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Executive Summary

1.1 Introduction

Air Quality Criteria for Ozone and Related Photochemical Oxidants evaluates the latest scientific information useful in deriving criteria that form the scientific basis for U.S. Environmental Protection Agency (EPA) decisions regarding the National Ambient Air Quality Standards (NAAQS) for ozone (O_3). This Executive Summary concisely summarizes key conclusions from the document, which comprises nine chapters. Following this Executive Summary is a brief Introduction (Chapter 2) containing information on the legislative and regulatory background for review of the O_3 NAAQS, as well as a brief discussion of the issues presented and the format for their discussion in the document. Chapter 3 provides information on the chemistry, sources, emissions, measurement, and transport of O_3 and related photochemical oxidants and their precursors, whereas Chapter 4 covers environmental concentrations, patterns, and exposure estimates of O_3 and oxidants. Chapter 5 deals with environmental effects, and Chapters 6, 7, and 8 discuss animal toxicological studies, human health effects, and extrapolation of animal toxicological data to humans, respectively. The last chapter, Chapter 9, provides an integrative, interpretative characterization of health effects associated with exposure to O_3. The following sections conform to the chapter organization of the criteria document.

1.2 Legislative and Regulatory Background

The photochemical oxidants found in ambient air in the highest concentrations are O_3 and nitrogen dioxide (NO_2). Other oxidants, such as hydrogen peroxide (H_2O_2) and peroxyacyl nitrates, also have been observed, but in lower and less certain concentrations. In 1971, EPA promulgated NAAQS to protect the public health and welfare from adverse effects of photochemical oxidants, at that time, defined on the basis of commercially available measurement methodology. After 1971, however, O_3-specific commercial analytical methods became available, as did information on the concentrations and effects of the related non-O_3 photochemical oxidants. As a result, the chemical designation of the standards was changed in 1979 from photochemical oxidants to O_3.

The EPA is required under Sections 108 and 109 of the Clean Air Act to evaluate periodically the air quality criteria that reflect the latest scientific information relevant to review of the O_3 NAAQS. These air quality criteria are useful for indicating the kind and

extent of all identifiable effects on public health or welfare that may be expected from the presence of O_3 and related photochemical oxidants in ambient air. The last O_3 criteria document was released in 1986, and a supplement was released in 1992. These documents were the basis for a March 1993 decision by EPA that revision of the existing 1-h NAAQS for O_3 was not appropriate at that time. That decision, however, did not take into consideration more recent scientific information that has been published since the last literature review in early 1989. The purpose of this revised criteria document, therefore, is to summarize the pertinent information contained in the previous O_3 criteria document and to critically evaluate and assess the more recent scientific data associated with exposure to O_3 and, to a lesser extent, to H_2O_2 and the peroxyacyl nitrates, particularly peroxyacetyl nitrate (PAN). This document will be used by EPA's Office of Air Quality Planning and Standards to provide a staff paper assessing the most significant scientific information and presenting staff recommendations on whether revisions to the O_3 NAAQS are appropriate.

1.3 Tropospheric Ozone and Its Precursors

Introduction

Ozone is found in the stratosphere, the "free" troposphere, and the planetary boundary layer (PBL) of the earth's atmosphere. In the PBL, background O_3 occurs as the result of (1) the intrusions of stratospheric O_3 into the "free" troposphere and downward transport into the PBL, and (2) photochemical reactions of methane (CH_4), carbon monoxide (CO), and nitrogen oxides (NO_x). These processes contribute to the background O_3 near the surface. The major source of O_3 in the PBL is the photochemical process involving anthropogenic and biogenic emissions of NO_x with the many classes of volatile organic compounds (VOCs).

The topics considered in this section of the document include: tropospheric O_3 chemistry; meteorological influences on O_3 formation and transport; precursor VOC and NO_x emissions, ambient concentrations of VOCs and NO_x, and source apportionment and reconciliation of measured VOC ambient concentrations with emission inventories; O_3 air quality models; and analytical methods for oxidants and precursors.

Tropospheric Ozone Chemistry

Ozone occurs in the stratosphere as the result of chemical reactions initiated by short-wavelength radiation from the sun. In the "free" troposphere, O_3 occurs as the result of incursions from the stratosphere; upward venting from the PBL (the layer next to the surface of the earth) through certain cloud processes; and photochemical formation from precursors, notably CH_4, CO, and NO_x.

The photochemical production of O_3 and other oxidants found at the surface of the earth (in the PBL, troposphere, or ambient air [used interchangeably in this summary]) is the result of atmospheric physical processes and complex, nonlinear chemical processes involving two classes of precursor pollutants: (1) reactive anthropogenic and biogenic VOCs and (2) NO_x. The only significant initiator of the photochemical production of O_3 in the polluted troposphere is the photolysis of NO_2, yielding nitric oxide (NO) and a ground-state oxygen atom that reacts with molecular oxygen to form O_3. The O_3 thus formed reacts with NO, yielding oxygen and NO_2. These cyclic reactions attain equilibrium in the absence of

VOCs. However, in the presence of VOCs, which are abundant in polluted ambient air, the equilibrium is upset, resulting in a net increase in O_3. Methane is the chief VOC found in the free troposphere and in most "clean" areas of the PBL. The VOCs found in polluted ambient air are much more complex and more reactive than CH_4, but, as with CH_4, their atmospheric oxidative degradation is initiated through attack on the VOCs by hydroxyl (OH) radicals. As in the CH_4 oxidation cycle, the conversion of NO to NO_2 during the oxidation of VOCs is accompanied by the production of O_3 and the efficient regeneration of the OH radical. The O_3, PAN, and higher homologues formed in polluted atmospheres increase with the NO_2/NO concentration ratio.

At night, in the absence of photolysis of reactants, the simultaneous presence of O_3 and NO_2 results in the formation of the nitrate (NO_3) radical. Reactions with NO_3 radicals appear to constitute major sinks for alkenes, cresols, and several other compounds, although the chemistry is not well characterized.

Most inorganic gas-phase processes (i.e., the nitrogen cycle and its interrelationships with O_3 production) are well understood. The chemistry of the VOCs in ambient air is not as well understood. It is well known, however, that the chemical loss processes of gas-phase VOCs include reaction with OH and NO_3 radicals and O_3, and photolysis. Reaction with the OH radical is the only important atmospheric reaction (loss process) for alkanes, aromatic hydrocarbons, and the higher aldehydes and ketones that lack >C=C< bonds; and the only atmospheric reaction of alcohols and ethers. Photolysis is the major loss process for formaldehyde and acetone. Reactions with OH and NO_3 radicals and with O_3 are all important loss processes for alkenes and for carbonyls containing >C=C< bonds.

Uncertainties in the atmospheric chemistry of the VOCs can affect quantification of the NO-to-NO_2 conversion and of O_3 yields, and can present difficulties in representation of chemical mechanisms, products, and product yields in O_3 air quality models. Major uncertainties in understanding the atmospheric chemistry of the VOCs with NO_x in both urban and rural atmospheres include chemistry of alkyl nitrate formation, mechanisms and products of >C4 *n*-alkanes and branched alkanes, mechanisms and products of alkene-O_3 reactions, and mechanisms and products of aromatic hydrocarbons.

It should be noted that the atmospheric chemical processes involved in the photooxidation of certain higher molecular weight VOCs and in the formation of O_3 also can lead to the formation of particulate-phase organic compounds. The OH radicals produced not only can oxidize VOCs to particulate-phase organic compounds but also can react with NO_2 and sulfur dioxide (SO_2) to form nitric acid (HNO_3) and sulfuric acid (H_2SO_4), respectively, portions of which become incorporated into aerosols as particulate nitrate and sulfate.

Meteorological Influences on Ozone Formation and Transport

The surface energy (radiation) budget of the earth strongly influences the dynamics of the PBL. The redistribution of energy through the PBL creates thermodynamic conditions that influence vertical mixing. Growing evidence indicates that the strict use of mixing heights in modeling is an oversimplification of the complex processes by which pollutants are redistributed within urban areas, and that it is necessary to treat the turbulent structure of the atmosphere directly and acknowledge the vertical variations in mixing. Energy balances therefore require study so that more realistic simulations can be made of the structure of the PBL.

Day-to-day variability in O_3 concentrations depends heavily on day-to-day variations in meteorological conditions, including temperature, solar radiation, and the degree of mixing that occurs between release of a pollutant or its precursors and their arrival at a receptor; the occurrence of inversion layers (layers in which temperature increases with height above ground level); and the transport of O_3 left overnight in layers aloft and subsequent downward mixing of that O_3 to the surface.

The transport of O_3 and its precursors beyond the urban scale (≤50 km) to neighboring rural and urban areas has been well documented. Episodes of high O_3 concentrations in urban areas are often associated with high concentrations of O_3 in the surroundings. Areas of O_3 accumulation usually are characterized by synoptic-scale subsidence of air in the free troposphere, resulting in development of an elevated inversion layer; relatively low wind speeds associated with the weak horizontal pressure gradient around a surface high pressure system; a lack of cloudiness; and high temperatures.

Ultraviolet (UV) radiation from the sun plays a key role in initiating the photochemical processes leading to O_3 formation and affects individual photolytic reaction steps. Still, there is little empirical evidence in the literature linking day-to-day variations in observed UV radiation levels to variations in O_3 levels. An association, however, between tropospheric O_3 concentrations and temperature has been demonstrated. Empirical data from four urban areas, for example, show an apparent upper bound on O_3 concentrations that increases with temperature. A similar qualitative relationship exists at a number of rural locations.

The relationship between wind speed and O_3 buildup varies from one part of the country to another.

Statistical techniques (e.g., regression techniques) can be used to help identify real trends in O_3 concentrations, both intra- and interannual, by normalizing meteorological variability.

Precursors

Volatile Organic Compound Emissions

Hundreds of VOCs, usually containing from 2 to 12 carbon atoms, are emitted by evaporative and combustion processes from a large number of source types. Total U.S. anthropogenic VOC emissions in 1991 were estimated at 21.0 Tg; the two largest source categories were (1) industrial processes (10.0 Tg) and (2) transportation (7.9 Tg). Emissions of VOCs from highway vehicles accounted for almost 75% of the transportation-related emissions; studies have shown that the majority of these VOC emissions come from about 20% of the automobiles in service, many, perhaps most, of which are older cars that are poorly maintained. The accuracy of VOC emission estimates is difficult to determine for both stationary and mobile sources.

Vegetation emits significant quantities of VOCs into the atmosphere, chiefly monoterpenes and isoprene, but also oxygenated VOCs, according to recent studies. The most recent biogenic VOC emissions estimate for the United States showed annual emissions of 29.1 Tg/year.

Although the biogenic VOC emission estimates exceed the anthropogenic estimates, the biogenic emissions are more diffusely distributed than the anthropogenic emissions, which tend to be concentrated in population centers. However, the large

uncertainties in both biogenic and anthropogenic VOC emission inventories prevent establishing the relative contributions of these two categories.

Nitrogen Oxides Emissions

Anthropogenic NO_x is associated with combustion processes. The primary pollutant emitted is NO, formed at high combustion temperatures from nitrogen and oxygen in the air and from nitrogen in the combustion fuel. Emissions of NO_x in 1991 in the United States totaled 21.39 Tg. The two largest single NO_x emission sources are electric power generating plants and highway vehicles. Because a large proportion of anthropogenic NO_x emissions come from distinct point sources, published annual estimates are thought to be much more reliable than VOC estimates.

Natural NO_x sources include stratospheric intrusion, oceans, lightning, soil, and wildfires. Lightning and soil emissions are the only two significant natural sources of NO_x in the United States. It is estimated that combined natural sources contribute about 2.2 Tg of NO_x to the troposphere over the continental United States; however, uncertainties in natural NO_x emission inventories are much greater than those for anthropogenic NO_x emissions.

Concentrations of Volatile Organic Compounds in Ambient Air

The VOCs most frequently analyzed in ambient air are the nonmethane hydrocarbons (NMHCs). Morning (6:00 to 9:00 a.m.) concentrations most often have been measured because of the use of morning data in the Empirical Kinetic Modeling Approach (EKMA) and in air quality simulation models.

Concurrent measurements of anthropogenic and biogenic NMHCs have shown that biogenic NMHCs usually constituted much less than 10% of the total NMHCs. For example, average isoprene concentrations ranged from 0.001 to 0.020 ppm carbon (C) and terpenes from 0.001 to 0.030 ppm C.

Concentrations of Nitrogen Oxides in Ambient Air

Measurements of NO_x made in 22 and 19 U.S. cities in 1984 and 1985, respectively, showed median 6:00-to-9:00 a.m. NO_x concentrations ranging from 0.02 to 0.08 ppm in most of these cities. Nonurban NO_x concentrations, reported as average seasonal or annual NO_x, range from <0.005 to 0.015 ppm.

Ratios of Concentrations of Nonmethane Organic Compounds to Nitrogen Oxides

Ratios of 6:00-to-9:00 a.m. nonmethane organic compounds (NMOC) to NO_x are higher in southeastern and southwestern U.S. cities than in northeastern and midwestern U.S. cities, according to data from EPA's multicity studies conducted in 1984 and 1985. Rural $NMOC/NO_x$ ratios tend to be higher than urban ratios. The $NMOC/NO_x$ ratios trended downward to well below 10 in the South Coast Air Basin and in cities in the eastern United States during the 1980s. Based on these low ratios, hydrocarbon control should be more effective than NO_x control within a number of cities. Morning (6:00-to-9:00 a.m.) $NMOC/NO_x$ ratios are used in the EKMA type of trajectory model. The correlation of $NMOC/NO_x$ ratios with maximum 1-h O_3 concentrations, however, was weak in a recent analysis.

Source Apportionment and Reconciliation

Source apportionment (regarded as synonymous with receptor modeling) refers to determining the quantitative contributions of various sources of VOCs to ambient air pollutant concentrations. Source reconciliation refers to the comparison of measured ambient VOC concentrations with emissions inventory estimates of VOC source emission rates for the purpose of validating the inventories.

Recent findings have shown that vehicle exhaust was the dominant contributor to ambient VOCs in seven of eight U.S. cities studied. Whole gasoline contributions were estimated to be equal to vehicle exhaust in one study and to 20% of vehicle exhaust in a second study.

Estimates of biogenic VOCs at a downtown site in Atlanta, GA, in 1990 indicated a lower limit of 2% (24-h average) for the biogenic percentage of total ambient VOCs at that location (isoprene was used as the biogenic indicator species). The percentage varies during the 24-h period because of the diurnal (e.g., temperature, light intensity) dependence of isoprene concentrations.

Source reconciliation data have shown disparities between emission inventory estimates and receptor-estimated contributions. For biogenics, emission estimates are greater than receptor-estimated contributions. The reverse has been true for natural gas contributions estimated for Los Angeles, CA; Columbus, OH; and Atlanta; and for refinery emissions in Chicago, IL.

Ozone Air Quality Models

Models and Their Components

Photochemical air quality models are used to predict how O_3 concentrations change in response to prescribed changes in source emissions of NO_x and VOCs. These models operate on sets of input data that characterize the emissions, topography, and meteorology of a region and produce outputs that describe air quality in that region.

Two kinds of photochemical models are recommended in guidelines issued by EPA: (1) the use of EKMA is accepted under certain circumstances, and (2) the grid-based Urban Airshed Model (UAM) is recommended for modeling O_3 over urban areas. The 1990 Clean Air Act Amendments mandate the use of three-dimensional (grid-based) air quality models such as UAM in developing state implementation plans for areas designated as "extreme", "severe", "serious", or "multistate moderate". General descriptions of EKMA and grid-based models were given in the 1986 EPA criteria document for O_3.

The EKMA-based method for determining O_3 control strategies has limitations, the most serious of which is that predicted emissions reductions are critically dependent on the initial NMHC/NO_x ratio used in the calculations. This ratio cannot be determined with any certainty and is expected to be quite variable in time and space in an urban area.

Spatial and temporal characteristics of VOC and NO_x emissions are major inputs to a grid-based photochemical air quality model. Greater accuracy in emissions inventories is needed for biogenics and for both mobile and stationary source components. Grid-based air quality models also require as input the three-dimensional wind field for the photochemical episode being simulated.

A chemical kinetic mechanism, representing the important chemical reactions that occur in the atmosphere, is used in an air quality model to estimate the net rate of formation of each pollutant simulated as a function of time.

Dry deposition is an important removal process for O_3 on both urban and regional scales and is included in all urban- and regional-scale models. Wet deposition is generally not included in urban-scale photochemical models, because O_3 episodes do not occur during periods of significant clouds or rain.

Concentration fields of all species computed by the model must be specified at the beginning of the simulation ("initial conditions"). These initial conditions are determined mainly with ambient measurements, either from routinely collected data or from special studies; but interpolation can be used to distribute the surface ambient measurements.

Use of Ozone Air Quality Models

Photochemical air quality models are used for control strategy evaluation by first demonstrating that a past episode or episodes can be simulated adequately. The hydrocarbon or NO_x emissions or both are reduced in the model inputs, and the effects of these reductions on O_3 in the region are assessed. The adequacy of control strategies based on grid-based models depends, in part, on the nature of input data for simulations and model validation, on input emissions inventory data, and on the mismatch between the spacial output of the model and the current form of the NAAQS for O_3. Uncertainties in models obviously can affect their outputs. Uncertainties exist in all components of grid-based O_3 air quality models: emissions, meteorological modules, chemical mechanisms, deposition rates, and determination of initial conditions.

Grid-based models that have been widely used to evaluate control strategies for O_3 or acid deposition, or both, are the UAM, the California Institute of Technology/Carnegie Institute of Technology model, the Regional Oxidant Model, the Acid Deposition and Oxidant Model, and the Regional Acid Deposition Model. The UAM (Version IV) is the grid model approved nationwide for control strategy development at this time.

Despite the many uncertainties in photochemical air quality modeling, including emission inventories, these models are essential for regulatory analysis and solving the O_3 problem. Grid-based O_3 air quality modeling is superior to the available alternatives for O_3 control planning, but the chances of its incorrect use must be minimized.

Analytical Methods for Oxidants and Their Precursors

Oxidants

Current methods used to measure O_3 are chemiluminescence (CL); UV absorption spectrometry; and newly developed spectroscopic and chemical approaches, including chemical approaches applied to passive sampling devices (PSDs) for O_3.

The CL method has been designated as the reference method by EPA. Detection limits of 0.005 ppm and a response time of <30 s are typical of currently available commercial instruments. A positive interference from atmospheric water vapor was reported in the 1970s and recently has been confirmed. Proper calibration can minimize this source of error.

Commercial UV photometers for measuring O_3 have detection limits of about 0.005 ppm and a response time of <1 min. Because the measurement is absolute, UV photometry is also used to calibrate O_3 methods. A potential disadvantage of UV photometry is that atmospheric constituents that absorb 254-nm radiation, the wavelength at which O_3 is measured, will cause a positive interference in O_3 measurements. Interferences have been reported in two recent studies, but assessment of the potential importance of such

interferences (e.g., toluene, styrene, cresols, nitrocresols) is hindered by lack of absorption spectra data in the 250-nm range and by lack of aerometric data for the potentially interfering species. There also can be some interference from water, possibly from the condensation of moisture in sampling lines.

Calibration of O_3 measurement methods (other than PSDs) is done by UV spectrometry or by gas-phase titration (GPT) of O_3 with NO. Ultraviolet photometry is the reference calibration method approved by EPA. Ozone is unstable and must be generated in situ at time of use to produce calibration mixtures.

Peroxyacetyl nitrate and the higher peroxyacyl nitrates normally are measured by gas chromatography (GC) using an electron capture detector. Detection limits have been extended to 1 to 5 ppt. The preparation of reliable calibration standards is difficult because PAN is unstable, but several methods are available.

Volatile Organic Compounds

The method recommended by EPA for total NMOC measurement involves the cryogenic preconcentration of NMOCs and the measurement of the revolatilized NMOCs using flame ionization detection (FID). The primary technique for speciated NMOC/NMHC measurements is cryogenic preconcentration followed by GC-FID. Systems for sampling and analysis of VOCs have been developed that require no liquid cryogen for operation.

Stainless steel canisters have become the containers of choice for collection of whole-air samples for NMHC/NMOC data. Calibration procedures for NMOC instrumentation require the generation, by static or dynamic systems, of dilute mixtures at concentrations expected to occur in ambient air.

Preferred methods for measuring carbonyl species (aldehydes and ketones) in ambient air are spectroscopic methods; on-line colorimetric methods; and, the most common method currently in use for measuring gas-phase carbonyl compounds in ambient air, the high-performance liquid chromatography method, which employs 2,4-dinitrophenylhydrazine derivatization in a silica gel cartridge. Use of an O_3 scrubber has been recommended to prevent interference by O_3 in this method in ambient air.

Oxides of Nitrogen

Nitric oxide and NO_2 comprise the NO_x compounds involved as precursors to O_3 and other photochemical oxidants.

The most common method of NO measurement is the gas-phase CL reaction with O_3, which is essentially specific for NO. Commercial NO monitors have detection limits of a few parts per billion by volume (ppbv) in ambient air but may not have sensitivity sufficient for surface measurements in rural or remote areas or for airborne measurements. Direct spectroscopic methods for NO exist that have very high sensitivity and selectivity for NO, but their complexity, size, and cost restrict these methods to research applications. No PSDs exist for measurement of NO.

Chemiluminescence analyzers are the tools of choice for NO_2 measurement, even though they do not measure NO_2 directly. Minimum detection levels for NO_2 have been reported to be 5 to 13 ppb, but more recent evaluations have indicated detection limits of 0.5 to 1 ppbv. Reduction of NO_2 to NO is required for measurement. These analyzers actually measure NO_y (NO_x + PAN + HNO_3 + other reactive nitrogen species); however, for most urban atmospheres, NO_x is the predominant species measured diurnally.

Several spectroscopic approaches to NO_2 detection have been developed but share the drawbacks of spectroscopic NO methods. Passive samplers for NO_2 exist but are still in the developmental stage for ambient air monitoring.

Calibration of methods for NO measurement is done using standard cylinders of NO in nitrogen. Calibration of methods for NO_2 measurement include use of cylinders of NO_2 in nitrogen or air, use of permeation tubes, and GPT.

1.4 Environmental Concentrations, Patterns, and Exposure Estimates

Ozone is measured at concentrations above the minimum detectable level at all monitoring locations in the world. In this section, hourly average concentration and exposure information is summarized for urban, rural forested, and rural agricultural areas in the United States.

Because O_3 from urban area emissions is transported to rural downwind locations, elevated O_3 concentrations can occur at considerable distances from urban centers. Urban O_3 concentration values are often depressed because of titration by NO. Because of the absence of chemical scavenging, O_3 tends to persist longer in nonurban areas than in urban areas, and nonurban exposures may be higher than those in urban locations.

Trends

Ozone hourly average concentrations have been recorded for many years by the state and local air pollution agencies who report their data to EPA. The 10-year (1983 to 1992) composite average trend for the second highest daily maximum hourly average concentration during the O_3 season shows that the 1992 composite average for the trend sites was 21% lower than the 1983 average. The 1992 value was the lowest composite average of the 10-year period and was significantly less than each of the previous nine years, 1983 to 1991. The relatively high O_3 concentrations in 1983 and 1988 likely were attributable, in part, to hot, dry, stagnant conditions in some areas of the country, which were especially conducive to O_3 formation.

From 1991 to 1992, the composite mean of the second highest daily maximum 1-h O_3 concentrations decreased 7%, and the composite average of the number of estimated exceedances of the O_3 standard decreased by 23%. Nationwide VOC emissions decreased 3% from 1991 to 1992. The composite average of the second daily maximum concentrations decreased in 8 of the 10 EPA regions from 1991 to 1992, and remained unchanged in Region VII. Except for Region VII, the 1992 regional composite means were lower than the corresponding 1990 levels. Although meteorological conditions in the east during 1993 were more conducive to O_3 than those in 1992, the composite mean level for 1993 was the second lowest composite average of the decade, 1984 to 1993.

Surface Concentrations

Published data provide evidence showing the occurrence at some sites of multihour periods within a day of O_3 at levels of potential health effects. Although most of these analyses were made using monitoring data collected from sites in or near nonattainment areas, in one analysis of five sites (two in New York state, two in rural California, and one in rural

Oklahoma), none of which was in or near a nonattainment area, O_3 concentrations showed only moderate peaks but showed multihour levels above 0.1 ppm.

A small amount of the O_3 concentration measured at a monitoring site is produced by sources distant to the photochemical reactions occurring on an urban or regional scale. Typical sources include stratospheric intrusions into the troposphere, photochemical production by the $CH_4/CO/NO_x$ cycle in the troposphere, and transport of very distant anthropogenic or biogenic VOCs and NO_x. The specific concentrations of this "background" O_3 vary with averaging times ranging from the daily 1-h maximum to daily, monthly, seasonal, or annual values. The background concentrations also vary with geographical region and with elevation of the monitoring site.

On the basis of O_3 data from isolated monitoring sites, EPA has indicated that a reasonable estimate of O_3 background concentration near sea level in the United States is from 0.020 to 0.035 ppm for an annual average, 0.025 to 0.045 ppm for an 8-h daily summer seasonal average, and from 0.03 to 0.05 ppm for the average summertime 1-h daily maximum. This estimate includes a 0.005 to 0.015 ppm O_3 contribution from stratospheric intrusions into the troposphere.

Diurnal Variations

Diurnal patterns of O_3 may be expected to vary with location, depending on the balance among the many factors affecting O_3 formation, transport, and destruction. Although they vary with locality, diurnal patterns of O_3 typically show a rise in concentration from low levels, or levels near minimum detectable amounts, to an early afternoon peak. The diurnal pattern of concentrations can be ascribed to three simultaneous processes: (1) downward transport of O_3 from layers aloft, (2) destruction of O_3 through contact with surfaces and through reaction with NO at ground level, and (3) in situ photochemical production of O_3.

Seasonal Patterns

Seasonal variations in O_3 concentrations in urban areas usually show the pattern of high O_3 in the late spring or in the summer and low levels in the winter; however, weather conditions in a given year may be more favorable for the formation of O_3 and other oxidants than during the prior or following year.

Average O_3 concentrations tend to be higher in the second versus the third quarter of the year for many isolated rural sites. This observation has been attributed to either stratospheric intrusions or an increasing frequency of slow-moving, high-pressure systems that promote the formation of O_3. However, for several clean rural sites, the highest exposures have occurred in the third quarter rather than in the second. For rural O_3 sites in the southeastern United States, the daily maximum 1-h average concentration was found to peak during the summer months.

Spatial Variations

Concentrations of O_3 vary with altitude and with latitude. There appears to be no consistent conclusion concerning the relationship between O_3 exposure and elevation.

Indoor Ozone

Until the early 1970s, very little was known about the O_3 concentrations experienced inside buildings; to date, the database on this subject is not large, and a wide range of indoor/outdoor O_3 concentration relationships can be found in the literature (reported indoor/outdoor values for O_3 are highly variable). Indoor/outdoor O_3 concentration ratios generally fall in the range from 0.1 to 0.7 and indoor concentrations of O_3 almost invariably will be less than outdoors.

Estimating Exposure

Both fixed-site monitoring information and human exposure models are used to estimate risks associated with O_3 exposure. Because, for most cases, it is not possible to estimate population exposure solely from fixed-station data, several human exposure models have been developed. These models also contain submodels depicting the sources and concentrations likely to be found in each microenvironment, including indoor, outdoor, and in-transit settings. Two distinct types of O_3 exposure models exist: (1) those that focus narrowly on predicting indoor O_3 levels and (2) those that focus on predicting O_3 exposures on a community-wide basis. These latter models and their distinguishing features are:

1. pNEM/O_3 based on the National Air Quality Standards Exposure Model (NEM) series of models
   - Uses mass-balance approach and seasonal considerations for I/O ratio estimation.
   - Variables affecting indoor exposure obtained by Monte Carlo sampling from empirical distributions of measured data.
2. Systems Applications International (SAI)/NEM
   - More districts and microenvironments and more detailed mass-balance model than pNEM/O_3.
   - Human activity data outdated and inflexible.
3. Regional Human Exposure Model (REHEX)
   - More detailed geographic resolution than NEM.
   - Uses California-specific activity data and emphasizes in-transit and outdoor microenvironments.
4. Event probability exposure model (EPEM)
   - Estimates probability that a randomly selected person will experience a particular exposure regime.
   - Lacks multiday continuity.

Few data are available for individuals using personal exposure monitors. Results from a pilot study demonstrated that fixed-site ambient measurements may not adequately represent individual exposures. Models based on time-weighted indoor and outdoor concentrations explained only 40% of the variability in personal exposures.

Peroxyacyl Nitrates

Peroxyacetyl nitrate and peroxypropionyl nitrate (PPN) are the most abundant of the non-O_3 oxidants in ambient air in the United States, other than the inorganic nitrogenous oxidants such as NO_2, and possibly HNO_3. Most of the available data on concentrations of PAN and PPN in ambient air are from urban areas. The levels to be found in nonurban areas

will be highly dependent on the transport of PAN and PPN or their precursors from urban areas, because the concentrations of the NO_x precursors to these compounds are considerably lower in nonurban areas than in urban areas.

Co-occurrence

Studies of the joint occurrence of gaseous NO_2/O_3 and SO_2/O_3 at rural sites have concluded that the periods of co-occurrence represent a small portion of the potential plant-growing period. For human ambient exposure considerations, in most cases, the simultaneous co-occurrence of NO_2/O_3 and SO_2/O_3 was infrequent. Some researchers have reported the joint occurrence of O_3, nitrogen, and sulfur in forested areas, combining cumulative exposures of O_3 with data on dry deposition of sulfur and nitrogen. One study reported that several forest landscapes with the highest dry deposition loadings of sulfur and nitrogen tended to experience the highest average O_3 concentrations and largest cumulative exposure. Although the authors concluded that the joint concentrations of multiple pollutants in forest landscapes were important, nothing was mentioned about the hourly co-occurrences of O_3 and SO_2 or O_3 and NO_2. Acid sulfates, which are usually composed of H_2SO_4, ammonium bisulfate, and ammonium sulfate, have been measured at a number of locations in North America. The potential for O_3 and acidic sulfate aerosols to co-occur at some locations in some form (i.e., simultaneously, sequentially, or complex-sequentially) is real and requires further characterization. For human ambient exposures, the simultaneous co-occurrence of NO_2 and O_3 was infrequent.

In one study, the relationship between O_3 and hydrogen ions in precipitation was explored using data from sites that monitored both O_3 and wet deposition simultaneously and within one minute latitude and longitude of each other. It was reported that individual sites experienced years in which both hydrogen ion deposition and total O_3 exposure were at least moderately high. With data compiled from all sites, it was found that relatively acidic precipitation occurred together with relatively high O_3 levels approximately 20% of the time, and highly acidic precipitation occurred together with a high O_3 level approximately 6% of the time. Sites most subject to relatively high levels of both hydrogen ions and O_3 were located in the eastern part of the United States, often in mountainous areas.

The co-occurrence of O_3 and acidic cloudwater in high-elevation forests has been characterized. The frequent O_3-only and pH-only single-pollutant episodes, as well as the simultaneous and sequential co-occurrences of O_3 and acidic cloudwater, have been reported. Both simultaneous and sequential co-occurrences were observed a few times each month above cloud base.

1.5 Environmental Effects of Ozone and Related Photochemical Oxidants

Ozone is the gaseous pollutant most injurious to agricultural crops, trees, and native vegetation. Exposure of vegetation to O_3 can inhibit photosynthesis, alter carbon (carbohydrate) allocation, and interfere with mycorrhizal formation in tree roots. Disruption of the important physiological processes of photosynthesis and carbon allocation can suppress the growth of crops, trees, shrubs, and herbaceous vegetation by decreasing their capacity to form the carbon (energy) compounds needed for growth and maintenance and their ability to

absorb the water and mineral nutrients that they require from the soil. In addition, loss of vigor impairs the ability of trees and crops to reproduce and increases their susceptibility to insects and pathogens. The following section summarizes key environmental effects associated with O_3 exposure.

Effects on Agroecosystems

Methodologies Used in Vegetation Research

Most of the knowledge concerning the effects of O_3 on vegetation comes from the exposure-response studies of important agricultural crop plants and some selected forest and urban tree species, mostly as seedlings. A variety of methodologies have been used, ranging from field exposures without chambers to open-top chambers and to exposures conducted in chambers under highly controlled conditions. In general, the more controlled conditions are most appropriate for investigating specific responses and for providing the scientific basis for interpreting and extrapolating results. The greatest body of knowledge is from OTC studies.

Mode of Action

Leaves are important regulators of plant stress and function. Stress resulting from exposure to O_3 produces a leaf-mediated response. Effects expressed within cells in the leaf (i.e., inhibition of photosynthesis) affect a plant's carbon (energy) budget. Plant processes are impaired only by the O_3 that enters the plant through the stomata (opening in the leaves). An effect will occur only if sufficient O_3 reaches sensitive sites within the leaf cells. The uptake and movement of O_3 to sensitive cellular sites within a leaf are subject to various biochemical and physiological controls. Leaf injury will not be detected if the rate of uptake is small enough for the plant to detoxify or metabolize O_3 and its derivatives, or the plant is able to repair or compensate for the impact at a rate equal to or greater than the rate of uptake. Impairment of leaf cellular processes is the basis for all other plant effects. The diurnal pattern of stomatal opening plays a critical role in O_3 uptake, particularly at the canopy level.

Visible injury is usually the first observable indication of cellular response; injury can occur, however, with no visible effects. Early senescence of leaves or needles is also a result of cellular response. Impairment of cellular processes inhibits the rate of photosynthesis, reduces carbon (sugars, carbohydrate) production, and alters carbon allocation, causing a shift in growth pattern that favors shoots over roots. The reduced allocation of carbon to leaf repair and new leaf formation limits the availability of carbon for reproduction; stem and root growth; and, particularly, the formation of the mycorrhizae on roots necessary for nutrient and water uptake. Reduction of plant vigor by O_3 can result in mortality, particularly when plant susceptibility to insects and pathogens is increased.

Factors That Modify Plant Response

Plant response to O_3 exposure is influenced by a variety of biological, chemical, and physical factors. When determining the impact of O_3 exposure on plants, both the influence of environmental factors on plant response and the effects of O_3 on that response must be considered. Biological factors within plants that affect their response to stresses include, genetic composition, stage of development, and the diurnal pattern of stomatal opening. Genotype significantly influences plant sensitivity to O_3. Individuals, varieties, and cultivars of a species are known to differ greatly in their responses to a given O_3 exposure.

Genotype also influences the ability of plants to compete with one another for space, nutrients, light, and water.

The magnitude of response of a particular species, variety, or cultivar depends on a number of environmental factors. The plant's present and past environmental milieu, which includes the temporal exposure pattern and stage of development, dictates the plant response. The corollary is also true: exposure to O_3 can modify plant response to other environmental variables. Available light, temperature, atmospheric turbulence and moisture, in both the atmosphere and soil; soil nutrition; and exposure to and interaction with other pollutants such as agricultural chemical sprays also influence the magnitude of plant response.

Drought can reduce visible injury and the adverse effects of O_3 on growth and yield of crops. However, in the case of crops, drought, per se, much more adversely affects yield than the effects of O_3. Ozone, on the other hand, tends to reduce the water-use efficiency of well-watered crops. In some plants, O_3 exposure reduces cold/winter hardiness. Although exposure to O_3 tends to reduce attacks by obligate pathogens, susceptibility of plants to facultative pests and pathogens increases.

Effects-Based Air Quality Exposure Indices

Environmental scientists for many years have attempted to characterize and mathematically represent plant exposures to O_3. A variety of averaging times have been used. Although most studies have characterized exposure by using mean concentrations, such as seasonal, monthly, weekly, daily, or peak hourly means, other studies have used cumulative measures (e.g., the number of hours above selected concentrations). None of these statistics completely characterizes the relationships among O_3 concentration, exposure duration, interval between exposures, and plant response.

The use of a mean concentration with long averaging times implies that all concentrations of O_3 are equally effective in causing plant responses and minimizes the contributions of the peak concentrations to the response. Ozone effects are cumulative; therefore, exposure duration should be included in any index if it is to be biologically relevant. Present evidence suggests that cumulative effects of episodic exposures to either peak or mid-range concentrations, or both, can play an important role in producing growth responses. The key to plant response is timing because peak and mid-range concentrations do not occur at the same time. Potentially, the greatest effect of O_3 on plants will occur when stomatal conductance is greatest. When peaks occur at the time of greatest stomatal conductance, the effect of mid-range concentrations will not be observable. Atmospheric conductivity also strongly influences plant response because O_3 must be in contact with the leaf surface if it is to be taken up by a plant. Effects on vegetation appear when the amount of pollutant entering exceeds the ability of the plant to repair or compensate for the impact. Increasing uptake of O_3 will inhibit photosynthesis and result in increased reductions in biomass production.

An index of ambient exposures that relates well to plant response should incorporate, directly or indirectly, environmental influences (e.g., temperature, humidity, soil-moisture status) and exposure dynamics. Peak indices (e.g., second highest daily maximum) imply that a single high-concentration exposure (1- or 8-h concentration) during the course of a 70- to 120-day growing season is related to eventual yield or growth reductions. On the other hand, mean indices (e.g., 7-h seasonal mean) imply that duration of the exposure is not important, and that all concentrations have equal effect on plants. Neither of these indices

relates ambient O_3 concentrations to biological effects on plants because these indices do not consider the duration of exposure. An index that cumulates all hourly concentration during the season and gives greater weight to higher concentrations appears to be a more appropriate index for relating ambient exposures to growth or yield effects.

No experimental studies have been designed specifically to evaluate the adequacy of the various peak-weighted indices that have been proposed. In retrospective analyses in which O_3 is the primary source of variation in response, year-to-year variations in plant response are minimized by peak-weighted, cumulative exposure indices. However, a number of different forms of peak-weighted, cumulative indices have been examined for their ability to properly order yield responses from the large number of studies of the National Crop Loss Assessment Network (NCLAN) program. These exposure indices (i.e., SUM00, SUM06, SIGMOID, W126) all performed equally well, and it is not possible to distinguish among them on the basis of statistical fits of the data. The biological basis for these indices has not been determined.

Exposure Response of Plant Species

The emphasis of experimental studies usually has been on the more economically important crop plants and tree species, as seedlings. Crop species usually are monocultures that are fertilized and, in many cases, watered. Therefore, because crop plants are usually grown under optimal conditions, their sensitivity to O_3 exposures can vary from that of native trees, shrubs, and herbaceous vegetation.

The concept of limiting values was used in both the 1978 and 1986 criteria documents to summarize visible foliar injury. Limiting values are defined as concentrations and durations of exposure below which visible injury does not occur. The limit for visible injury indicating reduced plant performance was an O_3 exposure of 0.05 ppm for several hours per day for more than 16 days. When the exposure period was decreased to 10 days, the O_3 concentration required to cause injury was increased to 0.10 ppm. A short, 6-day exposure further increased the concentration to 0.30 ppm. These exposure and concentration periods apply for those crops where appearance or aesthetic value (e.g, spinach, cabbage, lettuce) is considered important. Limiting values for foliar injury to trees and shrubs range from 0.06 to 0.10 ppm for 4 h.

The following assertions can be made based on information from the 1986 criteria document, its 1992 supplement, and literature published since 1986. Ambient O_3 concentrations in several regions of the country are high enough to impair growth and yield of sensitive plant species. This clearly is indicated by comparison of data obtained from crop yield in charcoal-filtered and unfiltered (ambient) exposures. These elevated levels are further supported by data from studies using chemical protectants. These response data make possible the extrapolation to plants not studied experimentally. Both approaches mentioned above indicate that effects occur with only a few exposures above 0.08 ppm. Data from regression studies conducted to develop an exposure-response function for estimating yield loss indicated that at least 50% of the species and cultivars tested could be predicted to exhibit a 10% yield loss at 7-h seasonal mean O_3 concentrations of 0.05 ppm or less.

Effects on Natural Ecosystems

The responses of the San Bernardino mixed forest of Southern California to 50 or more years of chronic ozone exposures based on many studies, present a classic example of

ecosystem response to severe stress. Data from an inventory conducted from 1968 through 1972 indicated that for 5 mo of each year, trees were exposed to O_3 concentrations greater than 0.08 ppm for more than 1,300 h. Concentrations rarely decreased below 0.05 ppm at night near the crest of the mountain slope, approximately 5,500 ft. In addition, during the years 1973 to 1978, average 24-h O_3 concentrations ranged from a background of 0.03 to 0.04 ppm in the eastern part of the San Bernardino Mountains to a maximum of 0.10 to 0.12 ppm in the western part during May through September.

Plants accumulate, store, and use the energy in carbon compounds (sugars) produced during photosynthesis to build their structures and to maintain the physiological processes necessary for life. The patterns of carbon allocation to roots, stems, and leaves directly influence growth. The strategy for carbon allocation changes during the life of a plant, as well as with environmental conditions. Mature trees have a higher ratio of respiration to photosynthetic tissue. Impairment of photosynthesis shifts carbon allocation from growth and maintenance to repair; increased respiration can result in resource imbalances. The significant changes observed in the San Bernardino forest ecosystem were a possible outcome of the combined influences of O_3 on carbon, water, and nutrient allocation.

The biochemical changes within the leaves of ponderosa and Jeffrey pine in the San Bernardino forest, expressed as visible foliar injury, premature needle senescence, reduced photosynthesis, and reduced carbohydrate production and allocation, resulted in reduced tree vigor, growth, and reproduction. Reduced vigor increases susceptibility of trees to insect pests and fungal pathogens. Premature needle senescence alters microorganismal succession on confer needles and changes the detritus-forming process and associated nutrient cycling.

Altered carbon allocation is important in the formation of mycorrhizae (fungus roots), which are an extremely important but unheralded component of all ecosystems; the majority of all plants depend on them because they are integral in the uptake of mineral nutrients and water from the soil. Carbon-containing exudates from the roots are necessary for the formation of mycorrhizae. Reduced carbon allocation to plant roots affects mycorrhizal formation and impacts plant growth. Exposure to ozone, therefore, affects plant growth both above and below ground.

Small changes in photosynthesis or carbon allocation can alter profoundly the structure of a forest. Ecosystem responses to stress begin with the response of the most sensitive individuals of a population. Stresses, whose primary effects occur at the molecular level (within the leaves), must be propagated progressively through more integrated levels of organ physiology (e.g., leaf, branch, root) to whole plant physiology, then to populations within the stand (community), and finally to the landscape level to produce ecosystem effects. Only a small fraction of stresses at the molecular level become disturbances at the tree, stand, or landscape level. The time required for a stress to be propagated from one level to the next (it can take years) determines how soon the effects of the stress can be observed or measured.

The primary effect of O_3 on ponderosa and Jeffrey pine, two of the more susceptible members of the San Bernardino forest community, was that the trees were no longer able to compete effectively for essential nutrients, water, light, and space. Decline in the sensitive trees, a consequence of altered competitive conditions, permitted the enhanced growth of more tolerant species. Removal of the ecosystem dominants at the population level changed its structure and altered the processes of energy flow and nutrient cycling, returning the ecosystem to a less complex stage.

The San Bernardino Mountains continue to experience exposure to O_3; however, there has been a gradual decline in concentrations and length of exposure. Ozone concentrations of 0.06 ppm or higher of varying durations capable of causing injury to trees in forest ecosystems have been observed during the past 5 years in the Sierra Nevada Mountains and the Appalachian Mountains from Georgia to Maine. Visible injury to forest trees and other vegetation in these areas has been observed.

Injury to sensitive trees from exposure to ozone concentrations 0.06 ppm or greater in the Sierra Nevada Mountains and the Appalachian Mountains has never had the impact on these ecosystems that it did on the San Bernardino forest. Forest stands differ greatly in age, species composition, stability, and capacity to recover from disturbance. In addition, the position in the stand or community of the most sensitive species is extremely important. Ponderosa and Jeffrey pine were the dominant species in the San Bernardino forest. Removal of populations of these trees altered both ecosystem structure and function. Both the Sierra Nevada Mountains and the Appalachian Mountains are biologically more diverse. Removal of sensitive individuals of eastern white pine and black cherry has not visibly altered the forest ecosystems along the Appalachian Mountains, possibly because of the absence of population changes in these species. Decline and dieback of trees on Mt. Mitchell, NC, and Camel's Hump, VT, cannot be related solely to O_3 injury.

Effects on Agriculture, Forestry, and Ecosystems: Economics

A number of economic assessments of the effects of O_3 on agriculture have been performed over the last decade. All use NCLAN response data to predict crop yield changes. Although these studies employ somewhat different economic assessment methodologies, each shows national-level economic losses to major crops in excess of $1 billion (1990 dollars) from exposure to ambient concentrations of O_3. These studies also evaluate the sensitivity of the economic estimates to uncertainties in data, including the NCLAN response data. The economic assessment models used could be adapted to future O_3-crop yield response findings, if available.

The plant science literature shows that O_3 adversely influences physiological performance of both urban and native tree species; the limited economic literature also demonstrates that changes in growth have economic consequences. However, the natural science and economic literature on the topic are not yet mature enough to conclude unambiguously that ambient O_3 is imposing economic costs. The economic effects of O_3 on ecosystems have not yet been addressed in the published literature. There is, however, an emerging interest in applying economic concepts and methods to the management of ecosystems.

Effects on Materials

Over four decades of research show that O_3 damages certain materials such as elastomers, textile fibers, and dyes. The amount of damage to actual in-use materials and the economic consequences of that damage are poorly characterized.

Natural rubber and synthetic polymers of butadiene, isoprene, and styrene, used in products like automobile tires and protective outdoor electrical coverings, account for most of the elastomer production in the United States. The action of O_3 on these compounds is well known, and concentration-response relationships have been established and corroborated by several studies. These relationships, however, must be correlated with adequate exposure

information based on product use. For these and other economically important materials, protective measures have been formulated to reduce the rate of oxidative damage. When antioxidants and other protective measures are incorporated in elastomer production, the O_3-induced damage is reduced considerably, although the extent of reduction differs widely according to the material and the type and amount of protective measures used.

Both the type of dye and the material in which it is incorporated are important factors in the resistance of a fabric to O_3. Some dyed fabrics, such as royal blue and red rayon-acetate and plum cotton are resistant to O_3. On the other hand, anthraquinone dyes on nylon fibers are sensitive to fading by O_3. Field studies and laboratory work show a positive association between O_3 levels and dye fading of nylon materials. At present, the available research is insufficient to quantify the amount of damaged materials attributable to O_3 alone.

The degradation of fibers from exposure to O_3 is poorly characterized. In general, most synthetic fibers, such as modacrylic and polyester, are relatively resistant, whereas cotton, nylon, and acrylic fibers have greater but varying sensitivities to O_3. Ozone reduces the breaking strength of these fibers, and the degree of strength reduction depends on the amount of moisture present. The limited research in this area indicates that O_3 in ambient air may have a minimal effect on textile fibers, but additional research is needed to verify this conclusion.

A number of artists' pigments and dyes are sensitive to O_3 and other oxidants; in particular, many organic pigments are subject to fading or other color changes when exposed to O_3. Although most, but not all, modern fine arts paints are more O_3 resistant, many older works of art are at risk of permanent damage due to O_3-induced fading.

A great deal of work remains to be done to develop quantitative estimates of the economic damage to materials from photochemical oxidants. Most of the available studies are outdated in terms of O_3 concentrations, technologies, and supply-demand relationships. Additionally, little is known about the physical damage functions, so cost estimates have been simplified to the point of not properly recognizing many of the scientific complexities of the impact of O_3.

1.6 Toxicological Effects of Ozone and Related Photochemical Oxidants

Respiratory Tract Effects of Ozone

Biochemical Effects

Knowledge of molecular targets provides a basis for understanding mechanisms of effects and strengthening animal-to-human extrapolations. Ozone reacts with polyunsaturated fatty acids and sulfhydryl, amino, and some electron-rich compounds. These elements are shared across species. Several types of reactions are involved, and free radicals may be created. Based on this knowledge, it has been hypothesized that the O_3 molecule is unlikely to penetrate the liquid linings of the respiratory tract (RT) to reach the tissue, raising the possibility that reaction products exert effects.

In acute and short-term exposure studies, a variety of lung lipid changes occur, including an increase in arachidonic acid, the further metabolism of which produces a variety of biologically active mediators that can affect host defenses, lung function, the immune system, and other functions.

The level of lung antioxidant metabolism increases after O_3 exposure, probably as a result of the increase in the number of Type 2 cells, which are rich in antioxidant enzymes.

Collagen (the structural protein involved in fibrosis) increases in O_3-exposed lungs in a manner that has been correlated to structural changes (e.g., increased thickness of the tissue between the air and blood after prolonged exposure). Some studies found that the increased collagen persists after exposure ceases.

Generally, O_3 enhances lung xenobiotic metabolism after both short- and long-term exposure, possibly as a result of morphological changes (increased numbers of nonciliated bronchiolar epithelial cells). The impact of this change is dependent on the xenobiotics involved; for example, the metabolism of benzo[*a*]pyrene to active metabolites was enhanced by O_3.

Lung Inflammation and Permeability Changes

Elevated concentrations of O_3 disrupt the barrier function of the lung, resulting in the entry of compounds from the airspaces into the blood and the entry of serum components (e.g., protein) and white blood cells (especially polymorphonuclear leukocytes [PMNs]) into the airspaces and lung tissue. This latter impact reflects the initial stage of inflammation. These cells can release biologically active mediators that are capable of a number of actions, including damage to other cells in the lung. In lung tissue, this inflammation also can increase the thickness of the air-blood barrier.

Increases in permeability and inflammation have been observed at levels as low as 0.1 ppm O_3 (2 h/day, 6 days; rabbits). After acute exposures, the influence of the time of exposure (from two to several hours) increases as the concentration of O_3 increases. Long-term exposure effects are discussed under lung morphology.

The impacts of these changes are not fully understood. At higher O_3 concentrations (e.g., 0.7 ppm, 28 days), the diffusion of oxygen into the blood decreases, possibly because the air-blood barrier is thicker; cellular death may result from the enzymes released by the inflammatory cells; and host defense functions may be altered by mediators.

Effects on Host Defense Mechanisms

Exposure to elevated concentrations of ozone results in alterations of all defense mechanisms of the RT, including mucociliary and alveolobronchiolar clearance, functional and biochemical activity of the alveolar macrophage (AM), and immunologic competence. These effects can cause susceptibility to bacterial respiratory infections.

Mucociliary clearance, which removes particles and cellular debris from the conducting airways, is slowed by acute, but not repeated exposures to O_3. Ciliated epithelial cells that move the mucous blanket are altered or destroyed by acute and chronic exposures. Neonatal sheep exposed to O_3 do not have normal development of the mucociliary system. Such effects could prolong the retention of unwanted substances (e.g., inhaled particles) in the lungs, allowing them to exert their toxicity for a longer period of time.

Alveolar clearance mechanisms, which center on the functioning of AMs, are altered by O_3. Short-term exposure to levels as low as 0.1 ppm O_3 (2 h/day, 1 to 4 days; rabbits) accelerates clearance, but longer exposures do not. Even so, after a 6-week exposure of rats to an urban pattern of O_3, the retention of asbestos fibers in a region protected by alveolar clearance is prolonged.

Alveolar macrophages engulf and kill microbes, as well as clear the deeper regions of the lungs of nonviable particles; AMs also participate in immunological responses, but little is known about the effects of O_3 on this function. Acute exposures of rabbits to levels as low as 0.1 ppm O_3 decrease the ability of AMs to ingest particles. This effect is displayed in decreases in the ability of the lung to kill bacteria after acute exposure of mice to levels as low as 0.4 ppm O_3.

Both the pulmonary and systemic immune system are affected by O_3, but in a poorly understood way. It appears that the part of the immune system dependent on T-cell function is more affected than is the part dependent on B-cell function.

Dysfunction of host defense systems results in enhanced susceptibility to bacterial lung infections. For example, acute exposure to O_3 concentrations as low as 0.08 ppm for 3 h can overcome the ability of mice to resist infection with streptococcal bacteria, resulting in mortality. However, more prolonged exposures (weeks, months) do not cause greater effects on infectivity.

Effects on antiviral defenses are more complex and less well understood. Only high concentrations (1.0 ppm O_3, 3 h/day, 5 days; mice) increase viral-induced mortality. Apparently, O_3 does not impact antiviral clearance mechanisms. Although O_3 does not affect acute lung injury from influenza virus infection, it does enhance later phases of the course of an infection (i.e., postinfluenzal alveolitis).

Morphological Effects

Elevated concentrations of O_3 cause similar types of alterations in lung structure in all laboratory animal species studied, from rats to monkeys. In the lungs, the most affected cells are the ciliated epithelial cells of the airways and Type 1 epithelial cells of the gas-exchange region. In the nasal cavity, ciliated cells are also affected.

The centriacinar region (CAR; the junction of the conducting airways and gas-exchange regions) is the primary target, possibly because this area receives the greatest dose of O_3. The ciliated cells can be killed and replaced by nonciliated cells (i.e., cells not capable of clearance functions that also have increased ability to metabolize some foreign compounds). Mucous-secreting cells are affected, but to a lesser degree. Type 1 cells, across which gas exchange occurs, can be killed; they are replaced by Type 2 cells, which are thicker and produce more lipids. An inflammatory response also occurs in the tissue. The tissue is thickened further in later stages when collagen (a structural protein increased in fibrosis) and other elements accumulate. Although fibrotic changes have been observed in the CAR, they have not been distributed throughout the whole lung.

The distal airway is remodeled; more specifically, bronchiolar epithelium replaces the cells present in alveolar ducts. Concurrent inflammation may play a role. This effect has been observed at 0.25 ppm O_3 (8 h/day, 18 mo) in monkeys; at a higher concentration, this remodeling persists after exposure stops.

The progression of effects during and after a chronic exposure is complex. Over the first few days of exposure, inflammation peaks and then drops considerably, plateauing for the remainder of exposure, after which it largely disappears. Epithelial hyperplasia increases rapidly over the first few days and rises slowly or plateaus thereafter; when exposure ends, it begins to return toward normal. In contrast, fibrotic changes in the tissue between the air and blood increase very slowly over months of exposure, and, after exposure ceases, the changes sometimes persist or increase.

The pattern of exposure can make a major difference in effects. Monkeys exposed to 0.25 ppm O_3 (8 h/day) every other month of an 18-mo period had equivalent changes in lung structure, more fibrotic changes, and more of certain types of pulmonary function changes than did monkeys exposed every day over the 18 mo. From this work and rat studies, it appears that natural seasonal patterns may be of more concern than more continuous exposures. Thus, long-term animal studies with uninterrupted exposures may underestimate some of the effects of O_3.

The morphologic lesions described in early publications on laboratory animals exposed to O_3 do not meet the current criteria for emphysema of the type seen in human lungs.

Effects on Pulmonary Function

Pulmonary function changes in animals resemble those observed in humans after acute exposure.

During acute exposure, the most commonly observed alterations are increased frequency of breathing and decreased tidal volume (i.e., rapid, shallow breathing). This has been reported at exposures as low as 0.2 ppm O_3 for 3 h (rats). Typically, higher concentrations (around 1 ppm) are required to affect breathing mechanics (compliance and resistance). Extended characterizations of pulmonary function show types of changes generally seen in humans. For example, there are decreased lung volumes at levels ≥0.5 ppm O_3 (a few hours; rats).

When rats are exposed to O_3 for 2 h/day for 5 days, the pattern of attenuation of pulmonary function responses is similar to that observed in humans. Other biochemical indicators of lung injury did not return to control values by Day 5, and morphological changes increased in severity over the period of exposure. Thus, attenuation did not result in protection against all the effects of O_3.

Long-term exposures have provided mixed results on pulmonary function, including no or minimal effects, restrictive effects, and obstructive effects. When changes occurred and postexposure examinations were performed, pulmonary function recovered.

Genotoxicity and Carcinogenicity of Ozone

The chemical reactivities of O_3 give it the potential to be a genotoxic agent.

In vitro studies are difficult to interpret because the culture systems used allowed the potential formation of artifacts, and high or very high concentrations of O_3 often were used. Generally, in these studies, O_3 causes DNA strand breaks, sometimes is weakly mutagenic, and causes cellular transformation and chromosomal breakage. The latter finding has been investigated in vivo, with mixed results in animals.

The few earlier long-term carcinogenic studies in laboratory animals, with or without coexposure to known carcinogens, are either negative or ambiguous.

The National Toxicology Program (NTP) completed chronic rat and mouse cancer bioassays using commonly accepted experimental approaches and designs. Both male and female rats and mice were studied. Animals were exposed for 2 years (6 h/day, 5 days/week) to 0.12, 0.5, and 1.0 ppm O_3 or for a lifetime to the same levels (except 0.12 ppm). Following their standard procedures for determination of weight-of-evidence for carcinogenicity, the NTP reported "no evidence" in rats, "equivocal evidence" in male mice, and "some evidence" in female mice. The increases in adenomas and carcinomas were observed only in the lungs.

There was no concentration response. One of the reasons for the designation of "some evidence" in female mice was that when the 2-year and lifetime exposure studies were combined, there was a statistically significant increase in total tumors at 1.0 ppm. Lung tumors from control and O_3-exposed mice also were examined for the presence of mutated Ha-ras oncogenes. Although the types of mutations found were similar in both groups, a higher incidence of mutations was found in lung tumors from the O_3-exposed mice. At the present time, however, there is inadequate information to provide mechanistic support for the finding in mice. Thus, the potential for animal carcinogenicity is uncertain.

In a companion NTP study, male rats were treated with a tobacco carcinogen and exposed for 2 years to 0.5 ppm O_3. Ozone did not affect the response and therefore had no tumor promoting activity.

Systemic Effects of Ozone

Ozone causes a variety of effects on tissues and organs distant from the lung. Because O_3 itself is not thought to penetrate the lung, these systemic effects are either secondary to lung alterations or result from reaction products of O_3. Effects have been observed on clinical chemistry, white blood cells, red blood cells, the circulatory system, the liver, endocrine organs, and the central nervous system. Most of these effects cannot be interpreted adequately at this time and have not been investigated in humans, but it is of interest to note that O_3 exposures causing effects on the RT of animals cause a wide array of effects on other organs also.

Several behavior changes occur in response to O_3. For example, 0.12 ppm O_3 (6 h, rats) decreases wheel-running activity, and 0.5 ppm (1 min) causes mice to avoid exposure. These effects are not fully understood, but they may be related to lung irritation or decreased ability to exercise.

Although cardiovascular effects, such as slowed heart rate and decreased blood pressure, occur in O_3-exposed rats, some observed interactions with thermoregulation prevent qualitative extrapolation of these effects to humans at this time.

Developmental toxicity studies in pregnant rats summarized in the 1986 O_3 criteria document showed that levels up to about 2.0 ppm O_3 did not cause birth defects. Rat pups from females exposed to 1.0 ppm O_3 during certain periods of gestation weighed less or had delays in development of behaviors (e.g., righting, eye opening). No "classical" reproductive assays with O_3 were found.

Other studies have indicated that O_3 can affect some endocrine organs (i.e., pituitary-thyroid-adrenal axis, parathyroid gland). It appears that the liver has less ability to detoxify drugs after O_3 exposure, but assays of liver enzymes involved in xenobiotic metabolism are inconsistent.

Interactions of Ozone with Other Co-occurring Pollutants

Animal studies of the effects of O_3 in combination with other air pollutants show that antagonism, additivity, and synergism can result, depending on the animal species, exposure regimen, and health endpoint. Thus, these studies clearly demonstrate the major complexities and potential importance of interactions but do not provide a scientific basis for predicting the results of interactions under untested ambient exposure scenarios.

1.7 Human Health Effects of Ozone and Related Photochemical Oxidants

This section summarizes key effects associated with exposure to O_3, the major component of photochemical oxidant air pollution that is clearly of most concern to the health of the human population. Another, often co-occurring photochemical oxidant component of "smog" is PAN, but this compound has been demonstrated to be primarily responsible for induction of smog-related eye irritation (stinging of eyes). Limited pulmonary function studies have shown no effects of PAN at concentrations below 0.13 to 0.30 ppm, which are much higher than the generally encountered ambient air levels in most cities.

Controlled Human Studies of Acute Ozone Effects

Effects on Lung Function

Controlled studies in healthy adult subjects have demonstrated O_3-induced decrements in pulmonary function, characterized by alterations in lung volumes and flow and airway resistance and responsiveness. Respiratory symptoms, such as cough and pain on deep inspiration, are associated with these changes in lung function.

Ozone-induced decreases in lung volume, specifically forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), largely can be attributed to decreases in inspiratory capacity (the ability to take a deep breath), although at higher exposure concentrations, there is clearly an additional component that is not volume dependent. Lung volumes recover to a large extent within 2 to 6 h; normal baseline function typically is reestablished within 24 h, but not fully with more severe exposures.

Ozone causes increased airway resistance and may cause reductions in expiratory flow and the FEV_1/FVC ratio.

Ozone causes an increase in airway responsiveness to nonallergenic stimuli (e.g., histamine, methacholine) in healthy and asthmatic subjects. There is no clear evidence of a relationship between O_3-induced lung volume changes and changes in airway responsiveness.

Inflammation and Host Defense Effects

Controlled studies in healthy adult subjects also indicate that O_3 causes an inflammatory response in the lungs characterized by elevated levels of PMNs, increased epithelial permeability, and elevated levels of biologically active substances (e.g., prostaglandins, proinflammatory mediators, cytokines).

Inflammatory responses to O_3 can be detected within 1 h after a single 1-h exposure with exercise to concentrations $\geq$0.3 ppm; the increased levels of some inflammatory cells and mediators persist for at least 18 h. The temporal response profile is not defined adequately, although it is clear that the time course of response varies for different mediators and cells.

Lung function and respiratory symptom responses to O_3 do not seem to be correlated with airway inflammation.

Ozone also causes inflammatory responses in the nose, marked by increased numbers of PMNs and protein levels suggestive of increased permeability.

Alveolar macrophages removed from the lungs of human subjects after 6.6 h of exposure to 0.08 and 0.10 ppm O_3 have a decreased ability to ingest microorganisms, indicating some impairment of host defense capability.

Ozone Exposure-Response Relationships

Functional, symptomatic, and inflammatory responses to O_3 increase with increasing exposure dose of O_3. The major determinants of the exposure dose are O_3 concentration (C), exposure duration (T), and the amount of ventilation (V_E).

Exercise increases response to O_3 by increasing V_E (greater mass delivered), tidal volume, inspiratory flow (greater percentage delivery), and the intrapulmonary O_3 concentration.

Repeated daily exposures to relatively high levels of O_3 doses ($C \times T \times V_E$) causing substantial reductions in FEV_1 (≥20% decrement) typically cause exacerbation of the lung function and respiratory symptom responses on the second exposure day. However, attenuation of these responses occurs with continued exposures for a few days. Most inflammatory responses also attenuate; for example, the PMN influx is absent after five consecutive exposures.

Multihour exposures (e.g., for up to 7 h) to O_3 concentrations as low as 0.08 ppm cause small but statistically significant decrements in lung function, increases in respiratory symptoms, and increases in PMNs and protein levels. Ozone C is a more important factor than exercise V_E or T in predicting responses to multihour low-level O_3 exposure. There is clear evidence of a response plateau in terms of lung volume response to prolonged O_3 exposure. This evidence suggests that for a given combination of exercise and O_3 concentration (i.e., dose rate), there is a response plateau; continued exposure (i.e, increased T) at that dose rate will not increase response. Therefore, quantitative extrapolation of responses to longer exposure durations is not valid.

Mechanisms of Acute Pulmonary Responses

The mechanisms leading to the observed pulmonary responses induced by O_3 are beginning to be better understood. The available descriptive data suggest a number of mechanisms leading to the alterations in lung function and respiratory symptoms, including O_3 delivery to the tissue (i.e., the inhaled concentration, breathing pattern, airway geometry; O_3 reactions with the airway lining fluid and epithelial cell membranes; local tissue responses, including injury and inflammation; and stimulation of neural afferents (bronchial C-fibers) and the resulting reflex responses and symptoms. The cyclooxygenase inhibitors block production of prostaglandin E_2 and interleukin-6 as well as reduce lung volume responses; however, these drugs do not reduce inflammation and levels of cell damage markers such as lactate dehydrogenase.

Effects on Exercise Performance

Maximal oxygen uptake, a measure of peak exercise performance capacity, is reduced in healthy young adults if preceded by O_3 exposures sufficient to cause marked changes in lung function (i.e., decreases of at least 20%) and increased subjective symptoms of respiratory discomfort. Limitations in exercise performance may be related to increased symptoms, especially those related to breathing discomfort.

Factors Modifying Responsiveness to Ozone

Many variables have the potential for influencing responsiveness to O_3; however, most are addressed inadequately in the available clinical data to make definitive conclusions.

Active smokers are less responsive to O_3 exposure, which may reverse following smoking cessation, but these results should be interpreted with caution.

The possibility of age-related differences in response to O_3 has been explored, although young adults historically have provided the subject population for controlled human studies. Children and adolescents have lung volume responses to O_3 similar to those of young adults, but lack respiratory symptoms. Pulmonary function responsiveness in adults appears to decrease with age, whereas symptom rates remain similar to young adults. Group mean lung function responses of adults over 50 years of age are less than those of children, adolescents, and young adults.

The available data have not demonstrated conclusively that men and women respond differently to O_3. Likewise, pulmonary function responses of women have been compared during different phases of the menstrual cycle, but the results are conflicting. If gender differences exist for lung function responsiveness to O_3, they are not based on hormonal changes, differences in lung volume, or the ratio of FVC to V_E.

There is no compelling evidence, to date, suggesting that any ethnic or racial groups have a different distribution of responsiveness to O_3.

Seasonal and ambient factors may vary responsiveness to O_3, but further research is needed to determine how they affect individual subjects. Individual sensitivity to O_3 may vary throughout the year, related to seasonal variations in ambient O_3 concentrations.

The specific inhalation route appears to be of minor importance in exercising adults. Exposure to O_3 by oral breathing (i.e., mouthpiece) yields results similar to exposure by oronasal breathing (i.e., chamber exposures).

Population Groups at Risk from Ozone Exposure

Population groups that have demonstrated increased responsiveness to ambient concentrations of O_3 consist of exercising healthy and asthmatic individuals, including children, adolescents, and adults.

Available evidence from controlled human studies on subjects with preexisting disease suggests that mild asthmatics have similar lung volume responses, but greater airway resistance responses to O_3 than nonasthmatics; and that moderate asthmatics may have, in addition, greater lung volume responses than nonasthmatics.

Of all the other population groups studied, those with preexisting limitations in pulmonary function and exercise capacity (e.g., chronic obstructive pulmonary disease, chronic bronchitis, ischemic heart disease) would be of primary concern in evaluating the health effects of O_3. Unfortunately, limitations of subject selection, standardized methods of subject characterization, and range of exposure hamper the ability to make definitive conclusions regarding the relative responsiveness of most chronic disease subjects.

Effects of Ozone Mixed with Other Pollutants

No significant enhancement of respiratory effects has been demonstrated consistently for simultaneous exposures of O_3 mixed with SO_2, NO_2, H_2SO_4, HNO_3, particulate aerosols, or combinations of these pollutants. It is fairly well established that simultaneous exposure of healthy adults and asthmatics to mixtures of O_3 and other pollutants

for short periods of time (<2 h) induces pulmonary function responses not significantly different from those following O_3 alone when studies are conducted at the same O_3 concentration. Exposure to PAN has been reported to induce greater pulmonary function responses than exposure to O_3 alone, but at PAN concentrations (>0.27 ppm) much higher than ambient levels. Unfortunately, only a limited number of pollutant combinations and exposure protocols have been investigated, and subject groups are small and are representative of only small portions of the general population. Thus, much is unknown about the relationships between O_3 and the complex mix of pollutants found in the ambient air.

Prior exposure to O_3 in asthmatics may cause an increase in response to other pollutant gases, especially SO_2. Likewise, prior exposure to other pollutants can enhance responses to O_3 exposure.

Controlled Human Studies of Ambient Air Exposures

Mobile laboratory studies of lung function and respiratory symptoms in a local subject population exposed to ambient photochemical oxidant pollution provide quantitative information on exposure-response relationships for O_3. A series of these studies from Los Angeles has demonstrated pulmonary function decrements at mean ambient O_3 concentrations of 0.14 ppm in exercising healthy adolescents and increased respiratory symptoms and pulmonary function decrements at 0.15 ppm in heavily exercising athletes and at 0.17 ppm in lightly exercising healthy and asthmatic subjects. Comparison of the observed effects in exercising athletes with controlled chamber studies at comparable O_3 concentrations showed no significant differences in lung function and symptoms, suggesting that coexisting ambient pollutants have a minimal contribution to the measured responses under typical summer ambient conditions in Southern California.

Field and Epidemiology Studies of Ambient Air Exposures

Individual-level field studies and aggregate-level time-series studies have addressed the acute effects of O_3 on lung function decrements and increased morbidity and mortality in human populations exposed to real-world conditions of O_3 exposure.

Camp and exercise studies of lung function provide quantitative information on exposure-response relationships linking lung function declines with O_3 exposure occurring in ambient air. Combined statistical analysis of six recent camp studies in children yields an average relationship between decrements in FEV_1 and previous-hour O_3 concentration of −0.50 mL/ppb. Two key studies of lung function measurements before and after well-defined outdoor exercise events in adults have yielded exposure-response slopes of −0.40 and −1.35 mL/ppb. The magnitude of pulmonary function declines with O_3 exposure is consistent with the results of controlled human studies.

Daily life studies support a consistent relationship between O_3 exposure and acute respiratory morbidity in the population. Respiratory symptoms (or exacerbation of asthma) and decrements in peak expiratory flow rate are associated with increasing ambient O_3, particularly in asthmatic children; however, concurrent temperature, particles, acidity (hydrogen ions), aeroallergens, and asthma severity or medication status also may contribute as independent or modifying factors. Aggregate results show greater responses in asthmatic individuals than in nonasthmatics, indicating that asthmatics constitute a sensitive group in epidemiologic studies of oxidant air pollution.

Summertime daily hospital admissions for respiratory causes in various locations of eastern North America have consistently shown a relationship with ambient levels of O_3, accounting for approximately one to three excess respiratory hospital admissions per hundred parts per billion O_3 per million persons. This association has been shown to remain even after statistically controlling for the possible confounding effects of temperature and copollutants (e.g., hydrogen ions, sulfate, and particles less than 10 μm), as well as when considering only concentrations below 0.12 ppm O_3.

Many of the time-series epidemiology studies looking for associations between O_3 exposure and daily human mortality have been difficult to interpret because of methodological or statistical weaknesses, including the a failure to account for other pollutant and environmental effects. One of the two most useful new studies on O_3-mortality found a small but statistically significant association in Los Angeles when peak 1-h maximum O_3 concentrations reached concentrations greater than 0.2 ppm during the study period. A second study in regions with lower ($\leq$0.15 ppm) maximum 1-h O_3 concentrations (St. Louis, MO, and Kingston-Harriman, TN) did not detect a significant O_3 association with mortality.

Only suggestive epidemiologic evidence exists for health effects of chronic ambient O_3 exposure in the population. All of the available studies of chronic respiratory system effects in exposed children and adults are limited by a simplistic assignment of exposure or by their inability to isolate potential effects related to O_3 from those of other pollutants, especially particles.

1.8 Extrapolation of Animal Toxicological Data to Humans

There have been significant advances in O_3 dosimetry since 1986 that better enable quantitative extrapolation with marked reductions in uncertainty. Experiments and models describing the uptake efficiency and delivered dose of O_3 in the RT of animals and humans are beginning to present a clearer picture than has existed previously.

The total RT uptake efficiency of rats at rest is approximately 50%. Within the RT of the rat, 50% of the O_3 taken up by the RT is removed in the head, 7% in the larynx/trachea, and 43% in the lungs.

In humans at rest, the total RT uptake efficiency is between 80 and 95%. Total RT uptake efficiency falls as flow increases. As tidal volume increases, uptake efficiency increases and flow dependence lessens. Pulmonary function response data and O_3 uptake efficiency data in humans generally indicate that the mode of breathing (oral versus nasal versus oronasal) has little effect on upper RT or on total RT uptake efficiency, although one study suggests that the nose has a higher uptake efficiency than the mouth.

When all of the animal and human in vivo O_3 uptake efficiency data are compared, there is a good degree of consistency across data sets. This agreement raises the level of confidence with which these data sets can be used to support dosimetric model formulations.

Several mathematical dosimetry models have been developed since 1986. Generally, the models predict that net O_3 dose to lung lining fluid plus tissue gradually decreases distally from the trachea toward the end of the tracheobronchial region and then rapidly decreases in the pulmonary region.

When the dose of O_3 to lung tissue is computed theoretically, it is found to be very low in the trachea; to increase to a maximum in the terminal bronchioles of the first generation pulmonary region; and then to decrease rapidly, moving further into the pulmonary region. The increased tidal volume and flow, associated with exercise in humans, shifts O_3 dose further into the periphery of the lung and causes a disproportionate increase in distal lung dose.

Predictions of delivered dose have been used to investigate both acute and chronic O_3 responses in the context of intra- and interspecies comparisons. In the case of intraspecies comparisons, for example, the distribution of predicted O_3 tissue dose to a ventilatory unit in a rat as a function of distance from the bronchoalveolar duct junction is very consistent with the distribution of alveolar wall thickening. In the case of interspecies comparisons (using the delivered O_3 dose to the proximal alveolar regions), although the functional responses (e.g., rapid, shallow breathing) differ markedly between rats and humans, there is similarity of acute dose-response patterns in inflammation (influx of cells and protein) among species, with humans and guinea pigs more responsive than rats and rabbits, and similarity of chronic dose-response patterns for increased alveolar interstitial thickness in the CAR of the lung, with monkeys being more responsive than humans and rats less responsive. In other words, the quantitative relationship between animal and human responses is dependent on the animal species and the endpoint.

In summary, there is an emerging consistency among a variety of O_3 dosimetry data sets and between the experimental data and theoretical predictions of O_3 dose. The convergence of experimental data with theoretical predictions lends a degree of confidence to the use of theoretical models to predict total and regional O_3 dose. The use of O_3 dosimetry data and models is beginning to provide a useful extrapolation of effects between animals and humans. The data and models have thus far helped demonstrate that humans may be more responsive to O_3 than rats, but less responsive than monkeys with respect to acute and chronic inflammatory responses. However, the monkey, with its similarity to the human in distal airway structure, provides chronic effects data that may best reflect the degree to which a comparably exposed human would respond. These findings, therefore, suggest that long-term exposure to O_3 could impart a chronic effect in humans.

1.9 Integrative Summary of Ozone Health Effects

This section summarizes the primary conclusions derived from an integration of the known effects of O_3 provided by animal toxicological, human clinical, and epidemiological studies.

1. What are the effects of short-term (<8-h) exposures to ozone?

Recent epidemiology studies addressing the effects of short-term ambient exposure to O_3 in the population have yielded significant associations with a wide range of health outcomes, including lung function decrements, aggravation of preexisting respiratory disease, increases in daily hospital admissions and emergency department visits for respiratory causes, and increased mortality. Results from lung function epidemiology studies generally are consistent with the experimental studies in laboratory animals and humans.

Short-term O_3 exposure of laboratory animals and humans causes changes in pulmonary function, including tachypnea (rapid, shallow breathing), decreased lung volumes and flows, and increased airway responsiveness to nonspecific stimuli. Increased airway resistance occurs in both humans and laboratory animals, but typically at higher exposure levels than other functional endpoints. In addition, adult human subjects experience O_3-induced symptoms of airway irritation such as cough or pain on deep inspiration. The changes in pulmonary function and respiratory symptoms occur as a function of exposure concentration, duration, and level of exercise. Adult human subjects with mild asthma have responses in lung volume and airway responsiveness to bronchoconstrictor drugs that are qualitatively similar to those of nonasthmatics. Respiratory symptoms are also similar, but wheezing is a prevalent symptom in O_3-exposed asthmatics in addition to the other demonstrated symptoms of airway irritation. Airway resistance, however, increases relatively more in asthmatics from an already higher baseline. Recovery from the effects of O_3 on pulmonary function and symptoms is usually complete within 24 h of the end of exposure, although other responses may persist somewhat longer.

- An association between daily mortality and O_3 concentration for areas with high O_3 levels (e.g., Los Angeles) has been suggested, although the magnitude of such an effect is unclear.
- Increased O_3 levels are associated with increased hospital admissions and emergency department visits for respiratory causes. Analyses from data in the northeastern United States suggest that O_3 air pollution is associated with a substantial portion (on the order of 10 to 20%) of all summertime respiratory hospital visits and admissions.
- Pulmonary function in children at summer camps in southern Ontario, Canada, in the northeastern United States, and in Southern California is associated with O_3 concentration. Meta-analysis indicates that a 0.5-mL decrease in FEV_1 is associated with a 1-ppb increase in O_3 concentration. For preadolescent children exposed to 120 ppb (0.12 ppm) ambient O_3, this amounts to an average decrement of 2.4 to 3.0% in FEV_1. Similar responses are reported for children and adolescents exposed to O_3 in ambient air or O_3 in purified air for 1 to 2 h while exercising.
- Pulmonary function decrements generally are observed in healthy subjects (8 to 45 years of age) after 1 to 3 h of exposure as a function of the level of exercise performed and the O_3 concentration inhaled during the exposure. Group mean data from numerous controlled human exposure and field studies indicate that, in general, statistically significant pulmonary function decrements beyond the range of normal measurement variability (e.g., 3 to 5% for FEV_1) occur
  (1) at >0.50 ppm O_3 when at rest,
  (2) at >0.37 ppm O_3 with light exercise (slow walking),
  (3) at >0.30 ppm O_3 with moderate exercise (brisk walking),
  (4) at >0.18 ppm O_3 with heavy exercise (easy jogging), and
  (5) at >0.16 ppm O_3 with very heavy exercise (running).
  Smaller group mean changes (e.g., <5%) in FEV_1 have been observed at lower O_3 concentrations than those listed above. For example, FEV_1 decrements have been shown to occur with very heavy exercise in healthy adults at 0.15 to 0.16 ppm O_3, and such effects may occur in healthy young adults at levels as

low as 0.12 ppm. Also, pulmonary function decrements have been observed in children and adolescents at concentrations of 0.12 and 0.14 ppm O_3 with heavy exercise. Some individuals within a study may experience FEV_1 decrements in excess of 15% under these exposure conditions, even when the group mean decrement is less than 5%.

- For exposures of healthy subjects performing moderate exercise during longer duration exposures (6 to 8 h), 5% group mean decrements in FEV_1 were observed at
  (1) 0.08 ppm O_3 after 5.6 h,
  (2) 0.10 ppm O_3 after 4.6 h, and
  (3) 0.12 ppm O_3 after 3 h.
  For these same subjects, 10% group mean FEV_1 decrements were observed at 0.12 ppm O_3 after 5.6 and 6.6 h. As in the shorter duration studies, some individuals experience changes larger than those represented by the group mean changes.
- An increase in the incidence of cough has been reported at O_3 concentrations as low as 0.12 ppm in healthy adults during 1 to 3 h of exposure with very heavy exercise. Other respiratory symptoms, such as pain on deep inspiration, shortness of breath, and lower respiratory scores (a combination of several symptoms), have been observed at 0.16 to 0.18 ppm O_3 with heavy and very heavy exercise. Respiratory symptoms also have been observed following exposure to 0.08, 0.10, and 0.12 ppm O_3 for 6.6 h with moderate levels of exercise.
- Increases in nonspecific airway responsiveness in healthy adults have been observed after 1 to 3 h of exposure to 0.40 but not 0.20 ppm O_3 at rest and have been observed at concentrations as low as 0.18 but not to 0.12 ppm O_3 during exposure with very heavy exercise. Increases in nonspecific airway responsiveness during 6.6-h exposures with moderate levels of exercise have been observed at 0.08, 0.10, and 0.12 ppm O_3.

Short-term O_3 exposure of laboratory animals and humans disrupts the barrier function of the lung epithelium, permitting materials in the airspaces to enter lung tissue, allowing cells and serum proteins to enter the airspaces (inflammation), and setting off a cascade of responses.

- Increased levels of PMNs and protein in lung lavage fluid have been observed following exposure of healthy adults to 0.20, 0.30, and 0.40 ppm with very heavy exercise and have not been studied at lower concentrations for 1- to 3-h exposures. Increases in lung lavage protein and PMNs also have been observed at 0.08 and 0.10 ppm O_3 during 6.6-h exposures with moderate exercise; lower concentrations have not been tested.

Short-term O_3 exposure of laboratory animals and humans impairs AM clearance of viable and nonviable particles from the lungs and decreases the effectiveness of host defenses against bacterial lung infections in animals and perhaps in humans. The ability of AMs to engulf microorganisms is decreased in humans exposed to 0.08 and 0.10 ppm O_3 for 6.6 h with moderate exercise.

2. What are the effects of repeated, short-term exposures to ozone?

During repeated short-term exposures, some of the O_3-induced responses are partially or completely attenuated. Over a 5-day exposure, pulmonary function changes are typically greatest on the second day, but return to control levels by the fifth day of exposure. Most of the inflammatory markers (e.g., PMN influx) also attenuate by the fifth day of exposure, but markers of cell damage (e.g., lactate dehydrogenase enzyme activity) do not attenuate but continue to increase. Attenuation of lung function decrements is reversed following 7 to 10 days without O_3. Some inflammatory markers also are reversed during this time period, but others still show attenuation even after 20 days without O_3. The mechanisms and impacts involved in attenuation are not known, although animal studies show that the underlying cell damage continues throughout the attenuation process. In addition, attenuation may alter the normal distribution of O_3 within the lung, allowing more O_3 to reach sensitive regions, possibly affecting normal lung defenses (e.g., PMN influx in response to inhaled microorganisms).

3. What are the effects of long-term exposures to ozone?

Available data indicate that exposure to O_3 for months and years causes structural changes in several regions of the RT, but effects may be of the greatest importance in the CAR (where the alveoli and conducting airways meet); this region typically is affected in most chronic airway diseases of the human lung. This information on O_3 effects in the distal lung is extrapolated from animal toxicological studies because, to date, comparable data are not available from humans. The apparent lack of reversal of effects during periods of clean air exposure raises concern that seasonal exposures may have a cumulative impact over many years. The role of adaptive processes in this response is unknown but may be critically dependent on the temporal frequency or profile of exposure. Furthermore, the interspecies diversity in apparent sensitivity to the chronic effects of O_3 is notable, with the rat representing the lower limit of response, and the monkey the upper limit. Epidemiological studies attempting to associate chronic health effects in humans with long-term O_3 exposure provide only suggestive evidence that such a linkage exists.

Long-term exposure of one strain of female mice to high O_3 levels (1 ppm) caused a small, but statistically significant increase in lung tumors. There was no concentration-response relationship, and rats were not affected. Genotoxicity data are either negative or weak. Given the nature of the database, the effects in one strain of mice cannot yet be extrapolated qualitatively to humans. Ozone (0.5 ppm) did not show tumor-promoting activity in a chronic rat study.

4. What are the effects of binary pollutant mixtures containing ozone?

Combined data from laboratory animal and controlled human exposure studies of O_3 support the hypothesis that coexposure to pollutants, each at low-effect levels, may result in effects of significance. The data from human studies of O_3 in combination with NO_2, SO_2, H_2SO_4, HNO_3, or CO show no more than an additive response on lung spirometry or respiratory symptoms. The larger number of laboratory animal studies with O_3 in mixture with NO_2 and H_2SO_4 show that effects can be additive, synergistic, or even antagonistic, depending on the exposure regimen and the endpoint studied. This issue of exposure to copollutants remains poorly understood, especially with regard to potential chronic effects.

5. What population groups are at risk as a result of exposure to ozone?

Identification of population groups that may show increased sensitivity to O_3 is based on their biological responses to O_3, preexisting lung disease (e.g., asthma), activity patterns, personal exposure history, and personal factors (e.g., age, nutritional status).

The predominant information on the health effects of O_3 noted above comes from clinical and field studies on healthy, nonsmoking, exercising subjects, 8 to 45 years of age. These studies demonstrate that, among this group, there is a large variation in sensitivity and responsiveness to O_3, with at least a 10-fold difference between the most and least responsive individuals. Individual sensitivity to O_3 also may vary throughout the year, related to seasonal variations in ambient O_3 exposure. The specific factors that contribute to this large intersubject variability, however, remain undefined. Although differences in response may be due to the dosimetry of O_3 in the RT, available data show little difference on O_3 deposition in the lungs for inhalation through the nose or mouth.

Daily life studies reporting an exacerbation of asthma and decrease in peak expiratory flow rates, particularly in asthmatic children, appear to support the controlled studies; however, those studies may be confounded by temperature, particle or aeroallergen exposure, and asthma severity of the subjects or their medication use. In addition, field studies of summertime daily hospital admissions for respiratory causes show a consistent relationship between asthma and ambient levels of O_3 in various locations in the northeastern United States, even after controlling for independent contributing factors. Controlled studies on mild asthmatics suggest that they have similar lung volume responses but greater airway resistance changes to O_3 than nonasthmatics. Furthermore, limited data from studies of moderate asthmatics suggest that this group may have greater lung volume responses than nonasthmatics.

Other population groups with preexisting limitations in pulmonary function and exercise capacity (e.g., chronic obstructive pulmonary disease, chronic bronchitis, ischemic heart disease) would be of primary concern in evaluating the health effects of O_3. Unfortunately, not enough is known about the responses of these individuals to make definitive conclusions regarding their relative responsiveness to O_3. Indeed, functional effects in these individuals with reduced lung function may have greater clinical significance than comparable changes in healthy individuals.

Currently available data follow on personal factors or personal exposure history known or suspected of influencing responses to O_3.

- Human studies have identified a decrease in pulmonary function responsiveness to O_3 with increasing age, although symptom rates remain similar. Toxicological studies are not easily interpreted but suggest that young animals are not more responsive than adults.
- Available toxicological and human data have not demonstrated conclusively that males and females respond differently to O_3. If gender differences exist for lung function responsiveness to O_3, they are not based on differences in baseline pulmonary function.
- Data are not adequate to determine whether any ethnic or racial group has a different distribution of responsiveness to O_3. In particular, the responses of nonwhite asthmatics have not been investigated.

- Information derived from O_3 exposure of smokers is limited. The general trend is that smokers are less responsive than nonsmokers. This reduced responsiveness may wane after smoking cessation.
- Although nutritional status (e.g., vitamin E deficiency) makes laboratory rats more susceptible to O_3-induced effects, it is not clear if vitamin E supplementation has an effect in human populations. Such supplementation has no or minimal effect in animals. The role of such antioxidant vitamins in O_3 responsiveness, especially their deficiency, has not been well studied.

Based on information presented in this document, the population groups that have demonstrated increased responsiveness to ambient concentrations of O_3 consist of exercising, healthy and asthmatic individuals, including children, adolescents, and adults.