 (21.7), NF+50 (73.1) (Competition)	Total biomass (g DW/pot)	N/A (n.s.)	Bender et al. (2006)

Species Facility Location	Exposure Duration	O_3 Exposure (Additional Treatment)	Response Measured	percent change from CF (percent change from ambient)	Reference
Potato (*Solanum tuberosum*) OTC; CHIP 6 northern European locations	1988,1999. Emergence to harvest	AOT40:CF (0); Ambient (0.27-5.19); NF (0.002-2.93) NF+ (3.10-24.78 (N/A)	Tuber yield averaged across 5 field-sites; Tuber starch content regressed against [O_3] report sig. ± slope with increasing [O_3]	N/A (-27 % -+27%, most comparisons n.s.) Linear regression slope = -0.0098)	Vandermeiren et al. (2005)
Rice (*Oryza sativa*) OTC Raleigh, NC	1997-1998, June-September	12-h mean ppb: CF (27.5), Elevated (74.8) ($CO_{2)}$	Total biomass; Seed yield	-25(N/A) -13 to 20 (N/A)	Reid, et al. (2008)
Rice (*Oryza sativa*) 20 Asian cultivars OTC Gunma Prefecture, Japan	2008 growing season	Daily avg (ppb): CF (2), 0.8×ambient (23); 1 ×ambient (28); 1.5×ambient (42); 2×ambient (57) (Cultivar comparisons)	Yield	From n.s. to -30 across all cultivars	Sawada and Kohno (2009)
Seminatural grass FACE Le Mouret, Switzerland	5 yr	Seasonal AOT40: Ambient (0.1-7.2 ppm-h); Elevated. (1.8-24.1 ppm-h) (N/A)	Relative annual yield	N/A (2×faster decrease in yield/yr)	Volk et al. (2006)
Soybean OTC; CRA Bari, Italy	2003-2005 growing seasons	Seasonal AOT40 ppm-h: CF (0), Ambient (3.4), High (9.0) (Drought)	Yield	-46 (-9)	Bou Jaude et al. (2008)
Soybean (*Glycine max* cv. 93B15) SoyFACE Urbana, IL	2002, 2003 growing seasons	8-h avg: Ambient (62 & 50 ppb), Elevated (75 & 63 ppb) (N/A)	Yield	N/A (-15 in 2002; -25 in 2003)	Morgan et al. (2006)
Soybean (*Glycine max* cv. Essex) Chambers; 21 L Raleigh, NC	2×3 months	12-h avg: CF (28), Elevated (79), Elevated flux (112) (CO_2: 365 & 700)	Seed mass per plant	-30 (N/A)	Booker and Fiscus (2005)
Soybean (*Glycine max* cv. Essex) OTCs; 21-L pots Raleigh, NC	2×3 months	12-h avg: CF (18); Elevated (72) (CO_2: 367 & 718)	Seed mass per plant	-34 (N/A)	Booker et al. (2004a)
Soybean (*Glycine max* cv. Tracaja) Chambers; pots Brazil	20 days	12-h avg: CF & 30 ppb (N/A)	Biomass	-18 (N/A)	Bulbovas et al. (2007)
Soybean (*Glycine max*) 10 cultivars SoyFACE Urbana, IL	2007 & 2008	8-h avg: Ambient (46.3 & 37.9), Elevated (82.5 & 61.3) (Cultivar comparisons)	Yield	N/A (-17.20)	Betzelberger et al. (2010)
Spring Wheat (*Triticum aestivum* cv. Minaret; Satu; Drabant; Dragon) OTCs Belgium, Finland, & Sweden	1990-2006	Seasonal AOT40s ranged from 0 to16 ppm-h (N/A)	Seed protein content; 1,000-seed weight regressed across all experiments	N/A (significant negative correlation) N/A (sig negative correlation)	Piikki et al. (2008a)
Strawberry (*Fragaria x ananassa* Duch. Cv Korona & Elsanta) Growth chambers Bonn, Germany	2 months	8-h avg: CF (0 ppb) & Elevated (78 ppb) (N/A)	Fruit yield (weight/plant)	-16 (N/A)	Keutgen et al. (2005)
Sugarbeet (*Beta vulgaris* cv. Patriot) OTC Belgium	2003, 2004; 5 months	8-h avg: Ambient (36 ppb); Elevated (62 ppb) (N/A)	Sugar yield	N/A (-9)	De Temmerman et al. (2007)
Sugarcane (*Saccharum spp*) CSTR San Joaquin Valley, CA	2007; 11-13 wk.	12-h avg: CF (4 ppb); Ambient (58); Elevated (147) (N/A)	Total biomass (g/plant)	-40 (-30)	Grantz and Vu (2009)

Species Facility Location	Exposure Duration	O_3 Exposure (Additional Treatment)	Response Measured	percent change from CF (percent change from ambient)	Reference
Sweet Potato Growth chambers Bonn, Germany	4 wk	8-h avg: CF (0 ppb), Ambient (<40 ppb) Elevated (255 ppb) (N/A)	Tuber weight	-14 (-11.5)	Keutgen et al. (2008)
Tomato (*Lycopersicon esculentum*) OTC Valencia, Spain	133 days in 1998	8-h mean ppb: CF 16.3, NF 30.1, NF+ 83.2 (Various cultivars; early & late harvest)	Yield	n.s (n.s.)	Calvo et al. (2005)
Trifolium Subterraneum OTC; 2.5-L pots Madrid, Spain	29 days	12-h avg: CF (<7.9±6.3); Ambient (34.4±10.8); Elevated (56.4±22.3) (N: 5, 15 & 30 kg/ha)	Above-ground biomass	-45 (-35)	Sanz et al. (2005)
Watermelon (*Citrullus lanatus)* OTC Valencia, Spain	2000, 2001. 90 days	AOT40: CF (0 ppm-h) Ambient (5.7 ppm-h), Elevated (34.1 ppm-h) (N:0, 14.0 & 29.6 g/pot)	total fruit yield (kg)	n.s. (54)	Calatayud et al. (2006)
Yellow Nutsedge OTC; 9-L pots	8 wk	12-h avg: 12.8 ± 0.6; 79.9 ± 6.3; 122.7 ± 9.7 (N/A)	above-ground biomass	n.s. (n.s.)	Grantz and Shrestha (2006)

In studies where variables other than O_3 were included in the experimental design, response to O_3 is only provided for the control level of those variables.

Table 9-18 Summary of studies of effects of ozone exposure on growth of natural vegetation

Species Facility Location	Exposure Duration	O_3 Exposure (Additional Treatment)	Response Measured	Response	Reference
Yellow nutsedge (*Cyperus esculentus*) CSTR Parlier, CA	53 days in 2008	12-h mean ppb: CF (4); CF+ (60); CF2+ (115)	Above-ground biomass; tubers (g/plant)	ns; CF(4.1) CF+(3.9) CF2+(2.7)	Grantz et al. (2010b)
35 herbaceous species OTC Corvallis, OR	1999-2002, May-August	4-yr avg; yearly W126 ppm-h: CF (0), CF+ (21), CF 2+ (49.5)	Total community above-ground biomass (35 species) after 4 years	CF (459 g/m^2), CF+ (457 g/m^2), CF2+ (398 g/m^2)	Pfleeger et al. (2010)
Highbush blackberry (*Rubus argutus*) OTC Auburn, AL	2004, May-August	12-h mean ppb: CF (21.7), Ambient (32.3), Elevated (73.3)	Vegetative regrowth after pruning	CF (75.1 g/plant), Ambient (76.4 g/plant), Elevated (73.1 g/plant)	Ditchkoff et al. (2009)
Horseweed (*Conyza canadensis*) CSTR San Joaquin Valley, CA	2005, 2 runs, 28 days each (July-Aug, Sept)	W126 ppm-hr: CF(0), CF+ (11), CF 2+ (30) (Glyphosate resistance)	Total biomass (g/plant)	Glyphosate sensitive: CF (0.354) CF+ (0.197) CF2+ (0.106) Glyphosate resistant: CF(0.510) CF+ (0.313) CF2+ (0.143)	Grantz et al. (2008)
Red Oak (*Quercus rubrum*) Forest sites Look Rock & Twin Creeks Forests, TN	2001-2003, April-October	AOT60: 2001 (11.5), 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables)	Annual circumference increment (change relative to 2001 in year 2002;2003)	-42.8%; +1%	McLaughlin et al. (2007a)

Species Facility Location	Exposure Duration	O_3 Exposure (Additional Treatment)	Response Measured	Response	Reference
Pine species Forest sites Look Rock Forest, TN	2001-2003, April-October	AOT60: 2001 (11.5), 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables)	Annual circumference increment (change relative to 2001 in year 2002;2003)	-62.5%; -2.9%	McLaughlin et al. (2007a)
Hickory species Forest sites Look Rock Forest, TN	2001-2003, April-October	AOT60: 2001 (11.5), 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables)	Annual circumference increment (change relative to 2001 in year 2002;2003)	-14%; +30%	McLaughlin et al. (2007a)
Chestnut Oak (*Quercus prinus*) Forest sites Look Rock Forest, TN	2001-2003, April-October	AOT60: 2001 (11.5), 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables)	Annual circumference increment (change relative to 2001 in year 2002;2003)	+44%; +55%	McLaughlin et al. (2007a)
Black Cherry (*Prunus rigida*) Forest sites Twin Creeks Forest, TN	2002-2003, April-October	AOT60: 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables)	Annual circumference increment (change relative to 2003 in year 2002)	-75%	McLaughlin et al. (2007a)
Shortleaf pine (*Pinus echinata*) Forest sites Twin Creeks Forest, TN	2002-2003, April-October	AOT60: 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables)	Annual circumference increment (change relative to 2003 in year 2002)	-16.8%	McLaughlin et al. (2007a)
Hemlock (*Tsuga canadensis*) Forest sites Twin Creeks Forest, TN	2002-2003, April-October	AOT60: 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables)	Annual circumference increment (change relative to 2003 in year 2002)	-21.9%	McLaughlin et al. (2007a)
Red Maple (*Acer rubrum*) Forest sites Twin Creeks Forest, TN	2002-2003, April-October	AOT60: 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables)	Annual circumference increment (change relative to 2003 in year 2002)	-59.6%	McLaughlin et al. (2007a)
Yellow Poplar (*Liriodendron tulipifera*) Forest sites Look Rock, Oak Ridge, & Twin Creeks Forest, TN	2002-2003, April-October	AOT60: 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables)	Annual circumference increment (change relative to 2001 in years 2002; 2003)	-45.9%; -15.25%	McLaughlin et al. (2007a)

Species Facility Location	Exposure Duration	O_3 Exposure (Additional Treatment)	Response Measured	Response	Reference
Sugar Maple (*Acer saccharum*) Forest sites Twin Creeks Forest, TN	2002-2003, April-October	AOT60: 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables)	Annual circumference increment (change relative to 2003 in year 2002)	-63.8%	McLaughlin et al. (2007a)
Trembling aspen (*Populus tremuloides*), 5 genotypes Aspen FACE Rhinelander, WI	1998-2004, May-October	Cumulative avg 90-day 12-h W126. Ambient 3.1 ppm-h Elevated: 27.2 ppm-h (Competition with birch, maple)	main stem volume after 7 years	Ambient: 6.22 dm^3; Elevated: 4.73 dm^3	Kubiske et al. (2006)
Hybrid Poplar (*Populus trichocarpa* x *Populus deltoides*) OTC Seattle, WA	2003, 3 months	Daily mean (µg/g): CF(<9), Elevated (85-128)	Total biomass	CF to elevated: -12.9%	Woo and Hinckley (2005)

In studies where variables other than O_3 were included in the experimental design, response to O_3 is only provided for the control level of those variables.

9.7 References

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10 THE ROLE OF TROPOSPHERIC OZONE IN CLIMATE CHANGE AND UV-B EFFECTS

10.1 Introduction

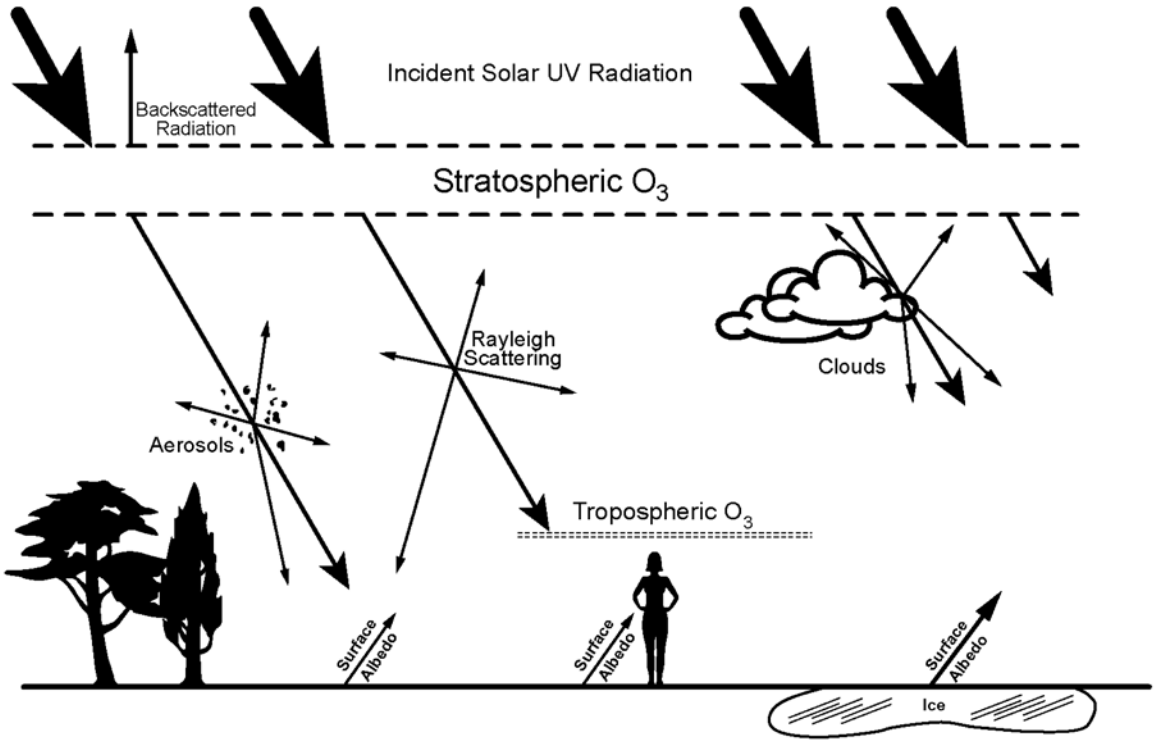
Atmospheric O_3 plays an important role in the Earth's energy budget by interacting with incoming solar radiation and outgoing infrared radiation. Over mid-latitudes, approximately 90% of the total atmospheric O_3 column is located in the stratosphere (Kar et al., 2010; Crist et al., 1994). Therefore, tropospheric O_3 makes up a relatively small portion (~10%) of the total column of O_3 over mid-latitudes, but it does play an important role in the overall radiation budget. The next section (Section 10.2) briefly describes the physics of the earth's radiation budget, providing background material for the subsequent two sections assessing how perturbations in tropospheric O_3 might affect (1) climate through its role as a greenhouse gas (Section 10.3), and (2) health, ecology and welfare through its role in shielding the earth's surface from solar ultraviolet radiation (Section 10.4).

10.2 Physics of the Earth's Radiation Budget

Radiant energy from the sun enters the atmosphere in a range of wavelengths, but peaks strongly in the visible (400 nm up to 750 nm) part of the spectrum. Longer wavelength infrared (750 nm up to ~1 mm) and shorter wavelength ultraviolet (400 nm down to 100 nm) radiation are also present in the solar electromagnetic spectrum. Since the energy possessed by a photon is inversely proportional to its wavelength, infrared (IR) radiation carries the least energy per photon, and ultraviolet (UV) radiation carries the most energy per photon. UV radiation is further subdivided into classes based on wavelength: UV-A refers to wavelengths from 400-315 nm; UV-B from 315-280 nm; and UV-C from 280-100 nm. By the same argument above describing the relationship between photon wavelength and energy, UV-A radiation is the least energetic and UV-C is the most energetic band in the UV spectrum.

The wavelength of radiation also determines how the photons interact with the complex mixture of gases, clouds, and particles present in the atmosphere (see Figure 10-1). UV-A radiation can be scattered but is not absorbed to any meaningful degree by atmospheric gases including O_3. UV-B radiation is absorbed and scattered in part within the atmosphere. UV-C is almost entirely blocked by the Earth's upper atmosphere, where it

participates in photoionization and photodissociation processes including absorption by stratospheric O_3.



Source: 2006 O_3 AQCD.

Figure 10-1 Diagram of the factors that determine human exposure to ultraviolet radiation.

Since UV-A radiation is less energetic and does not interact with O_3 in the troposphere or the stratosphere and UV-C radiation is almost entirely blocked by stratospheric O_3, UV-B radiation is the most important band to consider in relation to tropospheric O_3 shielding. Furthermore, tropospheric O_3 plays a "disproportionate" role in absorbing UV-B radiation compared with stratospheric O_3 on a molecule per molecule basis (Balis et al., 2002; Zerefos et al., 2002; Crist et al., 1994; Bruhl and Crutzen, 1989). This effect results from the higher atmospheric pressure present in the troposphere, resulting in higher concentrations of gas molecules present that can absorb or scatter radiation. For this reason, the troposphere is referred to as a "multiple scattering" regime for UV absorption, compared to the "single scattering" regime in the stratosphere. Thus, careful quantification of atmospheric absorbers and scatterers, along with a well-resolved

description of the physics of these interactions, is necessary for predicting the impact of tropospheric O_3 on UV-B flux at the surface.

Solar flux at all wavelengths has a temporal dependence, while radiative scattering and absorption have strong wavelength, path length, and gas/particle concentration dependencies. These combine to create nonlinear effects on UV flux at the Earth's surface. Chapter 10 of the 2006 O_3 AQCD(U.S. EPA, 2006b) describes in detail several key factors that influence the spatiotemporal distribution of ground-level UV radiation flux, including: (1) long-term solar activity including sunspot cycle; (2) solar rotation; (3) the position of the Earth in its orbit around the sun; (4) atmospheric absorption and scattering of UV radiation by gas molecules and aerosol particles; (5) absorption and scattering by stratospheric and tropospheric clouds; and (6) surface albedo. The efficiencies of absorption and scattering are highly dependent on the concentration of the scattering medium, particle size (for aerosols and clouds), and the altitude at which these processes are occurring. These properties are sensitive to meteorology, which introduces additional elements of temporal dependency in ground-level UV radiation flux.

About 30% of incoming solar radiation is directly reflected back to space, mainly by clouds or surfaces with high albedo (reflectivity), such as snow, ice, and desert sand. Radiation that does penetrate to the Earth's surface and is absorbed can be re-emitted in the longwave (infrared) portion of the spectrum (750 nm up to ~1 mm); the rest goes into evaporating water or soil moisture or emerges as sensible heat. The troposphere is opaque to the outgoing longwave radiation. Polyatomic gases such as CO_2, CH_4, and O_3 absorb and re-emit the radiation upwelling from the Earth's surface, reducing the efficiency with which that energy returns to space. In effect, these gases act as a blanket warming the Earth's surface. This phenomenon, known as the "Greenhouse Effect," was first quantified in the 19th century (Arrhenius, 1896), and gives rise to the term "greenhouse gas."

10.3 Effects of Tropospheric Ozone on Climate

Background

As a result of its interaction with incoming solar radiation and outgoing longwave radiation, tropospheric O_3 is a major greenhouse gas, and increases in its abundance may contribute to climate change (IPCC, 2007b). Models estimate that the global average concentration of O_3 in the troposphere has doubled since the preindustrial era (Gauss et al., 2006), while observations indicate that in some regions tropospheric O_3 may have

increased by factors as great as 4 or 5 (Marenco et al., 1994; Staehelin et al., 1994). These increases are tied to the rise in emissions of O_3 precursors from human activity, mainly fossil fuel consumption and agricultural processes.

The impact on climate of the tropospheric O_3 change since preindustrial times has been estimated to be about 25-40% of anthropogenic CO_2 impact and about 75% of anthropogenic CH_4 impact (IPCC, 2007b), ranking it third in importance of the greenhouse gases. In the 21st century as the Earth's population continues to grow and energy technology spreads to developing countries, a further rise in the global concentration of tropospheric O_3 is likely, with associated consequences for human health and ecosystems relating to climate change.

To examine the science of a changing climate and to provide balanced and rigorous information to policy makers, the World Meteorological Organization (WMO) and the United Nations Environment Programme (UNEP) formed the Intergovernmental Panel on Climate Change (IPCC) in 1988. The IPCC supports the work of the Conference of Parties (COP) to the United Nations Framework Convention on Climate Change (UNFCCC). The IPCC periodically brings together climate scientists from member countries of WMO and the United Nations to review knowledge of the physical climate system, past and future climate change, and evidence of human-induced climate change. IPCC climate assessment reports are issued every five to seven years.

This section draws in part on the fourth IPCC Assessment Report (AR4) (IPCC, 2007b), as well as other peer-reviewed published research. Section 10.3.1 reviews evidence of climate change in the recent past and projections of future climate change. It also offers a brief comparison of tropospheric O_3 relative to other greenhouse gases. Section 10.3.2 describes factors that influence the magnitude of tropospheric O_3 effects on climate. Section 10.3.3 considers the competing effects of O_3 precursors on climate. Finally, Section 10.3.4 describes the effects of changing tropospheric O_3 concentrations on present-day climate. Downstream effects resulting from climate change, such as ecosystem responses, are outside the scope of this assessment, which focuses on the direct effects of tropospheric O_3 on climate.

10.3.1 Climate Change Evidence and the Influence of Tropospheric Ozone

10.3.1.1 Climate Change in the Recent Past

From the end of the Last Ice Age 12,000 years ago until the mid-1800s, observations from ice cores show that concentrations of the long-lived greenhouse gases CO_2, CH_4,

and N_2O have been relatively stable. Unlike these greenhouse gases, O_3 is not preserved in ice, and no record of it before the late 1800s exists. Models, however, suggest that it, too, has remained relatively constant during this time period (Thompson et al., 1993; Thompson, 1992). The stable mix of greenhouse gases in the atmosphere has kept the global mean temperature of the Earth close to 15ºC. Without the presence of greenhouse gases in the atmosphere, the Earth's temperature would be about 30ºC cooler, or -15ºC.

Since the start of the Industrial Revolution, human activity has led to significant increases of greenhouse gases in the atmosphere, mainly through fossil fuel combustion. According to the IPCC AR4 (IPCC, 2007b), there is now "very high confidence" that the net effect of anthropogenic greenhouse gas emissions since 1750 has led to warming, and it is "very likely" that human activity contributed to the 0.76ºC rise in global mean temperature observed over the last century. The increase of tropospheric O_3 may have contributed 0.1-0.3ºC warming to the global climate during this time period (Hansen et al., 2005; Mickley et al., 2004). Global cooling due to anthropogenic aerosols (IPCC, 2007b) has likely masked the full warming effect of the anthropogenic greenhouse gases. Emissions of aerosols and their precursors in the United States and other developed countries are presently decreasing rapidly due to regulatory policies. The consequences of such decreases on regional climate could be large, as indicated by observations (e.g., Philipona et al., 2009; Ruckstuhl et al., 2008) and models (e.g., Kloster et al., 2009; Mickley et al., In Press).

10.3.1.2 Projections of Future Climate Change

The IPCC AR4 projects a warming of ~0.2ºC per decade for the remainder of the 21st century (IPCC, 2007b). Even at constant concentrations of greenhouse gases in the atmosphere, temperatures are expected to increase by about 0.1ºC per decade, due to the slow response of oceans to the warming applied so far. It is likely that the Earth will experience longer and more frequent heat waves in the 21st century, together with more frequent droughts and/or heavy precipitation events in some regions, due to perturbations in the hydrological cycle that result from changing temperatures (IPCC, 2007b). Sea levels could increase by 0.3-0.8 m by 2300 due to thermal expansion of the oceans. The extent of Arctic sea ice is expected to decline, and contraction of the Greenland ice sheet could further contribute to the sea level rise (IPCC, 2007b).

Projections of future climate change are all associated with some degree of uncertainty. A major uncertainty involves future trends in the anthropogenic emissions of greenhouse gases or their precursors. For the IPCC AR4 climate projections, a set of distinct "storylines" or emission pathways was developed (IPCC, 2000). Each storyline took into

account factors such as population growth, mix of energy technologies, and the sharing of technology between developed and developing nations, and each resulted in a different scenario for anthropogenic emissions. When these trends in emissions are applied to models, these scenarios yield a broad range of possible climate trajectories for the 21st century.

A second factor bringing large uncertainty to model projections of future climate is the representation of climate and, especially, climate feedbacks. A rise in surface temperatures would perturb a suite of other processes in the earth-atmosphere-ocean system, which may in turn either amplify the temperature increase (positive feedback) or diminish it (negative feedback). One important feedback involves the increase of water vapor content of the atmosphere that would accompany higher temperatures (Bony et al., 2006). Water vapor is a potent greenhouse gas; accounting for the water vapor feedback may increase the climate sensitivity to a doubling of CO_2 by nearly a factor of two (Held and Soden, 2000). The ice-albedo feedback is also strongly positive; a decline in snow cover and sea ice extent would diminish the Earth's albedo, allowing more solar energy to be deposited to the surface (Holland and Bitz, 2003; Rind et al., 1995). A final example of a climate feedback involves the effects of changing cloud cover in a warming atmosphere. Models disagree on the magnitude and even the sign of this feedback on surface temperatures (Soden and Held, 2006).

10.3.1.3 Metrics of Potential Climate Change

Two different metrics are frequently used to estimate the potential climate impact of some perturbation such as a change in greenhouse gas concentration: (1) radiative forcing; and (2) global warming potential (GWP).

Radiative forcing is a change in the radiative balance at a particular level of the atmosphere or at the surface when a perturbation is introduced in the earth-atmosphere-ocean system. In the global mean, radiative forcing of greenhouse gases at the tropopause (top of the troposphere) is roughly proportional to the surface temperature response (Hansen et al., 2005; NRC, 2005). It thus provides a useful metric for policymakers for assessing the response of the earth's surface temperature to a given change in the concentration of a greenhouse gas. Positive values of radiative forcing indicate warming in a test case relative to the control; negative values indicate cooling. The units of radiative forcing are energy flux per area, or W/m^2.

Radiative forcing requires just a few model years to calculate, and it shows consistency from model to model. However, radiative forcing does not take into account the climate feedbacks that could amplify or dampen the actual surface temperature response,

depending on region. Quantifying the change in surface temperature requires a climate simulation in which all important feedbacks are accounted for. As these processes are not well understood, the surface temperature response to a given radiative forcing is highly uncertain and can vary greatly among models and even from region to region within the same model.

GWP indicates the integrated radiative forcing over a specified period (usually 100 years) from a unit mass pulse emission of a greenhouse gas or its precursor, and are reported as the magnitude of this radiative forcing relative to that of CO_2. GWP is most useful for comparing the potential climate impacts of long-lived gases, such as N_2O or CH_4. Since tropospheric O_3 has a lifetime on the order of weeks to months, GWP is not seen as a valuable metric for quantifying the importance of O_3 on climate (Forster et al., 2007).

10.3.1.4 Tropospheric Ozone as a Greenhouse Gas

Tropospheric O_3 differs in important ways from other greenhouse gases. It is not emitted directly, but is produced through photochemical oxidation of CO, CH_4, and nonmethane volatile organic compounds (VOCs) in the presence of nitrogen oxide radicals (NO_X = NO + NO_2; see Section 3.2 for further details on the chemistry of O_3 formation). It is also supplied by vertical transport from the stratosphere. The lifetime of O_3 in the troposphere is typically a few weeks, resulting in an inhomogeneous distribution that varies seasonally; the distribution of the long-lived greenhouse gases like CO_2 and CH_4 are much more uniform. The longwave radiative forcing by O_3 is mainly due to absorption in the 9.6 μm window, where absorption by water vapor is weak. It is therefore less sensitive to local humidity than the radiative forcing by CO_2 or CH_4, for which there is much more overlap with the water absorption bands (Lenoble, 1993). And unlike other major greenhouse gases, O_3 absorbs in the shortwave as well as the longwave part of the spectrum.

Figure 10-2 shows the main steps involved in the influence of tropospheric O_3 on climate. Emissions of O_3 precursors including CO, VOCs, CH_4, and NO_X lead to production of tropospheric O_3. A change in the abundance of tropospheric O_3 perturbs the radiative balance of the atmosphere, an effect quantified by the radiative forcing metric. The earth-atmosphere-ocean system responds to the radiative forcing with a climate response, typically expressed as a change in surface temperature. Finally, the climate response causes downstream climate-related health and ecosystem impacts, such as redistribution of diseases or ecosystem characteristics due to temperature changes. Feedbacks from both the climate response and downstream impacts can, in turn, affect the abundance of tropospheric O_3 and O_3 precursors through multiple feedback

mechanisms. Direct feedbacks are discussed further in Section 10.3.3.4; the downstream climate impacts and their feedbacks are extremely complex and outside the scope of this assessment.

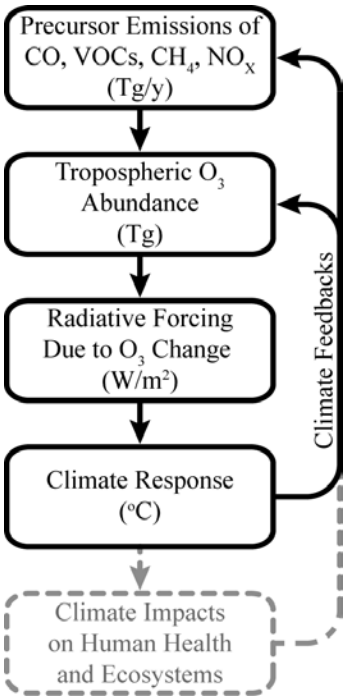
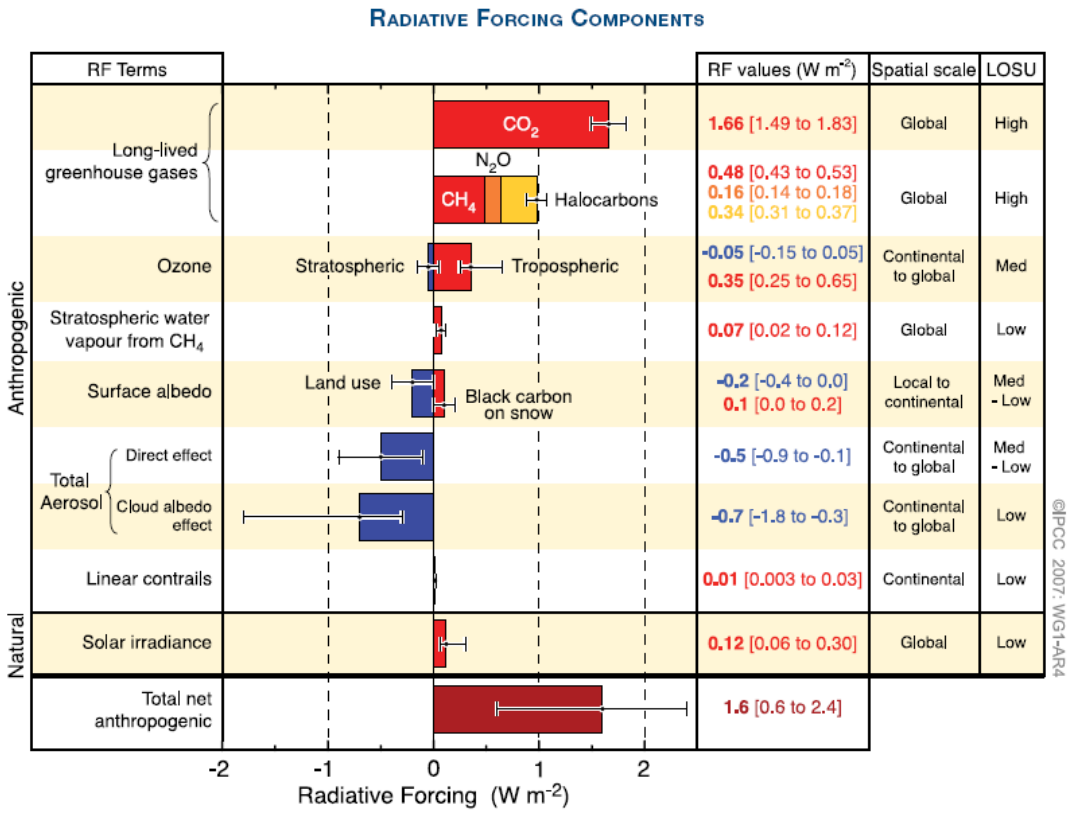


Figure 10-2 Schematic illustrating the effects of tropospheric ozone on climate. Figure includes the relationship between precursor emissions, tropospheric ozone abundance, radiative forcing, climate response, and climate impacts. Units shown are those typical for each quantity illustrated. Feedbacks from both the climate response and climate impacts can, in turn, affect the abundance of tropospheric ozone and ozone precursors through multiple feedback mechanisms. Climate impacts are deemphasized in the figure since these downstream effects are extremely complex and outside the scope of this assessment.

The IPCC (2007b) reported a radiative forcing of 0.35 W/m^2 for the change in tropospheric O_3 since the preindustrial era, ranking it third in importance after the greenhouse gases CO_2 (1.66 W/m^2) and CH_4 (0.48 W/m^2). Figure 10-3 shows the global average radiative forcing estimates and uncertainty ranges in 2005 for anthropogenic CO_2, CH_4, O_3 and other important agents and mechanisms. The error bars encompassing

the tropospheric O_3 radiative forcing estimate in the figure range from 0.25 to 0.65 W/m^2, making it relatively more uncertain than the long-lived greenhouse gases.



Source: Used with permission from Cambridge University Press, IPCC (2007b)

Figure 10-3 Global average radiative forcing (RF) estimates and uncertainty ranges in 2005 for anthropogenic CO_2, CH_4, ozone and other important agents and mechanisms. Figure shows the typical geographical extent (spatial scale) of the radiative forcing and the assessed level of scientific understanding (LOSU). The net anthropogenic radiative forcing and its range are also shown. These require summing asymmetric uncertainty estimates from the component terms, and cannot be obtained by simple addition. Additional radiative forcing factors not included here are considered to have a very low LOSU.

10.3.2 Factors that Influence the Effect of Tropospheric Ozone on Climate

This section describes the main factors that influence the magnitude of the climate response to changes in tropospheric O_3. They include: (1) trends in the concentration of tropospheric O_3; (2) the effect of surface albedo on O_3 radiative forcing; (3) the effect of vertical distribution on O_3 radiative forcing; (4) feedback factors that can alter the climate response to O_3 radiative forcing; and (5) the indirect effects of tropospheric O_3 on the carbon cycle. Trends in stratospheric O_3 may also affect temperatures at the Earth's surface, but aside from issues relating STE discussed in Chapter 3, Section 3.4.2, stratospheric O_3 assessment is beyond the scope of this document.

10.3.2.1 Trends in the Concentration of Tropospheric Ozone

To first order, the effect of tropospheric O_3 on climate is proportional to the change in tropospheric O_3 concentration. The earth's surface temperatures are most sensitive to O_3 perturbations in the mid to upper troposphere. This section therefore focuses mainly on observed O_3 trends in the free troposphere or in regions far from O_3 sources, where a change in O_3 concentrations may indicate change throughout the troposphere. Data from ozonesondes, mountaintops, and remote surface sites are discussed, as well as satellite data.

Observed Trends in Ozone Since the Preindustrial Era

Measurements of O_3 at two European mountain sites dating from the late 1800s to early 1900s show values at about 10 ppb, about one-fifth the values observed today at similar sites (Pavelin et al., 1999; Marenco et al., 1994). The accuracy of these early measurements is questionable however, in part because they exhibit O_3 concentrations equivalent to or only a couple of parts per billion greater than those observed at nearby low-altitude sites during the same time period (Mickley et al., 2001; Volz and Kley, 1988). A larger vertical gradient in tropospheric O_3 would be expected because of its stratospheric source and its longer lifetime aloft. In another study, Staehelin et al. (1994) revisited observations made in the Swiss mountains during the 1950s and found a doubling in O_3 concentrations from that era to 1989-1991.

Routine observations of O_3 in the troposphere began in the 1970s with the use of balloon-borne ozonesondes, but even this record is sparse. Trends from ozonesondes have been highly variable and dependent on region (Logan et al., 1999). Over most sites in the U.S., ozonesondes reveal little trend. Over Canada, observations show a decline in O_3 between 1980 and 1990, then a rebound in the following decade (Tarasick et al., 2005).

Ozonesondes over Europe give a mixed picture. European ozonesondes showed significant increases in the 1970s and 1980s, with smaller increases or even declines since then (Oltmans et al., 2006; Logan et al., 1999). Over Japan, O_3 in the lower troposphere increased about 0.2-0.4 ppb/y during the 1990s (Naja and Akimoto, 2004).

Ground-based measurements in remote regions provide a record of tropospheric O_3 extending as far back as the late 1960s or, for ship measurements, the late 1970s. A long-term record of O_3 in the San Bernardino Mountains of California reveals that the number of high O_3 days (defined as days with daily maximum O_3 levels above 95 ppb) rose from about 100 per summer in 1969 to over 160 in 1978 (Lee et al., 2003a). Over the next 20 years, the number of high O_3 days dropped slowly, to well below 100 per summer by the end of the record in 1999. Springtime O_3 observations from several other mountain sites in the western U.S. show a positive trend of about of 0.5-0.7 ppb/y since the 1980s (Cooper et al., 2010; Jaffe et al., 2003). Ship-borne O_3 measurements for the time period 1977 to 2002 indicate increases of 0.1-0.7 ppb/y over the tropical and South Atlantic, but no significant change over the North Atlantic (Lelieveld et al., 2004). The lack of trend for the North Atlantic would seem at odds with O_3 observations at Mace Head on the west coast of Ireland, which show a significant positive trend of about 0.5 ppb/y from 1987 to 2003 (Simmonds et al., 2004). Over Japan, O_3 at a remote mountain site has increased 1 ppb/y from 1998 to 2003 (Tanimoto, 2009), a rate more than double that recorded by ozonesondes in the lower troposphere over Japan during the 1990s (Naja and Akimoto, 2004). At Zugspitze, a mountain site in Germany, O_3 increased by 12% per decade during the 1970s and 1980s, consistent with European ozonesondes (Oltmans et al., 2006). Since then, O_3 continues to increase at Zugspitze, but more slowly. What little data exist for the Southern Hemisphere point to significant increases in tropospheric O_3 in recent decades, as much as ~15% at Cape Grim in the 1989-2004 time period (Oltmans et al., 2006).

The satellite record is now approaching a length that can be useful for diagnosing trends in the total tropospheric O_3 column (details on the use of satellites to measure tropospheric O_3 are covered in Section 3.5.5.5). In contrast to the surface data from ships, tropospheric O_3 columns from the Total Ozone Mapping Spectrometer (TOMS) show no trend over the tropical Atlantic for the period 1980-1990 (Thompson and Hudson, 1999). Over the Pacific, a longer, 25 year record of TOMS data again reveals no trend over the tropics, but shows increases in tropospheric column O_3 of about 2-3 Dobson Units (DU)[1] at midlatitudes in both hemispheres (Ziemke et al., 2005).

[1] The Dobson Unit is a typical unit of measure for the total O_3 in a vertical column above the Earth's surface. One DU is equivalent to the amount of O_3 that would exist in a 1 μm (10^{-5} m) thick layer of pure O_3 at standard temperature (0ºC) and pressure (1 atm), and corresponds to a column of O_3 containing 2.69 x 10^{20} molecules/m^2. A typical value for the amount of ozone in a column of the Earth's atmosphere, although highly variable, is 300 DU and approximately 10% (30 DU) of that exists in the troposphere at mid latitudes.

Interpreting these recent trends in tropospheric O_3 is challenging. The first difficulty is reconciling apparently contradictory trends in the observations, e.g., over tropical oceans. A second difficulty is that the O_3 trends depend on several factors, not all of which can be well characterized. These factors include (1) trends in emissions of O_3 precursors, (2) variation in the stratospheric source of O_3, (3) changes in solar radiation resulting from stratospheric O_3 depletion, and (4) trends in tropospheric temperatures (Fusco and Logan, 2003). The trends in O_3 in the San Bernardino Mountains reported by Lee et al. (2003a) likely reflects regional increases in population and motor vehicles usage, and subsequent implementation of more stringent motor vehicle emissions controls. More recent positive trends in the western U.S. and over Japan are consistent with the rapid increase in emissions of O_3 precursors from mainland Asia and transport of pollution across the Pacific (Cooper et al., 2010; Tanimoto, 2009). The satellite trends over the northern mid-latitudes are consistent with this picture as well (Ziemke et al., 2005). Increases in tropospheric O_3 in the Southern Hemisphere are also likely due to increased anthropogenic NO_X emissions, especially from biomass burning (Fishman et al., 1991). Recent declines in summertime O_3 over Europe can be partly explained by decreases in O_3 precursor emissions there (Jonson et al., 2005), while springtime increases at some European sites are likely linked to changes in stratospheric dynamics (Ordonez et al., 2007). Over Canada, Fusco and Logan (2003) found that O_3 depletion in the lowermost stratosphere may have reduced the stratospheric flux of O_3 into the troposphere by as much as 30% from the early 1970s to the mid 1990s, consistent with the trends in ozonesondes there.

Calculation of Ozone Trends for the Recent Past

Attempts to simulate trends in tropospheric O_3 allow us to test current knowledge of O_3 processes and to predict with greater confidence trends in future O_3 concentrations. Time-dependent emission inventories of O_3 precursors have also been developed (for 1850-2000, Lamarque et al., 2010; for 1890-1990, Van Aardenne et al., 2001). These inventories allow for the calculation of changing O_3 concentration over time.

One recent multi-model study calculated an increase in the O_3 concentration since preindustrial times of 8-14 DU, or about 30-70% (Gauss et al., 2006). The large spread in modeled estimates reveals our limited knowledge of processes in the pristine atmosphere. Models typically overestimate the late nineteenth and early twentieth century observations available in surface air and at mountain sites by 50-100% (Lamarque et al., 2005; Shindell et al., 2003; Mickley et al., 2001; Kiehl et al., 1999). Reconciling the differences between models and measurements will require more accurate simulation of the natural sources of O_3 (Mickley et al., 2001) and/or implementation of novel sinks

such as bromine radicals, which may reduce background O_3 in the pristine atmosphere by as much as 30% (Yang et al., 2005c).

For the more recent past (since 1970), application of time-dependent emissions reveals an equatorward shift in the distribution of tropospheric O_3 in the Northern Hemisphere due to the industrialization of societies at low-latitudes (Lamarque et al., 2005; Berntsen et al., 2000). By constraining a model with historical (1950s-2000) observations, Shindell et al. (2002) calculated a large increase of 8.2 DU in tropospheric O_3 over polluted continental regions since 1950. Their result appears consistent with the large change in tropospheric O_3 since preindustrial times implied by the observations from the late 1800s (Pavelin et al., 1999; Marenco et al., 1994).

10.3.2.2 The Effect of Surface Albedo on Ozone Radiative Forcing

The Earth's surface albedo plays a role in O_3 radiative forcing. Through most of the troposphere, absorption of incoming shortwave solar radiation by O_3 is small relative to its absorption of outgoing longwave terrestrial radiation. However, over surfaces characterized by high albedo (e.g., over snow, ice, or desert sand), incoming radiation is more likely to be reflected than over darker surfaces, and the probability that O_3 will absorb shortwave solar radiation is therefore larger. In other words, energy that would otherwise return to space may instead be deposited in the atmosphere. Several studies have shown that transport of O_3 to the Arctic from mid-latitudes leads to radiative forcing estimates greater than 1.0 W/m^2 in the region, especially in summer (Shindell et al., 2006; Liao et al., 2004b; Mickley et al., 1999). Because the Arctic is especially sensitive to radiative forcing through the ice-albedo feedback, the large contribution in the shortwave solar spectrum to the total radiative forcing in the region may be important.

10.3.2.3 The Effect of Vertical Distribution on Ozone Radiative Forcing

In the absence of feedbacks, O_3 increments near the tropopause produce the largest increases in surface temperature (Lacis et al., 1990; Wang et al., 1980). This is a result of the colder temperature of the tropopause relative to the rest of the troposphere and stratosphere. Since radiation emitted by the atmosphere is approximately proportional to the fourth power of its temperature[2], the colder the added O_3 is relative to the earth's

[2] As described by the Stefan-Boltzmann law, an ideal blackbody--which the atmosphere approximates--absorbs at all wavelengths and re-radiates proportional to the fourth power of its temperature.

surface, the weaker the radiation emitted and the greater the "trapping" of longwave radiation in the troposphere.

10.3.2.4 Feedback Factors that Alter the Climate Response to Changes in Ozone Radiative Forcing

Estimates of radiative forcing provide a first-order assessment of the effect of tropospheric O_3 on climate. In the atmosphere, climate feedbacks and transport of heat alter the sensitivity of Earth's surface temperature to addition of tropospheric O_3. Assessment of the full climate response to increases in tropospheric O_3 requires use of a climate model to simulate these interactions.

Due to its short lifetime, O_3 is heterogeneously distributed through the troposphere. Sharp horizontal gradients exist in the radiative forcing of O_3, with the greatest radiative forcing since preindustrial times occurring over the northern mid-latitudes (more on this in Section 10.3.4). If climate feedbacks are particularly powerful, they may obscure or even erase the correlation between regional radiative forcing and climate response (Harvey, 2004; Boer and Yu, 2003). For example, several model studies have reported that the horizontal pattern of surface temperature response from 2000-2100 trends in predicted short-lived species (including O_3) closely matches the pattern from the trends in the long-lived greenhouse gases over the same time period (Levy et al., 2008; Shindell et al., 2008; Shindell et al., 2007). This correspondence occurs even though the patterns of radiative forcing for the short-lived and long-lived species differ significantly. In a separate paper, Shindell (2007) found that Arctic temperatures are especially sensitive to the mid-latitude radiative forcing from tropospheric O_3.

Other studies have found that the signature of warming due to tropospheric O_3 does show some consistency with the O_3 radiative forcing. For example, Mickley et al. (2004) examined the change in O_3 since preindustrial times and found greater warming in the Northern Hemisphere than in the Southern Hemisphere (+0.4ºC versus +0.2ºC), as well as higher surface temperatures downwind of Europe and Asia and over the North American interior in summer. For an array of short-lived species including O_3, Shindell and Faluvegi (2009) found that radiative forcing applied over northern mid-latitudes yield more localized responses due to local cloud, water vapor, and albedo feedbacks than radiative forcing applied over the tropics.

Climate feedbacks can also alter the sensitivity of surface temperature to the vertical distribution of tropospheric O_3. The previous section (Section 10.3.2.3) described the greater impact of O_3 added to the upper troposphere (near the tropopause) on radiative forcing, relative to additions in the mid- to lower troposphere. However, warming

induced by increased O_3 in the upper troposphere could stabilize the atmosphere to some extent, limiting the transport of heat to the Earth's surface and mitigating the impact of the added O_3 on surface temperature (Joshi et al., 2003; Christiansen, 1999). Hansen et al. (1997) determined that allowing cloud feedbacks in a climate model meant that O_3 enhancements in the mid-troposphere had the greatest effect on surface temperature.

Finally, climate feedbacks can amplify or diminish the climate response of one greenhouse gas relative to another. For example, Mickley et al. (2004) found a greater temperature response to CO_2 radiative forcing than to an O_3 radiative forcing of similar global mean magnitude, due in part to the relatively weak ice-albedo feedback for O_3. Since CO_2 absorbs in the same bands as water vapor, CO_2 radiative forcing saturates in the middle troposphere and is also shifted toward the drier poles. A poleward shift in radiative forcing amplifies the ice-albedo feedback in the case of CO_2, and the greater mid-troposphere radiative forcing allows for greater surface temperature response, relative to that for O_3.

10.3.2.5 Indirect Effects of Tropospheric Ozone on the Carbon Cycle

A proposed indirect effect of tropospheric O_3 on climate involves the carbon cycle. By directly damaging plant life in ways discussed in Chapter 9, increases in tropospheric O_3 may depress the land-carbon sink of CO_2, leading to accumulation of CO_2 in the atmosphere and ultimately warming of the Earth's surface. Sitch et al. (2007) calculated that this indirect warming effect of O_3 on climate has about the same magnitude as the O_3 direct effect. Their results suggest a doubled sensitivity of surface temperatures to O_3 radiative forcing, compared to current model estimates.

10.3.3 Competing Effects of Ozone Precursors on Climate

Changes in O_3 precursors affect not just O_3 concentrations, but also other species that have importance to the radiative balance of the earth's climate system. More specifically, O_3 and its precursors exert a strong control on the oxidizing capacity of the troposphere (Derwent et al., 2001). For example, an increase in CO or VOCs would lead to a decrease in hydroxyl (OH) concentrations. Since OH is a major sink of the greenhouse gas CH_4, a decline in OH would lengthen the CH_4 lifetime, enhance the CH_4 concentration, and amplify surface warming. A rise in NO_X emissions, on the other hand, could lead to an increase in OH in certain locations, shortening the CH_4 lifetime and leading to surface cooling (Fuglestvedt et al., 1999). O_3 can itself generate OH through (1) photolysis

leading to excited oxygen atoms followed by reaction with water vapor and (2) reaction with HO_2.

Analyzing the net radiative forcing per unit emission for a suite of O_3 precursors, Shindell and Faluvegi (2009) calculated positive (+0.25 W/m^2) radiative forcing from the increase in anthropogenic emissions of CO and VOCs since preindustrial times, as well as for CH_4 (+1 W/m^2). These species also contribute to warming via their eventual contribution to CO_2. In contrast, Shindell and Faluvegi (2009) found negative (-0.29 W/m^2) radiative forcing from anthropogenic emissions of NO_X due mainly to the link between NO_X and CH_4. These results are consistent with those of Forster et al. (2007) who reported a net warming of +0.27 W/m^2 for combined anthropogenic CO and VOCs emissions and a net cooling of -0.21 W/m^2 for anthropogenic NO_X emissions. Other studies have found a near cancellation of the positive O_3 radiative forcing and the negative CH_4 radiative forcing that arise from an incremental increase in anthropogenic NO_X emissions (Naik et al., 2005; Fiore et al., 2002; Fuglestvedt et al., 1999).

The net effect of aircraft NO_X on climate is complex. While Isaksen et al. (2001) reported that the net radiative forcing effect of aircraft NO emissions is near zero, Wild et al. (2001) calculated a net warming due to increased O_3 production efficiency in the upper troposphere. More recently, Stevenson et al. (2004) completed a detailed analysis of the OH budget in the years following a pulse of aircraft NO_X emissions. They calculated that while such a pulse leads initially to warming through O_3 production over a few months, the long-term effect is cooling through the effects on CH_4. Both aircraft NO_X and the O_3 it generates enhance OH concentrations, with the longer-lived O_3 responsible for transferring the oxidizing effects of aircraft emissions away from flight corridors.

Finally, OH production from O_3 precursors can affect regional sulfate air quality and climate forcing by increasing gas-phase oxidation rates of SO_2. Using the A1B scenario in the IPCC AR4, Unger et al. (2006) reported that at 2030, enhanced OH from the A1B O_3 precursors increased surface sulfate aerosol concentrations by up to 20% over India and China, relative to the present-day, with a corresponding increase in radiative cooling over these regions. In this way, O_3 precursors may impose an indirect cooling via sulfate (Unger, 2006).

Taken together, these results point out the need for careful assessment of net radiative forcing involving multiple pollutants in developing climate change policy (Unger et al., 2008). Naik et al. (2005) calculated that a carefully combined reduction of CO, VOCs, and NO_X emissions could lead to net cooling, especially over the tropics. Several studies point to CH_4 as a particularly attractive target for emissions control since CH_4 is itself an important precursor of O_3 (West et al., 2007; Fiore et al., 2002). Shindell et al. (2005) calculated that the emissions-based radiative forcing of anthropogenic CH_4, which

includes both its own radiative forcing and that of CH_4-generated O_3, is 0.8-0.9 W/m^2, about double that of the CH_4 abundance-based radiative forcing. Fiore et al. (2002) found that reducing anthropogenic CH_4 emissions by 50% would lead to a global negative (-0.37 W/m^2) radiative forcing, mostly from CH_4. In later research, Fiore et al. (2008) reported that CH_4 reductions would most strongly affect tropospheric O_3 column amounts in a zonal band centered around 30 N, a region of strong downwelling and NO_X-saturated conditions near the surface.

10.3.4 Calculating Radiative Forcing and Climate Response to Past Trends in Tropospheric Ozone

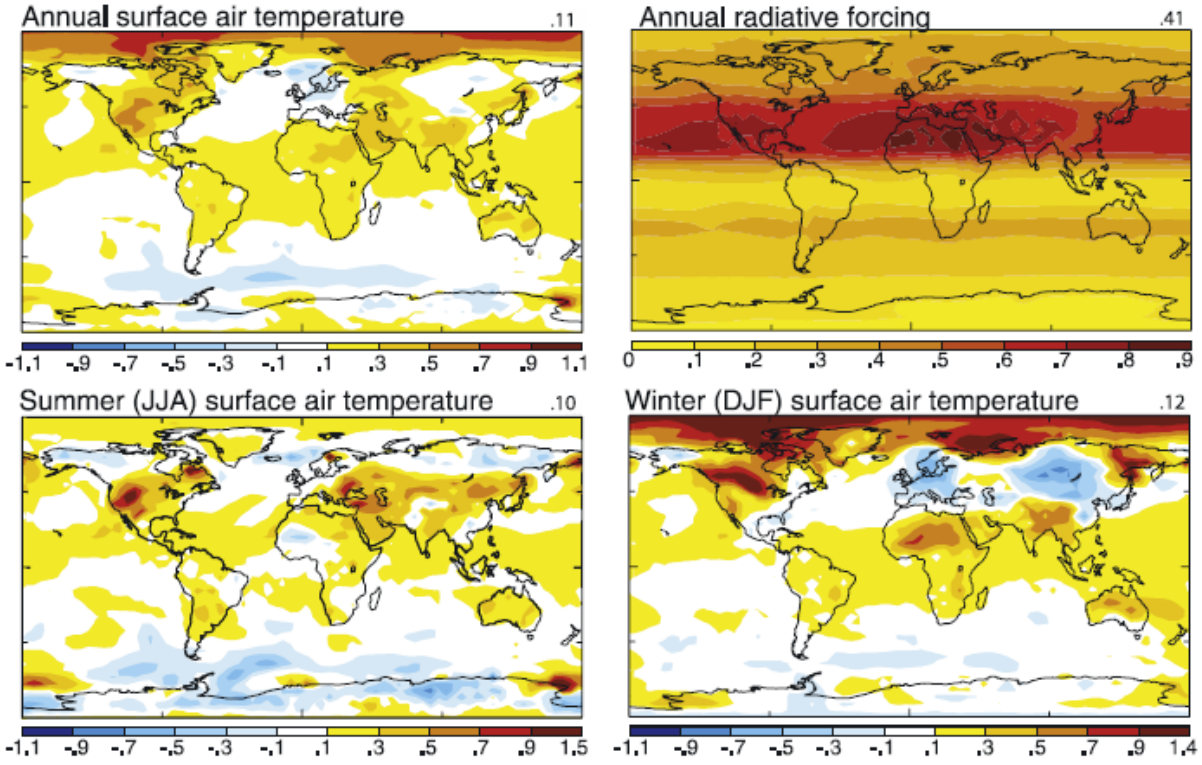
The magnitude of the radiative forcing from the change in tropospheric O_3 since the preindustrial era is uncertain. This uncertainty derives in part from the scarcity of early measurements and in part from our limited knowledge regarding processes in the natural atmosphere. As noted previously, the IPCC AR4 reports a radiative forcing of 0.35 W/m^2 from the change in tropospheric O_3 since 1750 (Forster et al., 2007), ranking it third in importance among greenhouse gases after CO_2 and CH_4. The O_3 radiative forcing could, in fact, be as large as 0.7 W/m^2, if reconstructions of preindustrial and mid-20th century O_3 based on the measurement record are valid (Shindell and Faluvegi, 2002; Mickley et al., 2001). In any event, Unger et al. (2010) showed that present-day O_3 radiative forcing can be attributed to emissions from many economic sectors, including on-road vehicles, household biofuel, power generation, and biomass burning. As much as one-third of the radiative forcing from the 1890 to 1990 change in tropospheric O_3 could be due to increased biomass burning (Ito et al., 2007a).

These calculated radiative forcing estimates can be compared to those obtained from satellite data. Using data from TOMS, Worden et al. (2008) estimated a reduction in clear-sky outgoing longwave radiation of 0.48 W/m^2 by O_3 in the upper troposphere over oceans in 2006. This radiative forcing includes contributions from both anthropogenic and natural O_3. Assuming that the concentration of O_3 has roughly doubled since preindustrial times (Gauss et al., 2006), the total O_3 radiative forcing estimated with TOMS is consistent with that obtained from models estimating just the anthropogenic contribution.

Calculation of the climate response to the O_3 radiative forcing is challenging due to complexity of feedbacks, as mentioned in Sections 10.3.1.2 and 10.3.2.4. In their modeling study, Mickley et al. (2004) reported a global mean increase of 0.28ºC since preindustrial times, with values as large as 0.8ºC in continental interiors. For the time period since 1870, Hansen et al. (2005) estimated a much smaller increase in global mean

surface temperature (0.11ºC), but they implemented 1880s anthropogenic emissions in their base simulation and also took into account trends in both stratospheric and tropospheric O_3; the modeled decline of lower stratospheric O_3, especially over polar regions, cooled surface temperatures in this study, counteracting the warming effect of increasing tropospheric O_3.

Figure 10-4 shows the Hansen et al. (2005) results as reported in Shindell et al. (2006). In that figure, summertime O_3 has the largest radiative impact over the continental interiors of the Northern Hemisphere. Shindell et al. (2006) estimated that the change in tropospheric O_3 over the 20th century could have contributed about 0.3ºC to annual mean Arctic warming and as much as 0.4-0.5ºC during winter and spring. Over eastern China, Chang et al. (2009) calculated a surface temperature increase of 0.4ºC to the 1970-2000 change in tropospheric O_3. It is not clear, however, to what degree regional changes in O_3 concentration influenced this response, as opposed to more global changes.



Source: Used with permission from American Geophysical Union (Shindell et al., 2006)

Figure includes the input radiative forcing (W/m^2), as computed by the NASA GISS chemistry-climate model. Values are surface temperature trends for the annual average (top left), June–August (bottom left), and December-February (bottom right) and annual average tropopause instantaneous radiative forcing from 1880 to 1990 (top right). Temperature trends greater than about 0.1ºC are significant over the oceans, while values greater than 0.3ºC are typically significant over land, except for northern middle and high latitudes during winter where values in excess of about 0.5ºC are significant. Values in the top right corner give area-weighted global averages in the same units as the plots.

Figure 10-4 Ensemble average 1900-2000 surface temperature trends (ºC per century) in response to tropospheric ozone changes.

10.4 UV-B Related Effects and Tropospheric Ozone

10.4.1 Background

UV radiation emitted from the Sun contains sufficient energy when it reaches the Earth to break (photolyze) chemical bonds in molecules, thereby leading to damaging effects on living organisms and materials. Atmospheric O_3 plays a crucial role in reducing exposure to solar UV radiation at the Earth's surface. Stratospheric O_3 is responsible for the majority of this shielding effect, as approximately 90% of total atmospheric O_3 is located there over mid-latitudes (Kar et al., 2010; Crist et al., 1994). Investigation of the

supplemental shielding of UV-B radiation provided by tropospheric O_3 is necessary for quantifying UV-B exposure and the incidence of related human health effects, ecosystem effects, and materials damage. The role of tropospheric O_3 in shielding of UV-B radiation is discussed in this section.

10.4.2 Human Exposure and Susceptibility to Ultraviolet Radiation

The factors that potentially influence UV radiation exposure were discussed in detail in Chapter 10 of the 2006 O_3 AQCD and are summarized here. These factors included outdoor activity, occupation, age, gender, geography, and protective behavior. Outdoor activity and occupation both influenced the amount of time people spend outdoors during daylight hours, the predominant factor for exposure to solar UV radiation. Participation in outdoor sports (e.g., basketball, soccer, golf, swimming, cycling) significantly increased UV radiation exposure (Thieden et al., 2004a; Thieden et al., 2004b; Moehrle, 2001; Moehrle et al., 2000). Occupations that substantially increased exposure to UV radiation included farming (Schenker et al., 2002; Airey et al., 1997), fishing (Rosenthal et al., 1988), landscaping (Rosenthal et al., 1988), construction (Gies and Wright, 2003), physical education (Vishvakarman et al., 2001), mail delivery (Vishvakarman et al., 2001), and various other occupations that require workers to spend the majority of their day outdoors during peak UV radiation hours.

Age and gender were found to be factors that influence human exposure to UV radiation, particularly by influencing other factors of exposure such as outdoor activity and risk behavior. Studies indicated that females generally spent less time outdoors and, consequently, had lower UV radiation exposure compared to males (Godar et al., 2001; Gies et al., 1998; Shoveller et al., 1998). The lowest exposure to UV radiation among Americans in the Godar et al. (2001) study was received in females during their child raising years (age 22-40 years); the highest exposure was observed in males aged 41-59 years. A similar Canadian survey found that younger adult males had the greatest exposures to UV radiation (Shoveller et al., 1998).

Geography influences the degree of solar UV flux to the surface, and hence exposure to UV radiation. In the U.S. study by Godar et al. (2001), northerners and southerners were found to spend an equal amount of time outdoors; however, the higher solar flux at lower latitudes significantly increased the annual UV radiation dose for southerners. The annual UV radiation doses in southerners were 25 and 40% higher in females and males, respectively, compared to northerners. Other studies also have shown that altitude and latitude influence personal exposure to UV radiation (Rigel et al., 1999; Kimlin et al., 1998).

Protective behaviors such as using sunscreen (Nole and Johnson, 2004), wearing protective clothing (Rosenthal et al., 1988), and spending time in shaded areas (Moise et al., 1999) were shown to reduce exposure to UV radiation. In one study, the use of sunscreen was associated with extended intentional UV radiation exposure (Autier et al., 1999); however, a follow-up study indicated that sunscreen use increased duration of exposures to doses of UV radiation that were below the threshold level for erythema (Autier et al., 2000).

Given these and other factors that potentially influence UV radiation exposure, the 2006 O_3 AQCD listed the following subpopulations potentially at risk for higher exposures to UV radiation:

- Individuals who engage in high-risk behavior (e.g., sunbathing);
- Individuals who participate in outdoor sports and activities;
- Individuals who work outdoors with inadequate shade (e.g., farmers, construction workers, etc.); and
- Individuals living in geographic areas with higher solar flux including lower latitudes (e.g., Honolulu, HI) and higher altitudes (e.g., Denver, CO).

The risks associated with all these factors are, of course, highly dependent on season and region (Sliney and Wengraitis, 2006).

10.4.3 Human Health Effects due to UV-B Radiation

Chapter 10 of the 2006 O_3 AQCD covered in detail the human health effects associated with solar UV-B radiation exposure. These effects include erythema, skin cancer, ocular damage, and immune system suppression. These adverse effects, along with protective effects of UV radiation through increased production of vitamin D are summarized in this section. For additional details, the reader is referred to Chapter 10 of the 2006 O_3 AQCD (U.S. EPA, 2006b) and references therein.

The most conspicuous and well-recognized acute response to UV radiation is erythema, or the reddening of the skin. Erythema is likely caused by direct damage to DNA by UV radiation (Matsumura and Ananthaswamy, 2004). Many studies discussed in the 2006 O_3 AQCD found skin type to be a significant risk factor for erythema. Additional risk factors include atopic dermatitis (ten Berge et al., 2009).

Skin cancer is another prevalent health effect associated with UV radiation. Exposure to UV radiation is considered to be a major risk factor for all forms of skin cancer (Diepgen and Mahler, 2002; Gloster and Brodland, 1996). Ultraviolet radiation is especially

effective in inducing genetic mutations and acts as both a tumor initiator and promoter. Keratinocytes have evolved DNA repair mechanisms to correct the damage induced by UV; however, mutations can occur, leading to skin cancers that are appearing with increasing frequency (Hildesheim and Fornace, 2004). The relationship between skin cancer and chronic exposure to UV radiation is further explored in Chapter 10 of the 2006 O_3 AQCD (U.S. EPA, 2006b).

Ocular damage from UV radiation exposure includes effects on the cornea, lens, iris, and associated epithelial and conjunctival tissues. The region of the eye affected by exposure to UV radiation depends on the wavelength of the incident UV radiation. Depending on wavelength, common health effects associated with UV radiation include photokeratitis (snow blindness; short wavelengths) and cataracts (opacity of the lens; long wavelengths).

Experimental studies have shown that exposure to UV radiation may suppress local and systemic immune responses to a variety of antigens (Clydesdale et al., 2001; Garssen and Van Loveren, 2001; Selgrade et al., 1997). In rodent models, these effects have been shown to worsen the course and outcome of some infectious diseases and cancers (Granstein and Matsui, 2004; Norval et al., 1999). Results from human clinical studies suggest that immune suppression induced by UV radiation may be a risk factor contributing to skin cancer induction (Ullrich, 2005; Caforio et al., 2000; Lindelof et al., 2000). There is also evidence that UV radiation has indirect involvement in viral oncogenesis through the human papillomavirus (Pfister, 2003), dermatomyositis (Okada et al., 2003), human immunodeficiency virus (Breuer-McHam et al., 2001) and other forms of immunosuppression (Selgrade et al., 2001).

A potential health benefit of increased UV-B exposure relates to the production of vitamin D in humans. Most humans depend on sun exposure to satisfy their requirements for vitamin D (Holick, 2004). Vitamin D deficiency can cause metabolic bone disease among children and adults, and also may increase the risk of many common chronic diseases, including type I diabetes mellitus and rheumatoid arthritis (Holick, 2004). Substantial in vitro and toxicological evidence also support a role for vitamin D activity against the incidence or progression of various forms of cancer (Giovannucci, 2005; John et al., 2005; Smedby et al., 2005; Grant and Garland, 2004; Hughes et al., 2004; Freedman et al., 2002; Grant, 2002a, b; John et al., 1999; Studzinski and Moore, 1995; Lefkowitz and Garland, 1994; Hanchette and Schwartz, 1992; Garland et al., 1990; Gorham et al., 1990). In some studies, UV-B related production of vitamin D had potential beneficial immunomodulatory effects on multiple sclerosis, insulin-dependent diabetes mellitus, and rheumatoid arthritis (Ponsonby et al., 2002; Cantorna, 2000). More

details on UV-B protective studies are provided in Chapter 10 of the 2006 O_3 AQCD (U.S. EPA, 2006b).

In establishing guidelines on limits of exposure to UV radiation, the International commission on Non-Ionizing Radiation Protection (ICNIRP) agreed that some low-level exposure to UV radiation has health benefits (ICNIRP, 2004). However, the adverse health effects of higher UV exposures necessitated the development of exposure limits for UV radiation. The ICNIRP recognized the challenge in establishing exposure limits that would achieve a realistic balance between beneficial and adverse health effects. As concluded by ICNIRP (2004), "[t]he present understanding of injury mechanisms and long-term effects of exposure to [UV radiation] is incomplete, and awaits further research."

10.4.4 Ecosystem and Materials Damage Effects Due to UV-B Radiation

A 2009 progress report on the environmental effects of O_3 depletion from the UNEP, Environmental Effects Assessment Panel (UNEP, 2009) lists many ecosystem and materials damage effects from UV-B radiation. An in-depth assessment of the global ecosystem and materials damage effects from UV-B radiation per se is out of the scope of this assessment. However, a brief summary of some mid-latitude effects is provided in this section to provide context for UV-B related issues pertaining to tropospheric O_3. The reader is referred to the UNEP report (UNEP, 2009) and references therein for further details. All of these UV-B related ecosystem and materials effects can also be influenced by climate change through temperature and other meteorological alterations, making quantifiable predictions of UV-B effects difficult.

Terrestrial ecosystem effects from increased UV-B radiation include reduced plant productivity and plant cover, changes in biodiversity, susceptibility to infection, and increases in natural UV protective responses. In general, however, these effects are small for moderate UV-B increases at mid-latitudes. A field study on wheat in southern Chile found no substantial changes in crop yield with moderate increases in UV-B radiation (Calderini et al., 2008). Similarly, field studies on silver birch (*Betula pendula*) in Finland found no significant effects in photosynthetic function with increases in UV-B radiation (Aphalo et al., 2009). Subtle, but important, changes in habitat and biodiversity have also been linked to increases in UV-B radiation (Mazza et al., 2010; Obara et al., 2008; Wahl, 2008). Some plants have natural coping mechanisms for dealing with changes in UV-B radiation (Favory et al., 2009; Jenkins, 2009; Brown and Jenkins, 2008; Ioki et al., 2008), but these defenses may have costs in terms of reduced growth (Snell et al., 2009; Clarke and Robinson, 2008; Semerdjieva et al., 2003; Phoenix et al., 2000).

Aquatic ecosystem effects from increased UV-B radiation include sensitivity in growth, immune response, and behavioral patterns of aquatic organisms. One study looking at coccolithophores, an abundant phytoplankton group, found a 25% reduction in cellular growth with UV-B exposure (Gao et al., 2009a). Exposure to relevant levels of UV-B radiation has been shown to modify immune response, blood chemistry, and behavior in certain species of fish (Markkula et al., 2009; Holtby and Bothwell, 2008; Jokinen et al., 2008). Adverse effects on growth and development from UV-B radiation have also been observed for amphibians, sea urchins, mollusks, corals, and zooplankton (Garcia et al., 2009; Romansic et al., 2009; Croteau et al., 2008a; Croteau et al., 2008b; Marquis et al., 2008; Marquis and Miaud, 2008; Oromi et al., 2008). Increases in the flux of UV-B radiation may also result in an increase in the catalysis of trace metals including mercury, particularly in clear oligotrophic lakes with low levels of dissolved organic carbon to stop the penetration of UV-B radiation (Schindler et al., 1996). This could then alter the mobility of trace metals including the potential for increased mercury volatilization and transport within and among ecosystems.

Biogeochemical cycles, particularly the carbon cycle, can also be influenced by increased UV-B radiation. A study on high latitude wetlands found UV-induced increases in CO_2 uptake through soil respiration (Haapala et al., 2009) while studies on arid terrestrial ecosystems found evidence for UV-induced release of CO_2 through photodegradation of above-ground plant litter (Brandt et al., 2009; Henry et al., 2008; Caldwell et al., 2007; Zepp et al., 2007). Changes in solar UV radiation may also have effects on carbon cycling and CO_2 uptake in the oceans (Brewer and Peltzer, 2009; Meador et al., 2009; Fritz et al., 2008; Zepp et al., 2008; Hader et al., 2007) as well as release of dissolved organic matter from sediment and algae (Mayer et al., 2009; Riggsbee et al., 2008). Additional studies showing effects on these and additional biogeochemical cycles including the water cycle and halocarbon cycle can be found in the UNEP report (UNEP, 2009) and references therein.

Materials damage from increased UV-B radiation include UV-induced photodegradation of wood (Kataoka et al., 2007) and plastics (Pickett et al., 2008). These studies and others summarizing photo-resistant coatings and materials designed to reduce photodegradation of materials are summarized in the UNEP report (UNEP, 2009) and references therein.

10.4.5 UV-B Related Effects Associated with Changes in Tropospheric Ozone Concentrations

There are multiple complexities in attempting to quantify the relationship between changes in tropospheric O_3 concentrations and UV radiation exposure. Quantifying the relationship between UV radiation and health or welfare effects is complicated by the uncertainties involved in the selection of an action spectrum and appropriate characterization of dose (e.g., peak or cumulative levels of exposure, timing of exposures, etc.) The lack of published studies that critically examine these issues together--that is the incremental health or welfare effects attributable specifically to UV-B changes resulting from reductions in tropospheric O_3 concentrations--reflects the significant challenges in this field.

As reported in the 2006 O_3 AQCD, one analysis by Lutter and Wolz (1997) attempted to estimate the effects of a nationwide 10 ppb reduction in seasonal average tropospheric O_3 on the incidence of nonmelanoma and melanoma skin cancers and cataracts in humans. Their estimate, however, depended upon several simplifying assumptions, ranging from an assumed generalized 10-ppb reduction in O_3 column density, national annual average incidence rates for the two types of skin cancer, and simple, linear biological amplification factors. Specifically, the decrease of 10 ppbv in seasonally averaged O_3 concentrations is likely an overestimate since it doesn't account for the influence of background O_3 coming from the global accumulation or generation of regional chemistry (Adamowicz et al., 2004). Further, the methodologies used in this analysis have ignored area-specific factors that are important in estimating the extent to which small, variable changes in ground-level O_3 mediate long-term exposures to UV-B radiation.

A more recent study by Madronich et al. (2011) used CMAQ to estimate UV radiation response to changes in tropospheric O_3 under different control scenarios projected out to 2020. This study focused on southeastern U.S. and accounted for spatial and temporal variation in tropospheric O_3 reductions, an important consideration since most controls are focused on reducing O_3 in populated urban areas. The contrasting control strategies considered in this study included a historical scenario designed to meet an 84 ppb 8-h daily max standard and a reduced scenario designed to bring areas predicted to exceed a similarly designed 70 ppb standard into attainment. A biologically effective irradiance was estimated by multiplying the modeled UV irradiance by a sensitivity function (action spectrum) for the induction of nonmelanoma skin cancer in mice corrected for human skin transmission, then integrating over UV wavelengths. The average relative change in skin cancer-weighted surface UV radiation between the two scenarios was about 0.11% over June, July and August. Weighting by population, this estimate increased to 0.19%. Madronich et al. (2011) report that their estimated UV radiation increment is an order of

magnitude less than that by Lutter and Wolz (1997) with the main reason for the discrepancy coming from the unrealistic uniform 10 ppb reduction in O_3 assumed in the former study. Madronich et al. (2011) did not attempt to link their predicted increase in UV radiation to a predicted increase in skin cancer incidence, however, due to several remaining and substantial uncertainties.

A handful of additional studies have addressed the relationship between changes in tropospheric pollutant concentrations and UV-B radiation exposure, providing some additional insight. A study by Palancar and Toselli (2002) looked at changes in measured UV-B radiation in relation to ground-level air pollutants during several air pollution episodes in Cordoba, Argentina. They found that changes in aerosol concentrations explained the majority of UV-B radiation fluctuations, and that changes in tropospheric O_3 and SO_2 had little effect. Repapis et al. (1998) performed a similar study on UV-B exposures during high and low air pollution days in Athens, Greece. They found cloud cover and aerosols to be the major factors in observed UV-B exposures reductions. Studies by Acosta and Evans (2000) in Mexico City and Koronakis et al. (2002) in Athens, Greece both found significant reductions in surface-level UV exposures during pollution episodes. Both these studies include tropospheric O_3 as a potential driver for the reductions, but neither study was able to quantify the influence of individual atmospheric components involved in the observed attenuation in UV-B radiation.

In the absence of reliable studies specifically addressing UV-B related health effects from a reduction in tropospheric O_3, inferences were made in the 2006 O_3 AQCD on the basis of studies focused on stratospheric O_3 depletion. Studies included in that review examined the potential effect of stratospheric O_3 depletion on the risk of erythema (Longstreth et al., 1998), skin cancer (Urbach, 1997; Slaper et al., 1996; De Gruijl, 1995; Longstreth et al., 1995; Madronich and De Gruijl, 1993), nonmelanoma skin cancer (Slaper et al., 1996; Longstreth et al., 1995), and cataracts (Longstreth et al., 1995). Note that several of the concerns expressed above in relation to the Lutter and Wolz (1997) analysis are relevant to these analyses as well. Furthermore, these studies have a high degree of uncertainty due to inadequate information on the action spectrum and dose-response relationships. As a result, caution is advised when assessing and interpreting the quantitative results of health risks due to stratospheric O_3 depletion in the context of tropospheric O_3 shielding.

Although the UV-B related health effects attributed to marginal reductions in tropospheric or ground-level O_3 that would result from reductions in O_3 concentrations have not been directly assessed, they would be expected to be small given the above findings and the fact that tropospheric O_3 makes up only ~10% of the total atmospheric O_3 column at mid-latitudes (Kar et al., 2010). Furthermore, O_3 present in the planetary

boundary layer makes up only ~10% of tropospheric O_3 (Thompson et al., 2007) and the NAAQS has only a fractional influence on those ground-level O_3 concentrations. The net result is a very small influence on total column O_3 through attainment of the O_3 standard. In addition, the health benefits of UV-B in the production of vitamin D suggests that increased risks of human disease due to a slight excess in UV-B radiation exposure may be offset by the benefits of enhanced vitamin D production. However, as with other impacts of UV-B on human health, this beneficial effect of UV-B has not been studied in sufficient detail to allow for a credible health benefits assessment. Hence, the above mentioned health and welfare effects associated with UV-B exposures resulting from changes in ground-level O_3 concentrations would likely be small or nonexistent based on current information.

More reasonable estimates of the human health impacts of enhanced UV-B penetration following reduced ground-level O_3 concentrations require both (a) a solid understanding of the multiple factors that define the extent of human exposure to UV-B, and (b) well-defined and quantifiable links between human disease and UV-B exposure. Within the uncertain context of presently available information on UV-B surface fluxes, a risk assessment of UV-B-related health effects would need to factor in human habits (e.g., daily activities, recreation, dress, and skin care) in order to adequately estimate UV-B exposure levels. Little is known about the impact of variability in these human factors on individual exposure to UV radiation. Furthermore, detailed information does not exist regarding the relevant type (e.g., peak or cumulative) and time period (e.g., childhood, lifetime, or current) of exposure, wavelength dependency of biological responses, and inter-individual variability in UV resistance. In conclusion, the effect of changes in surface-level O_3 concentrations on UV-induced health outcomes cannot yet be critically assessed within reasonable uncertainty. The reader is referred to the U.S. EPA 2002 Final Response to Court Remand (U.S. EPA, 2003) for detailed discussions of the data and scientific issues associated with the determination of public health benefits resulting from the attenuation of UV-B by surface-level O_3.

10.5 Summary

10.5.1 Summary of the Effects of Tropospheric Ozone on Climate

Tropospheric O_3 is a major greenhouse gas, third in importance after CO_2 and CH_4. While the developed world has successfully reduced emissions of O_3 precursors in recent decades, many developing countries have experienced large increases in precursor emissions and these trends are expected to continue, at least in the near term. Projections

of radiative forcing due to changing O_3 over the 21st century show wide variation, due in large part to the uncertainty of future emissions of source gases. In the near-term (2000-2030), projections of O_3 radiative forcing range from near zero to +0.3 W/m^2, depending on the emissions scenario (Stevenson et al., 2006). Reduction of tropospheric O_3 concentrations could therefore provide an important means to slow climate change in addition to the added benefit improving surface air quality.

It is clear that increases in tropospheric O_3 lead to warming. However the precursors of O_3 also have competing effects on the greenhouse gas CH_4, complicating emissions reduction strategies. A decrease in CO or VOC emissions would enhance OH concentrations, shortening the lifetime of CH_4, while a decrease in NO_X emissions could depress OH concentrations in certain regions and lengthen the CH_4 lifetime. Recent research, however, has indicated that a carefully combined reduction of CO, VOCs, and NO_X emissions could lead to net cooling (Naik et al., 2005). They calculate that such reductions would have the greatest impact for developing countries in tropical regions.

Abatement of CH_4 emissions would likely provide the most straightforward means to address climate change since CH_4 is itself an important precursor of background O_3 (West et al., 2007; West et al., 2006; Fiore et al., 2002). A reduction of CH_4 emissions would also improve air quality on its own right. A set of global abatement measures identified by West and Fiore (2005) could reduce CH_4 emissions by 10% at a cost savings, decrease background O_3 by about 1 ppb in the Northern Hemisphere summer, and lead to a global net cooling of 0.12 W/m^2. Unlike measures to reduce NO_X, which would have immediate impacts on surface O_3 but little net radiative forcing, the cooling effects of CH_4 controls would be realized gradually, over ~12 years. West et al. (2007) explored further the benefits of CH_4 abatement, finding that a 20% reduction in global CH_4 emissions would lead to significantly greater cooling per unit reduction in surface O_3, compared to 20% reductions in VOCs or CO.

Important uncertainties remain regarding the impact of tropospheric O_3 on future climate change. To address these uncertainties, further research is needed to: (1) enhance our knowledge of the natural atmosphere; (2) interpret observed trends of O_3 in the free troposphere and remote regions; (3) improve our understanding of the CH_4 budget, especially emissions from wetlands and agricultural sources, (4) understand the relationship between regional O_3 radiative forcing and regional climate change; and (5) determine the optimal mix of emissions reductions that would act to limit future climate change.

10.5.2 Summary of UV-B Related Effects on Human Health, Ecosystems, and Materials Relating to Changes in Tropospheric Ozone Concentrations

UV radiation emitted from the Sun contains sufficient energy when it reaches the Earth to break (photolyze) chemical bonds in molecules, thereby leading to damaging effects on living organisms and materials. Atmospheric O_3 plays a crucial role in reducing exposure to solar UV radiation at the Earth's surface. Ozone in the stratosphere is responsible for the majority of this shielding effect, as approximately 90% of total atmospheric O_3 is located there over mid-latitudes. Ozone in the troposphere provides supplemental shielding of radiation in the wavelength band from 280-315 nm, referred to as UV-B radiation. UV-B radiation has important effects on human health and ecosystems, and is associated with materials damage.

Adverse human health effects associated with solar UV-B radiation exposure include erythema, skin cancer, ocular damage, and immune system suppression. A potential human health benefit of increased UV-B exposure involves the UV-induced production of vitamin D which may help reduce the risk of metabolic bone disease, type I diabetes, mellitus, and rheumatoid arthritis, and may provide beneficial immunomodulatory effects on multiple sclerosis, insulin-dependent diabetes mellitus, and rheumatoid arthritis.

Adverse ecosystem and materials damage effects associated with solar UV-B radiation exposure include terrestrial and aquatic ecosystem impacts, alteration of biogeochemical cycles, and degradation of man-made materials. Terrestrial ecosystem effects from increased UV-B radiation include reduced plant productivity and plant cover, changes in biodiversity, susceptibility to infection, and increases in natural UV protective responses. In general, however, these effects are small for moderate UV-B increases at mid-latitudes. Aquatic ecosystem effects from increased UV-B radiation include sensitivity in growth, immune response, and behavioral patterns of aquatic organisms and the potential for increased catalysis and mobility of trace metals. Biogeochemical cycles, particularly the carbon cycle, can also be influenced by increased UV-B radiation with effects ranging from UV-induced increases in CO_2 uptake through soil respiration to UV-induced release of CO_2 through photodegradation of above-ground plant litter. Changes in solar UV radiation may also have effects on carbon cycling and CO_2 uptake in the oceans as well as release of dissolved organic matter from sediment and algae. Finally, materials damage from increased UV-B radiation includes UV-induced photodegradation of wood and plastic.

There is a lack of published studies that critically examine the incremental health or welfare effects (adverse or beneficial) attributable specifically to changes in UV-B exposure resulting from perturbations in tropospheric O_3 concentrations. While the

effects are expected to be small, they cannot yet be critically assessed within reasonable uncertainty.

10.6 References

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