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Air Quality Criteria for Ozone and Related Photochemical Oxidants

Review Draft (Do Not Cite or Quote)

Chapter 1. Executive Summary and Chapter 9. Integrative Summary of Ozone Health Effects

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Air Quality Criteria for Ozone and Related Photochemical Oxidants

Chapter 1. Executive Summary

and

Chapter 9. Integrative Summary of Ozone Health Effects

Environmental Criteria and Assessment Office
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PREFACE

In 1971, the U.S. Environmental Protection Agency (EPA) promulgated National Ambient Air Quality Standards (NAAQS) to protect the public health and welfare from adverse effects of photochemical oxidants. In 1979, the chemical designation of the standards was changed from photochemical oxidants to ozone (O_3). This document, therefore, focuses primarily on the scientific air quality criteria for O_3 and, to a lesser extent, for other photochemical oxidants like hydrogen peroxide and the peroxyacyl nitrates.

The EPA promulgates the NAAQS on the basis of scientific information contained in air quality criteria documents. The previous O_3 criteria document, *Air Quality Criteria for Ozone and Other Photochemical Oxidants*, was released in August 1986 and a supplement, *Summary of Selected New Information on Effects of Ozone on Health and Vegetation*, was released in January 1992. These documents were used as the basis for a March 1993 decision by EPA not to revise the existing 1-h NAAQS for O_3. That decision, however, did not take into account some of the newer scientific data that became available after the 1986 criteria document. This revised air quality criteria document for O_3 and related photochemical oxidants critically evaluates and assesses the latest scientific data associated with exposure to concentrations of these pollutants found in ambient air. Emphasis is placed on presentation of health and environmental effects data; however, other scientific data are presented and evaluated in order to provide a better understanding of the nature, sources, distribution, measurement, and concentrations of O_3 and related photochemical oxidants and their precursors in the environment. The document is not an exhaustive literature review; rather it assesses the most pertinent literature available through 1993.

The chapters in this volume summarize and interpret key information drawn from the other, more detailed chapters (Chapters 2 through 8) of the present document, which were prepared and peer reviewed by experts from various Federal and State governmental offices, academia, and private industry for use by EPA to support decision making regarding potential risks to public health and welfare. The Environmental Criteria and Assessment Office of EPA's Office of Health and Environmental Assessment acknowledges with appreciation the contributions provided by these authors and reviewers as well as the diligence of its staff and contractors in the preparation of this document at the request of the Office of Air Quality Planning and Standards.

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1. EXECUTIVE SUMMARY

1.1 INTRODUCTION

The external review draft document *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. 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. This is followed by Chapter 5, dealing with the environmental effects; Chapters 6, 7, and 8 discuss, respectively, animal toxicological studies, human health effects, and the extrapolation of animal toxicological data to humans. The last chapter, Chapter 9, provides an integrative, interpretative evaluation of health effects associated with exposure to O_3. The following subsections follow the chapter organization of the external review draft.

1.2 LEGISLATIVE AND REGULATORY BACKGROUND

The EPA is required under Sections 108 and 109 of the Clean Air Act to periodically evaluate the air quality criteria that reflect the latest scientific information relevant to review of the O_3 NAAQS. These air quality criteria, contained in the criteria document, 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 criteria document was released in 1986, and a supplement was released in 1992. These documents were used as the basis for a March 1993 decision by EPA to not revise the existing 1-h NAAQS for O_3 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 the concentrations of O_3 and related photochemical oxidants that are found in ambient air.

1.3 TROPOSPHERIC OZONE AND ITS PRECURSORS

Tropospheric Ozone Chemistry

Ozone is found in the stratosphere, the "free" troposphere, and the planetary boundary layer (PBL) of the earth's atmosphere. 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 earth's surface) through certain cloud processes; and photochemical formation from precursors, notably methane (CH_4), carbon monoxide (CO), and nitrogen oxides (NO_x). In the PBL, O_3 occurs as the result of downward mixing from the stratosphere and free troposphere and as the result of photochemical processes occurring within the PBL.

The photochemical production of O_3 and other oxidants found at the earth's surface (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, reactive volatile organic compounds (VOCs) and NO_x. The only significant initiator of the photochemical production of O_3 in the polluted troposphere is the photolysis of nitrogen dioxide (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 O_2 and NO_2. These cyclic reactions attain equilibrium in the absence of VOCs. In the presence, however, 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 relatively "clean" areas of the PBL. The VOCs found in polluted ambient air are 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 and peroxyacyl nitrates (PANs) 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 radical, NO_3. Reactions with NO_3 radicals appear to constitute major sinks for alkenes, cresols, and some other compounds, although alkyl nitrate chemistry is not well characterized.

Most inorganic gas-phase processes, that is, 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, with concomitant production of O_3, 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 mechanisms, products, and product yields in O_3 air quality models. Major uncertainties in current understanding of the atmospheric chemistry of the VOCs include (1) chemistry of alkyl nitrate formation, (2) products and reaction rates for >C4 alkanes and for branched

alkanes, (3) mechanisms and products of alkene-O_3 reactions, and (4) products of aromatic hydrocarbons in both urban and rural atmospheres.

It should be noted that the atmospheric chemical processes involved in the photooxidation of VOCs and the formation of O_3 and other photochemical oxidants can lead also to the formation of OH radicals and of particulate-phase organic compounds. The OH radicals produced can not only oxidize VOCs but can also react with NO_2 and sulfur dioxide (SO_2) to form nitric and sulfuric acids, respectively, 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, such as 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 ($\leq$50 km) to neighboring rural and urban areas has been well documented and was described in the 1986 EPA criteria document for O_3. 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 are characterized by (1) synoptic-scale subsidence of air in the free troposphere, resulting in development of an elevated inversion layer; (2) relatively low wind speeds associated with the weak horizontal pressure gradient around a surface high pressure system; (3) a lack of cloudiness; and (4) 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 with variations in O_3 levels. An association, however, between tropospheric O_3 concentrations and tropospheric 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. In the Southern Oxidant Study, for example, regression techniques were successfully used to forecast O_3 levels to ensure that specialized measurements were made on appropriate days.

Precursors

Nitrogen Oxides Emissions

Anthropogenic NO_x is associated with combustion processes. The primary pollutant emitted is NO formed at high combustion temperatures from the nitrogen and oxygen in 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 generation and highway vehicles. Because a large proportion of anthropogenic NO_x emissions come from distinct point sources, published annual estimates are thought to be very reliable.

Natural NO_x sources include stratospheric intrusion, oceans, lightning, soils, and wildfires. Lightning and soil emissions are the only two significant natural sources of NO_x in the United States. Combined natural sources contribute about 2.2 Tg of NO_x to the troposphere over the continental United States. Uncertainties in natural NO_x inventories are much larger, however, than for anthropogenic NO_x emissions.

Volatile Organic Compound Emissions

Hundreds of VOCs, commonly containing from 2 to about 12 carbon atoms, are emitted by evaporative and combustion processes from a large number of source types. Total U.S. VOC emissions in 1991 were estimated at 21.0 Tg. The two largest source categories were industrial processes (10.0 Tg) and 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, both for 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.

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

Concentrations of Volatile Organic Compounds in Ambient Air

The VOCs most frequently analyzed in ambient air are the nonmethane hydrocarbons (NMHCs). Morning concentrations (6:00 a.m. to 9:00 a.m.) have been measured most often because of the use of morning data in the Empirical Kinetics Modeling Approach (EKMA) and in air quality simulation models. Measurements made in 22 cities in 1984 and 19 cities in 1985 showed median NMHC concentrations ranging from 0.39 ppm C to 1.27 ppm C for 1984; and from 0.38 ppm C to 1.63 ppm C in 1985. Overall median values from all urban sites were about 0.72 ppm C in 1984 and 0.60 ppm C in 1985.

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 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 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. Median ratios ranged from 9.1 to 37.7 in 1984; in 1985, median ratios ranged from 6.5 to 53.2 in the cities studied. Rural NMOC/NO_x ratios tend to be higher than urban ratios. 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 (now 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 showed that vehicle exhaust was the dominant contributor to ambient VOCs in seven of eight U.S. cities studied. Whole gasoline contributions have been estimated to be equal to vehicle exhaust in one study and 20% of vehicle exhaust in a second study.

Estimates of biogenic VOCs at a downtown site in Atlanta 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, Columbus, and Atlanta; and for refinery emissions in Chicago.

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 has recently 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.

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 PANs are normally measured by gas chromatography using an electron capture detector (GC-ECD). Detection limits have now been extended to 1 to 5 ppt. The preparation of reliable calibration standards is difficult because PAN is unstable (explosive and subject to surface-related decomposition), but several methods are available.

Volatile Organic Compounds

Traditionally, NMHCs and other NMOCs have been measured by methods that employ a flame ionization detector (FID) as the sensing element that measures a change in ion intensity resulting from the combustion of air containing 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 FID. The main technique for speciated NMOC/NMHC measurements is cryogenic preconcentration followed by GC-FID. Systems for sampling and analysis of VOCs have now been developed that require no liquid cryogen for operation, yet provide sufficient resolution of species.

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 in current use for measuring gas-phase carbonyl compounds in ambient air, which is the high-performance liquid chromatography (HPLC) method employing 2,4-dinitrophenylhydrazine (DNPH) derivatization in a silica gel cartridge. Use of an O_3 scrubber has been recommended to prevent interference in this method by O_3 in ambient air. Several methods are available for preparing stable calibration mixtures.

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 presently exist for measurement of NO.

Chemiluminescence analyzers are the method 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. In practice, selective measurement of NO_x by this approach has proved difficult, and the NO_2 value inferred from such measurements may be significantly in error.

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.

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. They 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 acceptable 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 of 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 some 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 an urban area.

Grid-based, photochemical air quality models have their limitations as well. These are pointed out subsequently.

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 (a set of chemical reactions), representing the important 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, since 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 adequately simulated and then reducing hydrocarbon or NO_x emissions or both in the model inputs and assessing the effects of these reductions on O_3 in the region. 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 model output and the current form of the NAAQS for O_3. Uncertainties in models can obviously 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 (1) the Urban Airshed Model (UAM), (2) the California Institute of Technology/Carnegie Institute of Technology (CIT) model, (3) the Regional Oxidant Model (ROM), (4) the Acid Deposition and Oxidant Model (ADOM), and (5) the Regional Acid Deposition Model (RADM).

Conclusions

Urban air quality models are becoming readily available for application and have been applied in recent years in several urban areas. Significant progress has also been made in the development of regional models and the integration of state-of-the-art prognostic meteorological models as drivers.

Although there are still many uncertainties in photochemical air quality modeling, prime among which are emission inventories, models are nevertheless essential for regulatory analysis and constitute one of the major tools for attacking 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.

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 of the document, hourly average concentration and exposure information was summarized for urban, rural forested, and rural agricultural areas in the United States.

Because O_3 produced from urban area emissions is transported to more 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 than in urban areas and exposures may be higher than 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 the 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 is 21% lower than the 1983 average. The 1992 value is the lowest composite average of the past 10 years. The 1992 composite average is significantly less than all the previous nine years, 1983 to 1991. The relatively high O_3 concentrations in 1983 and 1988 were likely attributable in part to hot, dry stagnant conditions in some areas of the country that were especially conducive to O_3 formation.

Between 1991 and 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% between 1991 and 1992. The composite average of the second daily maximum concentrations decreased in 8 of the 10 EPA Regions between 1991 and 1992, and remained unchanged in Region VII. Except for Region VII, the 1992 regional composite means are lower than the corresponding 1990 levels.

Surface Concentrations

Published data provides 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 0.10 ppm.

On the basis of O_3 data from isolated monitoring sites, the EPA has indicated that a reasonable estimate of natural O_3 background concentration near sea level in the United States today, for an annual average, is from 0.020 to 0.035 ppm. This estimate included a 0.010- to 0.015-ppm contribution from the stratosphere and a 0.01-ppm contribution from photochemically affected biogenic NMHCs. An additional 0.010 ppm is possible from the photochemical reaction of biogenic methane. The EPA concluded that a reasonable estimate of natural O_3 background concentration for a 1-h daily maximum at sea level in the United States during the summer is on the order of 0.03 to 0.05 ppm. This estimate may be low, however, because available data from sites appearing to be isolated from anthropogenic sources in the western United States indicate that maximum hourly concentrations can reach 0.06 and 0.075 ppm with infrequent occurrences below 0.02 ppm (i.e., lack of scavenging).

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 for O_3 typically show a rise in concentration from low 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 late spring or in 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, and 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 will almost invariably 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. Some of these models include information on human activity patterns (i.e., the microenvironments people visit and the times they spend there). These models also

contain submodels depicting the sources and concentrations likely to be found in each microenvironment, including indoor, outdoor, and in-transit settings.

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.

Two distinct types of O_3 exposure models exist: those that focus narrowly on predicting indoor O_3 levels and those that focus on predicting O_3 exposures on a community-wide basis.

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 nitric acid (HNO_3). The concentrations of PAN that are of most concern are those to which vegetation could potentially be exposed, especially during daylight hours in agricultural areas. 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 upon 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 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 sulfuric acid, 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 portion 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 these important physiological processes 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 they require from the soil. In addition, loss of vigor increases susceptibility of trees and crops to insects and pathogens and impairs their ability to reproduce. 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 climates. In general, the more controlled conditions are most appropriate for investigating specific responses and for providing the scientific basis for interpreting and extrapolating results.

Mode of Action

Photosynthesis provides plants with the energy and structural building blocks necessary for their existence. The photosynthetic capacity of a plant (i.e., carbohydrate production) is an important aspect of plant response to stresses in natural environments and is strongly associated with leaf nitrogen content and with water movement. Continued acquisition of nitrogen and water uptake are necessary, if photosynthesis is to occur, and involves the

allocation of carbohydrates from the leaves to the roots. Leaf photosynthetic capacity is age dependent. As the plant grows, the canopy structure changes, altering the amount and angle of light hitting a leaf. Allocation of carbohydrates and nutrients to new leaves is especially important in stimulating growth production.

Ozone exposure results in a leaf-mediated plant response. Leaves are important regulators of plant stress response and function. As the major regulators of anatomical and morphological development of the shoot, they control the allocation of carbohydrates to the whole plant. The many regulatory systems contained in leaves change both as a function of leaf development and in response to different environmental stresses.

Only O_3 that enters the plant through stomata (openings in the leaves) can impair plant processes. In addition, an effect will occur only if sufficient O_3 reaches sensitive sites within leaf cells. Ozone injury will not be detected if (1) the rate of uptake is small enough for the plant to detoxify or metabolize O_3 or its derivatives, or (2) the plant is able to repair or compensate for its impacts at a rate equal to or greater than the rate of uptake. (If the rate of repair is very slow, there may be an effect.)

The uptake and movement of O_3 to sensitive cellular sites are subject to various biochemical and physiological controls. The magnitude of O_3-induced effects depends upon the physical environment of the plant, including both macro-and microclimatic factors, and the chemical environment of the plant, including other gaseous pollutants and biological factors. Visible foliar injury is usually the first indication of cellular plant response. Once sufficient O_3 enters the leaf, the plant can experience reduced photosynthesis, altered carbohydrate production and allocation, reduced plant vigor, reduced growth or yield or both, and sometimes death. The alterations in the biochemical and physiological processes mentioned above may occur with or without visible injury to the plant.

Reductions in photosynthesis caused by O_3 are likely to be accompanied by a shift in growth pattern that favors shoots. Plants compensate for differences in resource imbalances by allocating energy, water, and minerals to maintain optimal growth. Allocation of these resources to leaf repair or to new leaf formation and an overall reduction in carbohydrate formation decrease the availability of carbohydrates for both stem and root growth. Alteration of the normal allocation pattern affects all aspects of plant growth and reproduction.

Factors That Modify Plant Response

Plant response to O_3 may be modified by a variety of biological, chemical, and physical factors. Both the impact of environmental factors on plant response to O_3 and the effects of O_3 on the responses of plants to environmental factors have to be considered when determining the impact of oxidants on vegetation in the field.

Biological factors include those both within and external to the plant. Within the plant, its genetic composition and stage of development play critical roles in plant response to O_3 as well as other stresses. Different varieties or cultivars, as well as different individuals of a

species, due to differences in their genetic composition, are known to differ greatly in their responses to a given O_3 exposure.

The magnitude of the response of a particular species or variety depends on such environmental factors as temperature and humidity, soil moisture and nutrition, exposure to other pollutants or agricultural spray chemicals, and interaction with plant pests and pathogens. In other words, the plant's present and past environmental mileu, 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. For example, exposure to O_3 reduces the ability of trees to withstand winter injury caused by freezing temperatures and influences the success of pest and fungal infections by decreasing tree vigor.

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 to characterize exposure-response in plants. Though 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 (1) implies that all concentrations of O_3 are equally effective in causing plant responses, and (2) minimizes the contributions of the peak concentrations to the response. Present evidence suggests that higher concentrations, episodic peak occurrences, and duration of exposure have a relatively greater role in producing plant effects than mean concentrations; therefore, an index that cumulates hourly concentrations 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. From the toxicological perspective, it is the peak occurrences or concentrations above an unidentified effect level that are most likely to have an impact. Effects on vegetation appear when the amount of pollutant that has entered a plant exceeds its ability to repair or compensate for the impact.

An index of ambient exposure that relates well to plant response should directly or indirectly incorporate both environmental influences, (e.g., temperature, humidity, and soil-moisture status) and exposure dynamics.

No experimental studies have been designed specifically to evaluate the adequacy of the various peak-weighted indices that have been proposed. In retrospective analyses when 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,

and W126) all performed equally well, and it is not possible to distinguish between them on the basis of statistical fits of the data.

Exposure-Response of Plant Species

The number of crop species/cultivars for which information regarding O_3 exposure responses are available encompasses a mere fraction of the total of cultivated crops and even a smaller fraction of native plants. The emphasis of experimental studies has usually 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 undoubtedly varies 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 greater than 16 days. When the exposure period was decreased to 10 days, the O_3 concentration required to cause injury was increased to 0.1 ppm. A short, 6-day exposure further increased the concentration to 0.30 ppm. The exposure and concentration periods apply today 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 0.1 ppm for 4 h.

Several conclusions were drawn in the 1986 criteria document from the various experimental approaches used to estimate crop yield loss.

1. Ambient O_3 concentrations are sufficiently elevated in several regions of the country to impair growth and yield of plants. This is clearly 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 extrapolation to plants not studied experimentally. Both approaches mentioned above indicate that effects occur with only a few exposures above 0.08 ppm.

2. Several plant species exhibited growth and yield effects when the mean O_3 concentration exceeded 0.05 ppm for 4 to 6 h/day for at least 2 weeks.

3. Data from regression studies conducted to develop an exposure-response function for estimating yield loss indicated that at least 50% of the species/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.

Based on research published since the 1986 criteria document, the following conclusions can be drawn.

1. Monitoring data from 80 to 200 nonurban sites for a period of 10 years were analyzed to determine the ambient 7-h growing-season average O_3 concentrations. For periods of 3 and 5 mo, concentrations ranged from 0.05 to 0.06 ppm and 0.047 to 0.054 ppm, respectively.

2. Open-top chamber studies comparing yields at ambient O_3 exposures with those in filtered air, and retrospective analyses of crop data, indicate that current ambient O_3 concentrations at some sites in the United States are sufficient to reduce the yield of major crops. These results also indicate that visible injury that reduces the market value of certain crops and ornamentals (spinach, petunia, geranium, for example) occurs at O_3 concentrations ranging from 0.04 to 0.10 ppm for 4 h.

3. A growing season SUMO6 exposure of 26.4 ppm·h, corresponding to a 7-h growing season mean of 0.049 ppm, is estimated to prevent a 10% yield loss from O_3 in 50% of the 54 experimental cases analyzed within this document. It is estimated that a 12-h growing season mean of 0.045 ppm would restrict yield losses to 10% in major crop species.

Effects on Natural Ecosystems

Most of the information dealing with the possible responses of ecosystems to O_3 stress is based on the studies in the San Bernardino Forest ecosystem. This mixed conifer forest ecosystem in southern California has been studied more than any other ecosystem in the United States, over 20 years. Chronic O_3 exposures for a period of 50 or more years have been associated with major changes in the ecosystem.

Data from an inventory conducted from 1968 through 1972 indicated that for 5 mo of the 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. Although PAN and NO_2 were present in these studies, symptoms of PAN injury on forest herb-layer plant species could not be distinguished from those caused by O_3, and NO_2 concentrations were too low to cause injury.

Ecosystem responses to stress are hierachial. They 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 up through more integrated levels of organ physiology (e.g., leaf, branch, root) to whole plant physiology, to populations within the stand (community), and then to the landscape level to produce ecosystem effects.

Therefore, to understand the effects of a stress, one must utilize a framework of hierarchical scales. This is particularly true of low-level stresses because only a small fraction of stresses at the molecular level become disturbances at the tree, stand, or landscape

level. Insect defoliation, for example, may severely reduce the growth of one or several branches, whereas growth of the tree appears not to be affected. The time required for a stress to be propagated from one level to the next determines how soon the effects of the stress can be observed or measured.

Foliar injury is usually the first visible indication of O_3 exposure in plants. In the San Bernardino forest, injury was first observed on ponderosa pine, with Jeffrey pine, white fir, black oak, incense cedar, and sugar pine following in decreasing order of sensitivity. Foliar injury on sensitive ponderosa and Jeffrey pine was observed when 24-h-average O_3 concentrations were 0.05 to 0.06 ppm.

The biochemical changes within the leaves were expressed as (1) visible foliar injury; (2) premature needle senescence; (3) a reduction in photosynthesis; (4) a reduction in carbohydrate production; (5) altered carbohydrate allocation, reduced plant vigor; and (6) a reduction in growth and reproduction.

Tree growth is the culmination of biochemical and physiological processes, during which plants use, accumulate, and store carbon compounds (energy) to build and maintain their structure. Within the leaves during the process of photosynthesis, carbon dioxide absorbed from the atmosphere is converted to carbohydrates. The water and minerals necessary for growth are absorbed from the soil through the roots. Growth and seed formation depend not only on photosynthesis and the uptake of water and mineral nutrients, but also on subsequent metabolic processes and the allocation of carbohydrates to the rest of the plant. Impairment of any of these processes can decrease plant vigor and affect plant growth and reproduction.

Trees each year require energy to grow new leaves and needles, to produce new fine roots, and to increase radial growth. Factors that inhibit photosynthesis and limit carbohydrate formation shift carbohydrate allocation to new leaves, whereas factors that limit nitrogen or water availability will shift allocation to the roots. Increased carbohydrate allocation to new needles and to repair foliage injured by O_3 can place a drain on carbohydrate reserves. Reduced tree vigor, the result of altered carbohydrate allocation, increases susceptibility of trees to insect pests and fungal pathogens and reduces the formation of mycorrhizae required for water and nutrient uptake.

Premature needle senescence, as observed in ponderosa and Jeffrey pine, not only decreases the amount of foliage available to carry on photosynthesis, but alters microorganismal succession on conifer needles, thus altering the detritis-forming process and subsequent nutrient cycling.

The primary effect on the more susceptible members of the San Bernardino forest community (e.g., ponderosa and Jeffrey pine) was that they were no longer able to compete effectively for essential nutrients, water, light, and space. As a consequence of altered competitive conditions in the community, there was a decline in the sensitive species, permitting the enhanced growth of more tolerant species. In addition, changes in the dominant individuals in the ecosystem altered the processes of energy flow and nutrient cycling. These changes that began with the biochemical changes within the leaves of the

sensitive conifers were ultimately transferred upward to the whole ecosystem, from the individual, to the population, to the community, and finally, to the ecosystem.

Functional ecosystem changes associated with the deaths in the conifer populations altered the processes of carbohydrate (energy) flow, mineral nutrient cycling, and water movement. The altered processes also changed, either directly or indirectly, the functioning of other living ecosystem components and ultimately changed the vegetational community patterns. The continuum of changes beginning with injury to the individual trees resulted in ecosystem breakdown and a shift in dominance from ponderosa and Jeffrey pine to O_3-tolerant shrub and oak species.

The effects that a stress at one level of organization will have on a higher level are determined by variability and compensation. Variability in response to stress can mean that not all trees are equally susceptible to O_3, as was observed, in the San Bernardino Forest, in the Appalachian Mountains, and the Cumberland Plateau of eastern Tennessee. Individuals of Ponderosa, Jeffrey, and eastern white pine were designated as being sensitive, intermediate or tolerant, based on their responses to O_3 exposure. Compensation means that plants tolerant to the stress are able either to detoxify or metabolize O_3 entering the leaves or to repair the injury.

Variability and compensation can also occur at the population level and, all populations do not respond equally. Plant populations can respond in four different ways: (1) no response, the individuals are tolerant to the stress; (2) mortality of all individuals and local extinction of the extremely sensitive population, the most severe response; (3) physiological accomodation, resulting in growth and reproductive success of tolerant individuals; and (4) differential response, some individuals of the population exhibit better growth and reproductive success due to genetically determined traits.

The properties of variability and compensation at the individual level determine (1) the severity of the response, (2) whether the effect will be propagated to the next level, and (3) the length of time required for the effect to be expressed functionally and structurally. In most instances, the time required for response at the individual level is a period of at least 3 to 5 years. Variability and compensation at the population level determine whether there will be an ecosystem response. These properties help to explain the differences in responses between the San Bernardino Forest and the forest ecosystems in the eastern United States.

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 are controller species. Their removal altered energy flow, nutrient cycling, and water movement in the San Bernardino forest ecosystem and changed the ecosystem. The removal of the eastern white pine, on the other hand, did not alter the functional ecosystem processes sufficiently to bring about a recognizable change within the ecosystems. For this reason, data dealing with the responses of one forest type (e.g., San Bernardino) may not be applicable to other forest types such as those found in the Appalachian Mountains.

Individual eastern white pine trees varied in sensitivity to O_3, and, because of physiological accommodation and compensation, effects at the population level were not reported in the forest stands in the Appalachian Mountains. Plantation plantings of eastern white pine (a monoculture) on the Cumberland Plateau, however, did exhibit overall growth reductions.

Mycorrhizae (fungus roots) function in the uptake of water and minerals (e.g., nitrogen, phosphorus) and are required for optimal growth by most plants. Nitrogen is a critical element in the process of photosynthesis and is usually the element in shortest supply in both agricultural and natural ecosystems. Increased carbohydrate allocation to new needles and to foliage repair limits allocation to the roots and reduces formation of the mycorrhizae needed to take up water, nitrogen, and other nutrients. Mycorrhizae can also protect plants from attack by root pathogens.

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 rayon-acetate, red rayon-acetate, and plum cotton, are resistant to O_3. On the other hand, anthraquinone dyes on nylon fibers are sensitive to fading from 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 like 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 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. Many organic pigments in particular 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 now outdated in terms of the O_3 concentrations, technologies, and supply-demand relationships that prevailed when the studies were conducted. 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

Respiratory Tract Effects of Ozone

Biochemical Targets of Ozone Interaction

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 to reach the tissue, raising the possibility that reaction products exert effects.

Lung Inflammation and Permeability Changes

Ozone disrupts the barrier function of the lung, resulting in (1) the entry of compounds in the airspaces into the blood and (2) the entry of serum components (e.g., protein) and white blood cells (especially polymorphonuclear leukocytes) 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 can also increase the thickness of the air-blood barrier.

Increases in permeability and inflammation have been observed at levels as low as 0.1 ppm (2 h/day, 6 days; rabbits). After acute exposures, the influence of the time of exposure (from 2 h 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

Ozone exposure results in alterations of all defense mechanisms of the respiratory tract, including mucociliary and alveolobronchiolar clearance, functional and biochemical activity of the alveolar macrophage, 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 toxic potential for a longer period of time.

Alveolar clearance mechanisms, which center on the functioning of alveolar macrophages, are altered by O_3. Short-term exposure to levels as low as 0.1 ppm (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. They 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 decrease the ability of alveolar macrophages 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.

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 that part dependent on B-cell function.

Dysfunction of host defense systems results in enhanced susceptibility to bacterial lung infections. For example, exposure 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, 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, 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

Ozone causes 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 (the junction of the conducting airways and gas exchange regions) is the primary target, possibly because this area is predicted to receive the greatest dose of O_3. The ciliated cells can be killed and are 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.

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 (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 change sometimes persists or increases further.

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 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.

There is no evidence that O_3 causes emphysema.

Effects on Pulmonary Function

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

During acute exposure, the most commonly observed alteration is an 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 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 $\geq$0.5 ppm (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, or obstructive effects. When changes occurred and postexposure examinations were performed, pulmonary function recovered.

Biochemical 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 cells (Type 2 cells) 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, but not all, 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.

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 often high or very high concentrations of O_3 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. A well-designed human clinical study found no such effect.

The few earlier long-term carcinogenic studies, 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 males and females 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. It is not justified to extrapolate these mouse data to humans at the present time because rats were not affected, only a high level of O_3 (1.0 ppm) caused a limited degree of carcinogenic activity in one strain of mice, there was no concentration response, and there is inadequate information to provide a mechanistic support for the finding in mice.

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/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 organ(s), and the central nervous system. Most of these effects cannot be adequately interpreted 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 respiratory tract 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 (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 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 and 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 not consistent with each other.

Interactions of Ozone with Other Co-occurring Pollutants

Animals studies of the effects of O_3 in combination with other air pollutants show that antagonism, additivity, and synergism can result, depending upon the animal species, exposure regimen, and health endpoint. Thus, they 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 health effects associated with exposure to O_3, the major component of photochemical oxidant air pollution that is clearly of most health concern to 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, airway resistance, and airway 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), can be largely attributed to decreases in inspiratory capacity, or the ability to take a deep breath; although at higher exposure concentrations, there is clearly an additional component that is not volume dependent. They recover to a large extent within 2 to 6 h; normal baseline function is typically 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 or 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 neutrophils (a type of white blood cell), increased epithelial permeability, and elevated levels of biologically active substances (e.g., prostaglandins, proinflammatory mediators, and cytokines).

Inflammatory responses to O_3 can be detected within 1 h after a single 1-h exposure with exercise to concentrations $\geq$0.30 ppm; the increased levels of some inflammatory cells and mediators persist for at least 18 h. The temporal response profile is not adequately defined, 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 neutrophils (neutrophilia) and protein levels suggestive of increased permeability.

Alveolar macrophages removed from the lungs of human subjects after 6.6 h 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 ($\dot{V}_E$). Of these factors, C has more influence on the response than T or $\dot{V}_E$.

Exercise increases response to O_3 by increasing $\dot{V}_E$ (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 ($C \times T \times \dot{V}_E$) causing substantial reductions in FEV_1 ($\geq$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, neutrophilia 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 significant (1) decrements in lung function, (2) increases in respiratory

symptoms, and (3) increases in neutrophils and protein levels. Ozone C is a more important factor than exercise $\dot{V}_E$ or T in predicting responses to multihour low-level O_3 exposure. There is now 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 (1) O_3 delivery to the tissue (i.e., the inhaled concentration, breathing pattern, and airway geometry; (2) O_3 reactions with the airway lining fluid and/or epithelial cell membranes; (3) local tissue responses, including injury and inflammation; and (4) 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 neutrophilic 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; most, however, are inadequately addressed 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 similar lung volume responses to O_3 as young adults, but lack respiratory symptoms at levels to which they have been exposed. 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 conclusively demonstrated 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 $\dot{V}_E$.

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 similar results as oronasal breathing (i.e., chamber exposures).

Population Groups at Risk from Ozone Exposure

Population groups that have demonstrated 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 (1) mild asthmatics have similar lung volume responses, but greater airway resistance responses to O_3 than nonasthmatics; and (2) 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 (1) subject selection, (2) standardized methods of subject characterization, and (3) 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 consistently demonstrated for simultaneous exposures of O_3 mixed with SO_2, NO_2, sulfuric or nitric acid, particulate aerosols, or with multiple 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, CA, have demonstrated pulmonary function decrements at 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 -0.64 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 may also 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 ppb 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.

Two recent time-series epidemiologic studies indicate a small but statistically significant association between O_3 and total daily mortality in Los Angeles, CA, and New York City, NY, where peak 1-h maximum O_3 reached concentrations greater than 0.2 ppm during the study period. The results were significant even after controlling for the potentially confounding effects of temperature and particles. A third 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 respiratory tract (RT) of animals and humans are beginning to present a clearer picture than has previously existed.

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, though 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.

Preditions of delivered dose have been used to investigate 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 tachypneic responses (i.e., rapid, shallow breathing) differ markedly between rats and humans, there is similarity of dose-response patterns in inflammation among species, with humans and guinea pigs more responsive than rats and rabbits. 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 dosimery data and models is beginning to bear fruit in attempts to extrapolate 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 with respect to inflammatory responses. Thus, chronic effects data in rats may not accurately reflect the degree to which comparably exposed humans would respond.

1.9 INTEGRATIVE SUMMARY OF OZONE HEALTH EFFECTS

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

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

Acute 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. Recovery of pulmonary function and the absence of

O_3-induced symptoms is usually complete within 24 h of the end of exposure, although other responses may persist somewhat longer.

- Pulmonary function decrements are generally 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 >0.5 ppm when at rest,
  (2) at >0.37 ppm with light exercise (slow walking),
  (3) at >0.30 ppm with moderate exercise (brisk walking),
  (4) at >0.18 ppm with heavy exercise (easy jogging), and
  (5) at >0.16 ppm with very heavy exercise (running).

  For a number of studies, small group mean changes (e.g., <5%) in FEV_1, the medical significance of which is a matter of controversy, have been observed at lower O_3 concentrations than those listed above. For example, data from one specific study indicate that FEV_1 decrements occur with very heavy exercise in healthy adults at 0.15 to 0.16 ppm O_3, and data from two studies indicate that such effects may occur in healthy 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. Pulmonary function decrements were observed at 0.12 ppm O_3 in healthy young adults undergoing heavy exercise in a recent study. 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 have also 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 have been observed after 1 to 3 h of exposure to 0.40 ppm, but not 0.20 ppm, O_3 at rest, and have been observed at concentrations as low as 0.18 ppm, 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.

Acute 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 neutrophils and protein in lung lavage fluid have been observed following exposure of humans 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 protein and/or neutrophils have also 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.

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

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

During repeated acute 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., neutrophil influx) also attenuate by the fifth day of exposure, but markers of cell damage (e.g., lactate dehydrogenase enzyme activity) do not attenuate and continue to increase. Attenuation of lung function decrements is reversed following 7 to 10 days without O_3. Some inflammatory markers are also 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 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., neutrophil influx in response to inhaled microorganisms).

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

Exposure to O_3 for months and years causes structural changes in several regions of the respiratory tract, but effects may be of the greatest importance in the centriacinar regions where the alveoli and conducting airways meet because this region is typically affected in most chronic diseases of the human lung. This information on O_3 effects in the distal lung is derived from animal toxicological studies because, to date, such data are not available in humans. Epidemiological studies attempting to associate chronic health effects in humans with long-term O_3 exposure have yet to provide unequivocal evidence that such a linkage exists.

Chronic 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 qualitatively extrapolated to humans. Ozone did not show tumor-promoting activity in a chronic rat study (at 0.5 ppm O_3).

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

Combined data from laboratory animal and controlled human exposure studies on 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, sulfuric acid, nitric acid, 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 sulfuric acid show that effects can be additive, synergistic, or even antagonistic, depending upon the exposure regimen and the endpoint studied. This issue of exposure to copollutants remains poorly understood, especially with regard to chronic effects.

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

Identification of population groups that may show increased susceptibility to O_3 are based on their (1) biological responses to O_3; (2) physiological status (e.g., preexisting lung disease); (3) activity patterns; (4) personal exposure history; and (5) personal factors (e.g., age, nutritional status).

The predominant information on the health effects of O_3 noted above comes from 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 may also 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 may be due to the dosimetry of O_3 in the respiratory tract, available data show little effect on O_3 deposition after inhalation through the nose or mouth.

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 they may have greater lung volume responses than nonasthmatics. 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 are confounded by concurrent 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.

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 on personal factors or personal exposure history known or suspected of influencing responses to O_3 are the following.

- 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 conclusively demonstrated 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.

- There is no compelling evidence to date to suggest that any ethnic or racial group has a different distribution of responsiveness to O_3. However, data are not adequate to rule out the possibility of such differences.

- 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 effects 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 responsiveness to ambient concentrations of O_3 consist of exercising healthy and asthmatic individuals, including children, adolescents, and adults.

9. INTEGRATIVE SUMMARY OF OZONE HEALTH EFFECTS

9.1 INTRODUCTION

This chapter integrates the knowledge gained in animal toxicological, human clinical, and epidemiological studies of ozone (O_3) that were discussed in Chapters 6, 7, and 8 respectively, of the criteria document. Because each of these approaches has different strengths and weaknesses, a combined evaluation can better describe the full array of health effects that are known to occur with exposure to O_3.

The chapter is organized according to the health effects of short- and long-term exposures of O_3 alone and exposures to binary mixtures with O_3. The section on short-term exposures (i.e., less than 8 h) begins with a discussion of the relationship between exposure and dose, as this lays a foundation for inter- and intraspecies extrapolation. Effects on lung function, exacerbation of existing disease, and cellular-biochemical responses are then presented descriptively. Finally, quantitative exposure-response relationships for the effects of O_3 on pulmonary function (e.g., changes in lung volume) are summarized separately because the large number of studies allows more complex evaluations and modeling. For the other classes of effects, the exposure-response information is integrated with the description of the effects. The section on long-term exposures encompasses repeated exposures (i.e., 1 to 5 days), prolonged exposures (i.e., months), and genotoxicity and carcinogenicity. Because the data base on binary exposure studies has little predictive value, the emphasis is placed on the principles of interaction. The conclusions section is organized according to key questions.

Because this chapter integrates the results of a large number of studies from the current and earlier O_3 criteria documents, it is not practical to provide experimental details or cite specific references. Rather, emphasis is given to main findings which are supported by theory or other confirmatory studies, unless noted otherwise. Comprehensive details and references are provided in the previous chapters.

9.2 HEALTH EFFECTS OF SHORT-TERM EXPOSURES

9.2.1 Exposure-Dose Relationships

Qualitative and quantitative health assessment requires, among other things, the ability to relate exposure to dose and dose to effect. In the case of O_3 health assessment, this ability is necessary for two major reasons: (1) to develop unified predictive models of human population responses based upon exposure; and (2) to enable extrapolation from animals to humans for chronic effects. Physically and biologically based models of dose simplify the methods of predicting population responses and in turn significantly reduce the uncertainty of these predictions. For animal-to-human extrapolations, splitting the problem of exposure and response into an exposure-dose problem and a dose-response problem separates the issue of interspecies sensitivity from purely dosimetric considerations. Responses in animals may be homologous with humans but follow different dose-response curves. By measuring or computing delivered O_3 dose to relevant tissues in animals and humans, transfer functions can, in principle, be developed relating dose-response curves among different species. This section discusses the understanding of exposure-dose relationships and how they improve the ability to interpret and predict O_3 responses.

Historically, the first step beyond describing responses solely in terms of exposure concentration was the use of the product of concentration $\times$ time $\times$ minute ventilation ($C \times T \times \dot{V}_E$), yielding what has been often referred to as an "effective dose". Response modeling has examined the interaction of individual pairs of variables. However, no single model has been able to simply unify any response in terms of the product $C \times T \times \dot{V}_E$. This is due to the fact that $C \times T \times \dot{V}_E$ is a metric of exposure dose and not delivered dose and, furthermore, does not account for the mediation of responses in localized regions of the lung that would be responding to local O_3 doses. Advances in O_3 dosimetry modeling and experimental determinations of regional O_3 dose in animals and humans have enabled extensions beyond simple $C \times T \times \dot{V}_E$ modeling to interpret responses.

Ozone dosimetry models provide predictions on the dose distribution of O_3 in the respiratory tract from the trachea to the alveolar spaces of the lung. These models utilize the best available anatomical, physiological, and biochemical data available for animals and humans. These data are incorporated into mathematical formulations of convection, diffusion, and chemical reaction processes in the lung. The models predict that under resting

ventilatory conditions, the O_3 dose per airway generation to all respiratory tract constituents (tissue plus fluid) slowly decreases from the trachea to the terminal and respiratory bronchioles and then declines in the alveolated generations. When dose of O_3 to tissue alone is considered (taking account of reaction and diffusion kinetics in the liquid lining layer), there is a three order of magnitude increase in tissue dose from the trachea to the proximal alveolar regions, after which the tissue and total dose are virtually equal and fall rapidly in the alveolated generations. Currently, relationships between delivered regional dose and response are derived assuming that O_3 is the active agent directly responsible for effects. There is uncertainty, however, whether this assumption is correct. Reactive intermediates, such as peroxides and aldehydes formed when O_3 interacts with constituents of lung lining fluid, may be the agents mediating responses. Thus, the dose of the reactive intermediates may be more relevant than the dose of O_3. Despite this suggestion, the histopathological findings from chronic O_3 exposures in animals match the predicted distribution of O_3 dose (i.e., the sites of the highest predicted O_3 doses correspond with those regions of the lung with the greatest tissue alterations).

Experimental studies in humans have revealed some important features needed for health assessment. Among these is the observation that the dose of O_3 delivered to the lower respiratory tract is independent of the mode of breathing (i.e., oral versus nasal versus oronasal). This observation simplifies health assessment by eliminating the need for precise information on modes of breathing when considering population responses. Experimental studies in humans have also shown that increasing $\dot{V}_E$ with exercise (increasing both breathing frequency and tidal volume) only causes a small decrease in O_3 uptake efficiency by the total respiratory tract. Based on models of O_3 dose, it appears that the increased $\dot{V}_E$ in exercise, though having little effect on uptake efficiency by the total respiratory tract, causes the distribution of delivered O_3 dose to shift deeper into the respiratory tract. The shift in O_3 dose as a function of $\dot{V}_E$ could help explain the complex relationships seen between response and C, T, and $\dot{V}_E$. An important observation from the human experimental dosimetry studies is the general agreement between O_3 dosimetry models and the measured data.

Experiments in laboratory animals (particularly rats) have been valuable in providing, in conjunction with human experimental data and mathematical dosimetry models, the basis

for dosimetric extrapolation. Whereas the human total respiratory tract has an O_3 uptake efficiency between 70 and 100%, the respiratory tract of the rat only takes up about 50% of the inhaled O_3. Unlike the case with humans, the dosimetry models overestimate the uptake efficiency of the rat respiratory tract by approximately 25 to 50% (i.e., the predicted uptake efficiency is between 65 and 75%), but the models are still highly valuable for extrapolation purposes. An important finding has been that the models correctly relate the regional dose of O_3 to the increase in alveolar wall thickness, both of which decline with distance from the junction of the conducting airways and the alveolar regions of the lung.

Experimental O_3 dosimetry and predictive O_3 dosimetry models are informative about the feasibility of extrapolating animal responses to humans. Some responses to O_3 can be compared across species on a strict dose-response basis. For example, both animals and humans respond to O_3 in a dose-dependent manner by increasing breathing frequency and decreasing tidal volume (tachypnea). A qualitative comparison between rat and human tachypneic responses at a variety of O_3 concentrations and exercise levels indicate that when exercising, rats and humans have a similar response, but at rest rats are somewhat more responsive. However, when dose to the proximal alveolar region of the lung (normalized to body weight) is considered as the dose metric for tachypneic responses, rats appear to be much more responsive than humans. Another example is influx of protein into the alveolar spaces following O_3 exposure as measured in bronchoalveolar lavage (BAL) fluid. When BAL protein is plotted as a function of pulmonary tissue dose, the rat, guinea pig, rabbit, and human all respond with a similar dose-response pattern, reflecting a common mechanism of response. However, each curve is offset from the other, reflecting overall sensitivity differences among the species, with the human and guinea pig being more responsive than the rat and rabbit.

9.2.2 Physiological Responses to Ozone Exposure

Typical acute physiological responses to O_3 exposure in humans include a reduction in forced vital capacity (FVC), decreased expiratory flow rates, and increased respiratory symptoms. The most common symptoms include cough, airway irritation, and chest discomfort associated with a deep inhalation. These responses are often accompanied by increased airway resistance and tachypnea. The voluntary spirometry and symptom

responses cannot be elicited from animals, but their tachypneic response is well documented. Ozone exposure also increases airway responsiveness to nonallergenic airway stimuli (e.g., histamine) in humans and animals. There is a large range of responses among humans with at least a 10-fold difference between the most and least responsive individuals.

9.2.2.1 Respiratory Symptom Responses

The principal symptoms associated with O_3 exposure in humans include cough, irritation of the airways (described as a scratchy throat or discomfort under the sternum), and discomfort when taking a deep breath (described as chest tightness or pain in the chest). Eye irritation, sometimes reported as a symptom in field or epidemiological studies with exposure to oxidant mixtures, is not associated with exposure to O_3 alone. The receptors responsible for cough may be unmyelinated C-fibers or rapidly adapting receptors located in the larynx and the largest conducting airways. Thus, there appears to be a potential mechanistic linkage to changes in spirometry. Field and epidemiological studies also indicate an association between hourly or daily ambient O_3 levels and the presence of symptoms, particularly cough. Such associations may be most evident in asthmatic children. Although symptoms cannot be elicited from animals, indirect measures of symptom responses in animals include behavioral responses indicative of aversion to O_3 exposure.

Symptom responses to O_3 exposure follow a monotonic exposure-response relationship that has a similar form to that for spirometry responses. Increasing exposure levels elicit increasingly more severe symptoms that persist for longer periods. Symptom and spirometry responses follow a similar time course during an acute exposure and the subsequent recovery as well as over the course of several days in a repeated exposure study. Furthermore, medication interventions that block or reduce spirometry responses have a similar effect on symptom responses. Levels at which symptoms occur under various exposure conditions are discussed in Section 9.2.5.1. As with spirometry responses, symptom responses vary considerably among subjects, although the individual correlations between spirometry and symptom responses are relatively low. In several heavy or severe exercise studies of athletes exposed to O_3, the discomfort associated with the respiratory symptoms caused by O_3 concentrations in excess of 0.18 ppm was of sufficient severity that the athletes reported that they would have been unable to perform maximally, if the conditions of the exposure

were present during athletic competition. In workers or active people exposed to O_3, respiratory symptoms may cause reduced productivity or curb the desire to pursue leisure activity.

Symptom responses have also been reported in asthmatics exposed to O_3. In contrast to nonasthmatics, wheezing is a prevalent symptom in addition to cough, chest tightness, and shortness of breath that are reported by subjects without asthma.

9.2.2.2 Changes in Lung Volume

In humans, O_3 exposure reduces FVC primarily by decreasing inspiratory capacity. This is believed to be the result of neurogenic inhibition of maximal inspiration, possibly caused by stimulation of C-fiber afferents. C-fibers are also thought to be the receptors responsible for the cough reflex in humans. After exposure to O_3, coughing is frequently elicited during the deep inspiration prior to the forced expiratory maneuver used in dynamic spirometry tests such as FVC, forced expiratory volume in 1 s (FEV_1), and forced expiratory flow at 25 to 75% of FVC ($FEF_{25-75\%}$). The observation that nonsteroidal antiinflammatory drugs (e.g., indomethacin, ibuprofen) reduce or block spirometric responses to O_3 exposure and reduce levels of prostaglandin E_2 (PGE_2) within the lung suggest that mediators released by damaged epithelial cells and/or alveolar macrophages may play a role in the inhibition of maximal inspiration. Although it seems clear that the reduction in total lung capacity (TLC) is not attributable to reduced lung compliance (i.e., a stiffer lung) or inspiratory muscle weakness, the understanding of the mechanism(s) which cause this response remains incomplete. The O_3-induced tachypneic response, seen in many animal species and in exercising humans, may be related to the decrease in vital capacity. The tachypneic response in humans may not be entirely involuntary because it has been reported that O_3-exposed subjects may consciously modify their breathing pattern to relieve discomfort.

The time course of the spirometry responses to O_3 exposure depends on the exposure conditions. At low levels of exposure (e.g., light exercise and O_3 concentration ≤ 0.18 ppm), responses are induced slowly and progressively and they may or may not reach a plateau of response depending upon the duration of the exposure. At higher levels of exposure (e.g., very heavy exercise and O_3 concentration >0.25 ppm), responses occur rapidly (within 15 min) and the largest portion of the response tends to occur early in

exposure, indicative of a plateau of response that is not typically achieved because of termination of the exposure within 1 h to 2 h. The exposure-response relationships are discussed more extensively in Section 9.2.5.

9.2.2.3 Responses to Ambient Ozone Exposures

Responses of children and adolescents exposed to ambient O_3 (and other pollutants) at summer camps indicate qualitative changes in spirometry similar to those found in individuals exposed to O_3 under controlled experimental conditions. There is a substantial range of response among individuals in camp studies and between various locations. However, the average FEV_1 was lower when ambient O_3 was higher. Although direct comparisons cannot be made because of incompatible differences in experimental design and analytical approach, this range of response is comparable to the range of responses seen in chamber studies at low O_3 concentrations. The similarity of response between field and chamber studies leaves little doubt as to the relevance of controlled human exposure studies.

9.2.2.4 Changes in Airway Resistance

An increase in resistance is an indication of the response of large airways to O_3 exposure. Changes in airway resistance following O_3 exposure are small relative to those seen in asthmatics with an inhalation exposure to a bronchoconstricting drug (methacholine), a specific antigen, or to sulfur dioxide (SO_2). However, because the airways of healthy nonallergic people are relatively nonresponsive to a number of stimuli, including allergens, methacholine, and histamine, the fact that there is a small but statistically significant change in specific airway resistance in normal subjects should not be dismissed as an unimportant response. Even in asthmatics whose airways are much more sensitive, O_3 does not cause striking changes in resistance, although the changes are clearly greater than in healthy young subjects. In rats exposed to O_3, changes in resistance also tend to be small. The observation that changes in airway resistance are modest clearly indicates that reductions in maximum expiratory flow are not caused primarily by narrowing of large airways. The increase in airway resistance appears to be vagally mediated because it is sensitive to inhibition by atropine.

9.2.2.5 Changes in Breathing Pattern

A consistent finding across many animal species is that O_3 causes rapid shallow breathing (O_3-induced tachypnea), which in humans may be related to a sensation of discomfort associated with taking large tidal breaths. Of particular interest for comparing interspecies responses is that the responses of rats and guinea pigs fall within the same range as seen for humans from rest to heavy exercise.

9.2.2.6 Changes in Airway Responsiveness

Ozone exposure causes increased responsiveness of the pulmonary airways to subsequent challenge with bronchoconstrictor drugs such as histamine or methacholine. Although this phenomenon is seen even after regression of spirometric changes, it is typically no longer present after 24 h. One animal study has demonstrated decreased antigen-induced bronchoconstriction after O_3 exposure, and one human study is suggestive of an increase in such a response. An increased response to a specific antigen to which a human is sensitized is a plausible outcome of O_3 exposure but needs to be further investigated. Although changes in airway responsiveness tend to resolve somewhat more slowly and appear to be less likely to be attenuated with repeated exposure, the evidence for a persistent increase in responsiveness from animal studies is inconsistent. Changes in airway responsiveness in rats and guinea pigs tend to occur at higher O_3 concentrations and, as in humans, tend to be most pronounced shortly after the exposure and less so 24 h postexposure. Changes in airway responsiveness appear to occur independently of changes in pulmonary function. This response does not appear to be due to inflammation (at least PMNs) or to the release of arachidonic acid metabolites, but may be due to epithelial damage and the consequent increased access of these chemicals to smooth muscle in the airways or to the receptors in the airways responsible for reflex bronchoconstriction. The clinical relevance of this observation is that after O_3 exposure, human airways may be more susceptible to a variety of stimuli, including antigens, chemicals, and particles.

9.2.2.7 Small Airways Responses

There are several tests purported to be indicators of "small airways" function, although the morphological correlate of these functional tests is not clearly established.

Morphologically, the small airways of the centriacinar region of the lung, that segment between the last conducting airway and the gas exchange region, is highly susceptible to damage by O_3 and is the site of epithelial cell necrosis and remodelling of respiratory bronchioles. Numerous pulmonary function tests reputed to measure responses in small airways (e.g., closing volume, aerosol bolus) have been used in O_3 studies. Responses have been demonstrated, but it is not clear that these tests correlate with the morphological lesion observed in animals, which is presumed to occur but has not been demonstrated in humans. In dogs whose peripheral airways are directly exposed to O_3 through a wedged bronchoscope, the collateral resistance to airflow through nonairway channels is increased almost immediately.

9.2.2.8 Effects on Exercise Performance

A large number of studies show that O_3 exposure can interfere with exercise performance, either by reducing maximal sustainable levels of activity or reducing the duration of activity which can be tolerated at a particular work level. Such effects can be seen with very heavy exercise at O_3 concentrations of 0.18 ppm and above. Although there are a large number of factors which can alter maximal or submaximal exercise performance, many investigators have implicated the respiratory symptoms caused by O_3 exposure. Small changes in airway resistance have no effect on maximal or submaximal exercise performance, and even modest mechanical restriction of total lung capacity will not induce a respiratory limitation to maximal or submaximal exercise. Animals studies indicate decreased wheel running activity and decreased activity associated with obtaining food. Decreased worker productivity has also been associated with elevated O_3 levels.

9.2.3 Exacerbation of Existing Disease

9.2.3.1 Responses of Asthmatics to Controlled Ozone Exposure

Asthmatics have qualitatively similar responses to O_3 exposure as nonasthmatics. Although symptom and volume related responses (i.e., decreased FVC) tend to be similar, airway resistance increases relatively more, from an already higher baseline, in asthmatics exposed to O_3. Altered responsiveness to bronchoconstrictor drugs shows similar changes in asthmatics and nonasthmatics. There is no evidence at this time that O_3 induces a persistent

increase in airway responsiveness or that O_3-exposed asthmatics are more likely to have a late phase response to specific antigen challenge.

9.2.3.2 Increased Hospital Admissions and Asthma Attacks

A number of epidemiological studies have shown a consistent relationship between ambient oxidant exposure and acute respiratory morbidity in the population. Decreased lung function and increased respiratory symptoms, including exacerbation of asthma, occur with increasing ambient O_3, especially in children. Modifying factors, such as ambient temperature, aeroallergens, and other copollutants (e.g., particles) can also contribute to this relationship. Ozone air pollution may at least account for a portion of summertime hospital admissions for respiratory causes, because studies conducted in various locations in the eastern United States have consistently shown a relationship with increased incidence of admissions, even after controlling for modifying factors, as well as when considering only concentrations below 0.12 ppm O_3. It has been estimated from these studies that O_3 may account for roughly one to three excess respiratory hospital admissions per hundred parts per billion O_3, per million persons.

The association between elevated ambient O_3 concentrations during the summer months and increased hospital admissions has a plausible biologic basis in the physiologic, symptomatic, and field study evidence discussed earlier. Specifically, increased airway responsiveness, airway inflammation, increased airway permeability, and increased incidence of asthma attacks suggest that ambient O_3 exposure could be a cause of the increased hospital admissions, particularly for asthmatics.

9.2.4 Cellular-Biochemical Responses

9.2.4.1 Inflammation and Cell Damage

Ozone-induced cell injury may lead to effects including inflammation, altered permeability of the epithelial barrier, impaired host defense and particle clearance, irreversible structural alterations in the lung, exacerbation of preexisting disease (e.g., asthma), and increased sensitivity to biocontaminants (e.g., allergens). Of these, O_3-induced inflammation of the respiratory tract has been best documented and occurs in all species that have been studied. The mechanisms leading to the observed inflammatory responses induced

by O_3 are just beginning to be studied. Both animal morphological studies and in vitro studies indicate that airway ciliated epithelial cells and Type 1 cells are the most O_3-sensitive cells, and are initial targets of O_3. These cells are damaged by O_3 and produce a number of proinflammatory mediators (e.g., IL-6, IL-8, PGE_2) capable of initiating a cascade of events leading to neutrophil influx into the lung, activation of alveolar macrophages, inflammation, and increased permeability across the epithelial barrier.

Ozone-Induced Inflammation in the Lower Respiratory Tract

In general, inflammation can be considered as the host response to injury and the induction of inflammation as evidence that injury has occurred. Inflammation induced by exposure of humans to O_3 can have several outcomes: (1) inflammation induced by a single exposure (or several exposures over the course of a summer) can resolve entirely; (2) continued acute inflammation can evolve into a chronic inflammatory state; (3) continued inflammation can alter the structure and function of other pulmonary tissue, leading to diseases such as fibrosis; (4) inflammation can alter the body's host defense response to inhaled microorganisms, particularly in potentially vulnerable populations such as the very young and old; and (5) inflammation can alter the lung's response to other agents such as allergens or toxins. It is also possible that the profile of response can be altered in persons with preexisting pulmonary disease (e.g., asthma or COPD) or smokers.

The recent use of BAL as a research tool in humans has afforded the opportunity to sample the lung and lower airways of humans exposed to O_3 and to ascertain the extent and course of inflammation and its constitutive elements. Several studies have shown that humans exposed acutely (1 to 3 h) to 0.2 to 0.6 ppm O_3 had O_3-induced inflammation, cell damage, and altered permeability of epithelial cells lining the respiratory tract (allowing components from plasma to enter the lung). The lowest concentration of O_3 tested, 0.08 ppm for 6.6 h, also induced increases in these endpoints. Short-term (<8 h) exposure of animals to O_3 also results in cell damage, inflammation, and altered permeability, although, in general, higher O_3 concentrations are required to elicit a response equivalent to that of humans. Because humans were exposed to O_3 while exercising and most animal studies were done at rest, differences in ventilation likely play a significant role in the different response of humans and rodents to the same O_3 concentration. Studies in which

animals were exposed at night (during their active period), or in which ventilation was increased with CO_2, tend to support this idea.

Studies utilizing BAL techniques sample only free or loosely adherent cells in the lung; thus, it is possible that cellular changes have occurred in the interstitium that are not reflected in BAL studies. However, morphometric analyses of inflammatory cells present in lung and airway tissue sections of animals exposed to O_3 are in general agreement with BAL studies. Short-term O_3 exposure (<8 h) causes similar types of alterations in lung morphology in all laboratory animal species studied. The most affected cells are the ciliated epithelial cells of the airways and Type 1 cells in the alveolar region. The centriacinar region (the junction of the conducting airways and gas exchange region) is a primary target, possibly because it receives the greatest dose of O_3 delivered to the lower respiratory tract. Sloughing of ciliated epithelial and Type 1 cells occurs within 2 to 4 h of exposure of rats to 0.5 ppm O_3.

Ozone-Induced Inflammation in the Upper Respiratory Tract

Ozone causes inflammatory changes throughout the respiratory tract, including the nose. Humans and laboratory animals exposed to O_3 develop inflammation and increased permeability in the nasal passages. Thus O_3-induced changes in the nasal passages may reflect similar changes occurring in the lung. A recent study reported a positive correlation between nasal inflammation in children and measured ambient O_3 concentrations. Studies with rats suggest a potential competing mechanism between the nose and lung, with inflammation occurring preferentially in the nose at low O_3 concentrations and shifting to the lung at higher concentrations. It is unclear if this represents a specialization restricted to rats or is a more general phenomenon.

Time Course of Ozone-Induced Inflammatory Response

Findings from human and animal studies agree that the O_3-induced inflammatory response occurs rapidly and persists for at least 24 h. Increased levels of neutrophils and protein are observed in the BAL fluid within 1 h following a 2-h exposure of humans to O_3 and continue for at least 20 h. The kinetics of response during this time have not been well studied in humans, although a single study shows that neutrophil levels are higher at

6 h postexposure than at 1 or 20 h. Several animal studies suggest that neutrophil and BAL protein levels peak 12 to 16 h after an acute O_3 exposure, and begin to decline by 24 h, although some studies report detectable BAL neutrophils even 36 h after exposure. It is also clear that in humans the pattern of response differs for different inflammatory mediators. Mediators of acute inflammation, such as IL-6 and PGE_2, are more elevated immediately after exposure; whereas mediators that could potentially play a role in resolving inflammation, such as fibronectin and plasminogen activator, are preferentially elevated 18 h after exposure. The rapidity with which cellular and biochemical mediators are induced by O_3 makes it conceivable that some of them may play a role in O_3-induced changes in lung function—indeed there is some evidence that BAL PGE_2 levels are correlated with decrements in FEV_1, and anti-inflammatory medications that block PGE_2 production also reduce or block the spirometric responses to O_3. Although earlier studies suggested that O_3-induced PMN influx might contribute to the observed increase in airway hyperreactivity, animal studies show that when neutrophils are prevented from entering the lung, O_3-induced hyperreactivity or increases in many inflammatory mediators still occur. In addition, studies in which anti-inflammatory drugs are used to block O_3-induced lung function decrements, still show increases in neutrophils and most other inflammatory mediators (although PGE_2 is not increased).

Individuals and Populations Susceptible to Ozone

To date, there have been no studies that have examined the cellular/biochemical response of potentially susceptible subpopulations, such as asthmatics, to O_3; nor are there any data in humans addressing whether age, gender, or racial differences can modify the inflammatory response to O_3. However, inflammation is not induced to the same extent in all individuals. In moderately exercising humans exposed to 0.08 ppm O_3 for 6.6 h, the mean changes in inflammatory indices were low, but some individuals had increases comparable to those reported in heavily exercising subjects exposed to 0.4 ppm O_3 for 2 h, suggesting that some segments of the population may be more responsive to low levels of O_3. It has not yet been studied whether intersubject differences in inflammatory response to O_3 are reproducible over time for the same subject, as has been shown for intersubject differences in lung function. There seems to be no strong correlation between the various

mediators of inflammation, cell damage, and permeability (i.e., those individuals with the greatest neutrophil response are not necessarily those with the greatest BAL protein, PGE_2, or IL-6 response). Furthermore, the magnitude of lung function decrements and respiratory symptoms has not yet been shown to be correlated with mediators of inflammation, with the possible exception of PGE_2.

Animal studies also show large interspecies and interstrain differences in response to O_3 and suggest that genetic factors may play a role in susceptibility to O_3. Different rat strains respond to O_3 differently; for example, Wistar rats have the greatest neutrophil influx, whereas Fisher rats demonstrate the most epithelial cell damage. In addition, limited data suggest that dietary antioxidant levels may affect the response of rodents to O_3 and that very young rats produce more PGE_2 in response to O_3 than do older rats. Taken as a whole, both the human and animal studies suggest that the inflammatory response to O_3 is complex and that determinants of susceptibility may occur at several different genetic loci.

9.2.4.2 Host Defense

The mammalian respiratory tract has a number of closely integrated defense mechanisms that, when functioning normally, provide protection from the adverse effects of a wide variety of inhaled particles and microbes. Impaired mucociliary clearance can result in unwanted accumulation of cellular secretions and increased numbers of particles and microorganisms in the lung, leading to increased infections and bronchitis.

Mucociliary Clearance of Inhaled Particles

Animal studies consistently show that clearance of inhaled insoluble particles is slowed after acute exposure to O_3. Ozone-induced damage to cilia and increased mucus secretion likely contribute to a slowing of mucociliary transport rates. Interestingly, retarded mucociliary clearance is not observed in animals exposed repeatedly to O_3. The effects of O_3 on mucociliary clearance in humans has not been well studied, and the results are somewhat conflicting; one study reports an O_3-induced increase in particle clearance in subjects exposed to 0.4 ppm O_3 for 2 h, and another study reports no O_3-induced change in particle clearance with a similar exposure regimen.

Alveolar Macrophage Function

Macrophages represent the first line of defense against inhaled microorganisms and particles that reach the lower airways and alveoli. Studies in both humans and animals have shown that there is an immediate decrease in the number of BAL macrophages following O_3 exposure. Alveolar macrophages also have been shown to be crucial to the clearance of certain gram-positive bacteria from the lung. Several studies in both humans and laboratory animals have also shown that O_3 impairs the phagocytic capacity of alveolar macrophages, and some studies suggest that mice may be more impaired than rats. The production of superoxide anion (an oxygen radical used in bacterial killing) by alveolar macrophages also is depressed in both humans and animals exposed to O_3, and the ability of alveolar macrophages to directly kill bacteria is impaired. Decrements in alveolar macrophage function have been observed in moderately exercising humans exposed to the lowest concentration tested, 0.08 ppm O_3 for 6.6 h.

Interaction with Infectious Agents

Concern about the effect of O_3 on susceptibility to respiratory infection derives primarily from animal studies in which O_3-exposed mice die following a subsequent challenge with aerosolized bacteria. Mortality has been shown to be concentration-dependent, and exposure to as little as 0.08 ppm O_3 for 3 h can increase mortality of mice to a subsequent challenge with *Streptococcus* bacteria. In addition, younger mice are more susceptible to infection than older mice; this has been related to increased PGE_2 production in these animals, which likely decreases alveolar macrophage activity.

It has been suggested that impaired alveolar macrophage function is the mechanism likely responsible for enhanced susceptibility to bacteria. However, mortality is not observed with other rodent species, raising the question of whether this phenomenon is restricted to mice. Although both mice and rats show impaired macrophage killing of inhaled bacteria following O_3 exposure; rats mount a faster neutrophil response to O_3 to compensate for the deficit in alveolar macrophage function. The resulting slower clearance time in mice allows the *Streptococcus* strain to persist in lung tissue and subsequently elaborate a number of virulence factors that evade secondary host defense and lead to bacterial multiplication and death of the host. Mortality as an endpoint is not directly relevant to humans; however,

humans and laboratory animals share many host defense mechanisms being measured by mortality in the mouse model.

There is no compelling evidence from toxicological, human clinical, or epidemiological studies that O_3 increases the incidence of respiratory viral infection in humans. A study of experimental rhinovirus infection in susceptible volunteers failed to show any effect of 5 consecutive days of O_3 exposure (0.3 ppm, 8 h/day) on the clinical picture or on host response. Studies in which O_3-exposed mice were challenged with influenza virus report conflicting results, with some studies showing increased mortality, some showing decreased mortality, and still others showing no change at all. However, even when increased mortality was demonstrated, there was no difference in viral titers in the lung, suggesting virus-specific immune functions were not altered.

Taken as a whole, the data clearly indicate that an acute O_3 exposure impairs the host defense capability of both humans and animals, primarily by depressing alveolar macrophage function and perhaps also by decreasing mucociliary clearance of inhaled particles and microorganisms. This suggests that humans exposed to O_3 are likely to be predisposed to bacterial infections in the lower respiratory tract. The seriousness of such infections may depend on how quickly bacteria develop virulence factors and how rapidly neutrophils are mobilized to compensate for the deficit in alveolar macrophage function.

Ozone also has been reported to suppress natural killer cell activity in the lung, to suppress proliferative responses to bacterial antigen (Listeria) in both spleen and bronchial lymph nodes, and to induce delayed hypersensitivity responses to Listeria antigen. However, these effects occur at higher exposure levels (0.75 to 1.0 ppm O_3) than those that affect macrophage function.

9.2.5 Ozone Exposure-Response Relationships

A quantitative understanding of the relationship between O_3 exposure and subsequent response is useful both for a better understanding of the processes underlying outcomes of interest and for purposes of prediction. Examples of the utility of the latter include identification of exposures unlikely to produce effects, risk and benefits assessment, and prediction of responses based on exposures for which empirical data do not exist. Exposure-response relationships exist both for the population as a whole and for individuals within the

population. The form of the exposure-response relationship can be different for populations and individuals, and predicted magnitudes of effect for the population generally do not reflect the experience of all individuals.

Exposure-response relationships can be described in terms of concentration of O_3, dose rate of exposure, total inhaled dose, or dose at the active site. Most of the completed work to date has focused on describing the relationships between C, $\dot{V}_E$, and T (as introduced in Section 9.2.1) for either pulmonary function or BAL outcomes. Parallel work has been performed in both humans and in laboratory animals. While exposure-response relationships for individuals have been examined to a limited degree and are likely to be generally similar in form to those for populations, little work has focussed upon understanding or quantifying individual exposure-response relationships.

No single exposure-response model form has been adequately tested and identified as providing an accurate, precise description of the relationship between exposure and response in both humans and laboratory animals for lung function and BAL endpoints. Rather, for a given study, a particular model may have been selected a priori to describe the exposure-response data, or may have been identified as providing the best fit among several competing models. In many cases, models have been found to be deficient, but rarely has the performance of a number of possible models been systematically compared. The limiting factor in most of this work has been that no single study to date has included a wide enough range of the three exposure variables of interest, (i.e., C, $\dot{V}_E$, and T) to choose between models or to identify the appropriate method of describing exposure. From the individual studies, however, have come a number of observations which are qualitatively true for describing BAL and pulmonary function responses in both humans and laboratory animals and which should be considered in the selection of a model to describe population response as a function of exposure.

1. Response monotonically increases with increases in C, $\dot{V}_E$, and T.

2. C has generally been found to be a stronger predictor of response than $\dot{V}_E$ or T.

3. The relationship between response and T depends upon the level of C, and by logical extension upon $\dot{V}_E$. For example, the effect of duration of

exposure upon response will be different for high- and low-concentration exposures.

4. The relationship between response and each of the exposure variables is curvilinear over a wide range of exposure conditions, although it may appear linear over certain narrow ranges of exposure.

5. With increasing duration of exposure (and possibly with increasing concentration), the FEV_1 response may approach a plateau in humans. Some evidence exists suggesting that the level of the time-dependent response plateau is a function of C. Respiratory symptom responses may behave similarly, but have not been adequately studied, and this plateau has not been observed in animal studies or for BAL endpoints.

Models that meet these criteria to a greater or lesser degree and that have been utilized for purposes of prediction include the following.

1. Polynomial models including linear or second order terms of C, T, or $\dot{V}_E$, but not including crossproduct terms. These models describe linear or curvilinear functions, with each exposure variable having a different weight. They do not allow the level of C, however, to affect the relationship between response and T, nor do they allow a plateau in response. There is no simple biological interpretation of individual terms in such a model.

2. Polynomial models utilizing linear or higher order terms of the variable $C \times T \times \dot{V}_E$. The product $C \times T \times \dot{V}_E$ is conceptually pleasing in that it represents the total inhaled dose of O_3 for a given exposure and in the past has been referred to as "effective dose". These models describe a linear or curvilinear function in which the level of C affects the relationship between response and T, but do not allow the individual variables to be weighted differently. These models do not allow a plateau in response.

3. Exponential model utilizing $C \times T$ as the exposure variable (model previously tested only at constant $\dot{V}_E$). This model describes a nonlinear exposure-response relationship, with C and T having equal weight, allowing the level of C to affect the relationship between response and T. This model does not allow a plateau in response.

4. Cumulative normal probability model or logistic model utilizing $C^y \times T$ as the exposure variable (models previously tested only at constant $\dot{V}_E$). These models describe sigmoid-shaped exposure-response relationships with C having a different weight than T (identified by the exponent y) and allow the level of C to affect the relationship between response and T. These

models do not allow the level of the plateau in response to be a function of concentration.

5. Logistic model of C×T as the exposure variable, with C having a further effect upon the level of the time-dependent plateau (model previously tested only at constant $\dot{V}_E$). This model describes a sigmoid-shaped exposure-response relationship which allows C to have a different weight than T and allows the level of C to affect the relationship between response and T. This model describes a concentration-dependent plateau in response. A model of this form has recently been found to describe the relationship between change in FEV_1 and C and T for heavily exercising humans over a range of exposure conditions.

Each of the above models has been found under some circumstance to describe the relationship between exposure and response for a particular data set. Most single data sets, however, do not include a wide enough range of data to adequately test the performance of a particular model across a wide range of exposure conditions or to identify an appropriate exposure metric. In particular, recent efforts have focussed upon the relationship between response and C and T at constant $\dot{V}_E$. No definitive work has addressed the modeling of response and $\dot{V}_E$ for a given endpoint or for consideration of $\dot{V}_E$ changing as a function of T. Because animal and human studies are often conducted at different relative levels of $\dot{V}_E$ and because techniques to mathematically adjust for these differences are only now being developed, efforts to compare responses across species or to develop extrapolation models have been hampered.

Evidence indicates that, for humans and animals, the exposure-response relationship of BAL and pulmonary function outcomes may be modified by previous recent exposure to O_3, and the relationship for FEV_1 changes in humans may be modified by age. Previous exposure to O_3 has not been included in any exposure-response models. For young adults, the modification of the exposure-response relationship by age has been modeled.

In summary, no single universal model form has been identified which accurately and precisely describes the relationship between population exposure and response under all circumstances. In general, the ability of a predictive model based on one study to predict responses from an independent study has not been studied adequately. For purposes of prediction or risk estimation, the adequacy of fit of a given model in a given data set and the

size and representativeness of the sample should be assessed. Extrapolation beyond the range of observed data introduces additional uncertainty into predictions or risk estimates.

9.2.5.1 Prediction and Summary of Mean Responses

A selection of reports in which models of mean FEV_1 or BAL response have been developed is listed below, along with figures summarizing examples of predicted exposure-response relationships. Following this section on prediction of mean responses will be a further section which describes the individual responses within the population.

1. Hazucha (1987) predict mean FEV_1 decrements in humans as a function of C (0.0 to 0.75 ppm) for four levels of $\dot{V}_E$ for 2-h exposures (Figure 9-1).

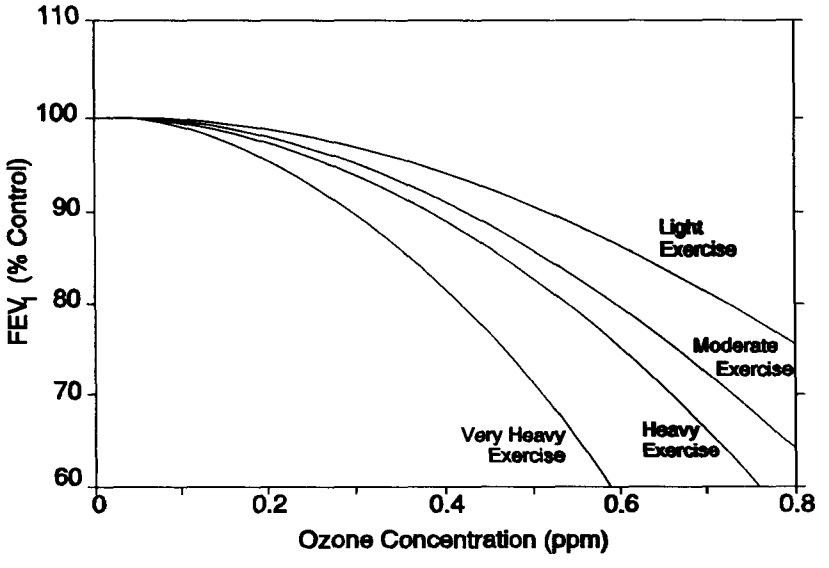

Figure 9-1. Mean predicted postexposure to preexposure changes in forced expiratory volume in 1 s (×100%) following 2-h exposures to ozone with intermittent exercise.

Source: Hazucha (1987).

2. McDonnell and Smith (1994) predict mean FEV_1 decrements in heavily exercising humans as a function of C (0.0 to 0.4 ppm) and T (1.0 to 6.6 h) (Figure 9-2).

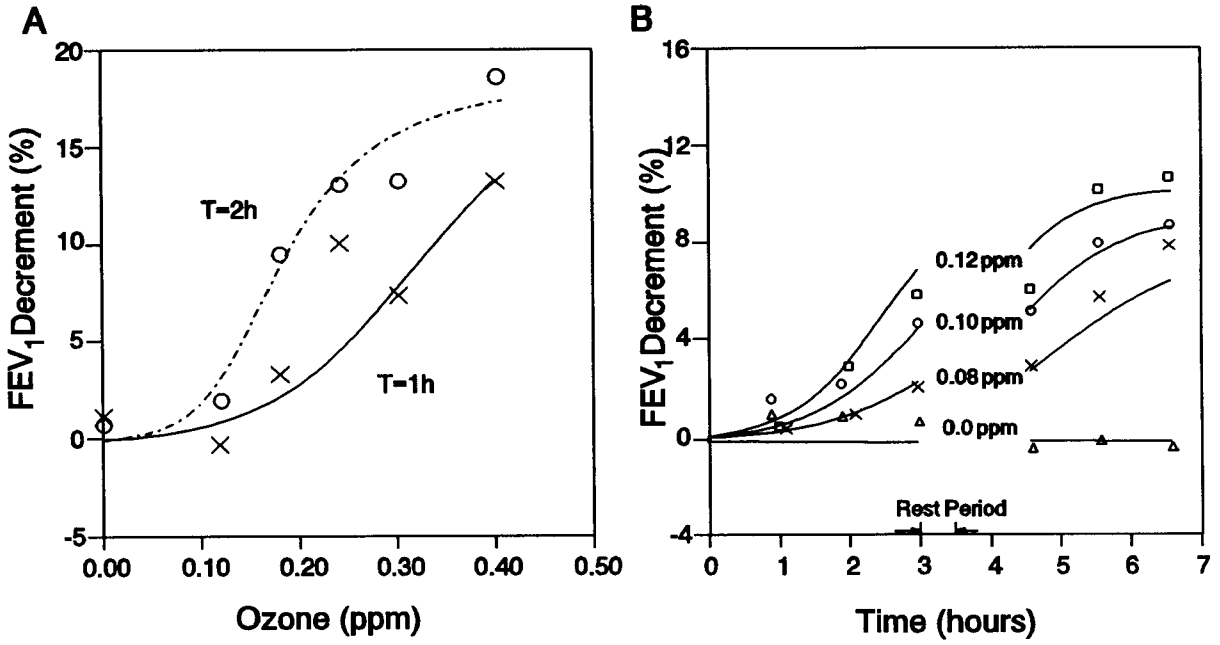

Figure 9-2. Predicted mean decrements in forced expiratory volume in 1 s for 1- and 2-h exposures to ozone with intermittent heavy exercise (A) and 6.6-h exposures with moderate prolonged exercise (B).

Source: McDonnell and Smith (1994).

3. Highfill et al. (1992) predict the BAL responses of resting rats and guinea pigs as a function of C (0.0 to 0.8 ppm) and T (2 to 8 h) (Figure 9-3).

4. Tepper et al. (1994) predict the FVC changes as a function of C (0.0 to 0.8 ppm) and T (2 to 7 h) for exposures conducted with rats breathing at three times resting $\dot{V}_E$ (Figure 9-4).

Other reports in which models are developed or that contain data potentially useful for further development or testing of models are listed below.

5. Seal et al. (1993) present data which would allow modeling of FEV_1 decrements in humans as a function of C (0.0 to 0.4 ppm) for 2-h exposures with moderate exercise.

6. Folinsbee et al. (1978) predict lung function changes in humans as a function of C (0.0 to 0.50 ppm) and $\dot{V}_E$ (10 to 65 L/min) for 2-h exposures.

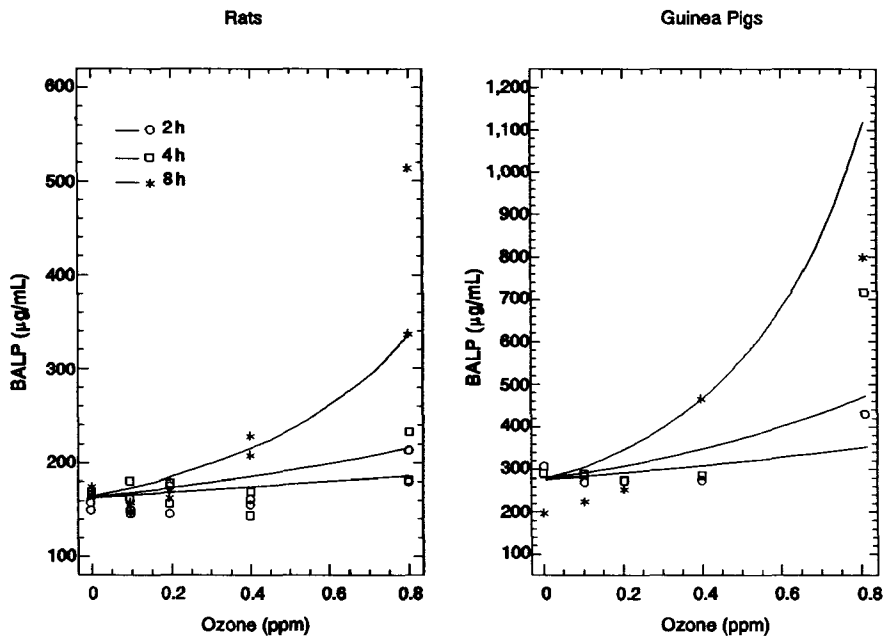

Figure 9-3. Derived means of BAL protein (BALP) denoted by symbols and the exponential model shown by lines as time of exposure varies from 2 to 8 h.

Source: Highfill et al. (1992).

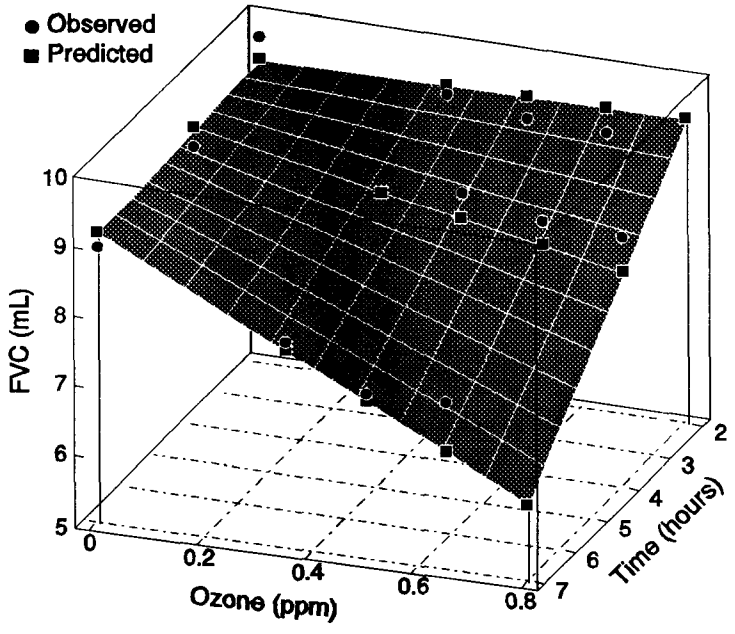

Figure 9-4. Predicted mean forced vital capacity for rats exposed to ozone while undergoing intermittent carbon dioxide-induced hyperpnea.

Source: Tepper et al. (1994).

7. Adams et al. (1981) predict lung function changes in humans as a function of the product of $C \times T \times \dot{V}_E$ for C = 0 to 0.4 ppm, T = 30 to 80 min, and $\dot{V}_E$ = 33 or 66 L/min.

8. Rombout et al. (1989) predict the concentration of protein in BAL fluid of rats as a function of C (0.25 to 4.0 mg/m^3) and T (0 to 12 h) for daytime and nighttime exposures.

9. Highfill and Costa (1994) compare the fits of quadratic, exponential, and sigmoid-shaped models to published human lung function data and O_3 laboratory animal BAL data.

The concentrations and durations of exposure which result in mean lung function and airway reactivity changes and mean changes in BAL endpoints in humans can be summarized as follows. The estimates are based directly upon studies that were performed at exposure conditions of interest rather than upon mathematical models.

Pulmonary function decrements are generally 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 >0.5 ppm when at rest,
(2) at >0.37 ppm with light exercise (slow walking),
(3) at >0.30 ppm with moderate exercise (brisk walking),
(4) at >0.18 ppm with heavy exercise (jogging), and
(5) at >0.16 with very heavy exercise (running).

For a number of studies, small group mean changes (e.g., <5%) in FEV_1, the medical significance of which is a matter of controversy, have been observed at lower O_3 concentrations than those listed above. For example, data from one specific study indicate that FEV_1 decrements occur with very heavy exercise in healthy adults at 0.15 to 0.16 ppm O_3, and data from two studies indicate that such effects may occur in healthy 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. Pulmonary function decrements were observed at 0.12 ppm O_3 in healthy young adults undergoing heavy exercise in a recent study. Some individuals may experience FEV_1

decrements in excess of 15% under these exposure conditions, even when the mean decrement is less than 5%.

An increase in the incidence of cough has been reported at levels as low as 0.12 ppm O_3 in healthy adults during exposure with very heavy exercise and at levels as low as 0.18 ppm with 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.

Increases in nonspecific airway responsiveness have been observed following exposure to 0.40, but not 0.20 ppm O_3 at rest, and have been observed at concentrations as low as 0.18 ppm but not to 0.12 ppm O_3 during exposure with very heavy exercise.

Increases in BAL protein concentration and/or PMNs have been observed following exposure 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.

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% 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.

Increases in the respiratory symptoms (i.e., cough, shortness of breath, and pain on deep inspiration) and in nonspecific airway responsiveness 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 have been observed at 0.08, 0.10, and 0.12 ppm O_3 during 6.6 h exposures with moderate levels of exercise.

Increases in BAL protein and/ or PMN have also been observed following 6.6 h exposure to 0.08 and 0.10 ppm O_3. No 6- to 8-h exposure studies have been conducted using O_3 concentrations less than 0.08 ppm.

9.2.5.2 Prediction and Summary of Individual Responses

It is well known that considerable inter-individual differences in the magnitude of response to O_3 exposure exist. The individual lung function and, to a lesser extent, respiratory symptom responses to O_3 have been demonstrated to be reproducible over a period of time, indicating that some individuals are consistently more responsive to O_3 than are others. The basis for these differences are not known, with the exception that young adults have been observed to be more responsive than older adults (see Figure 9-5).

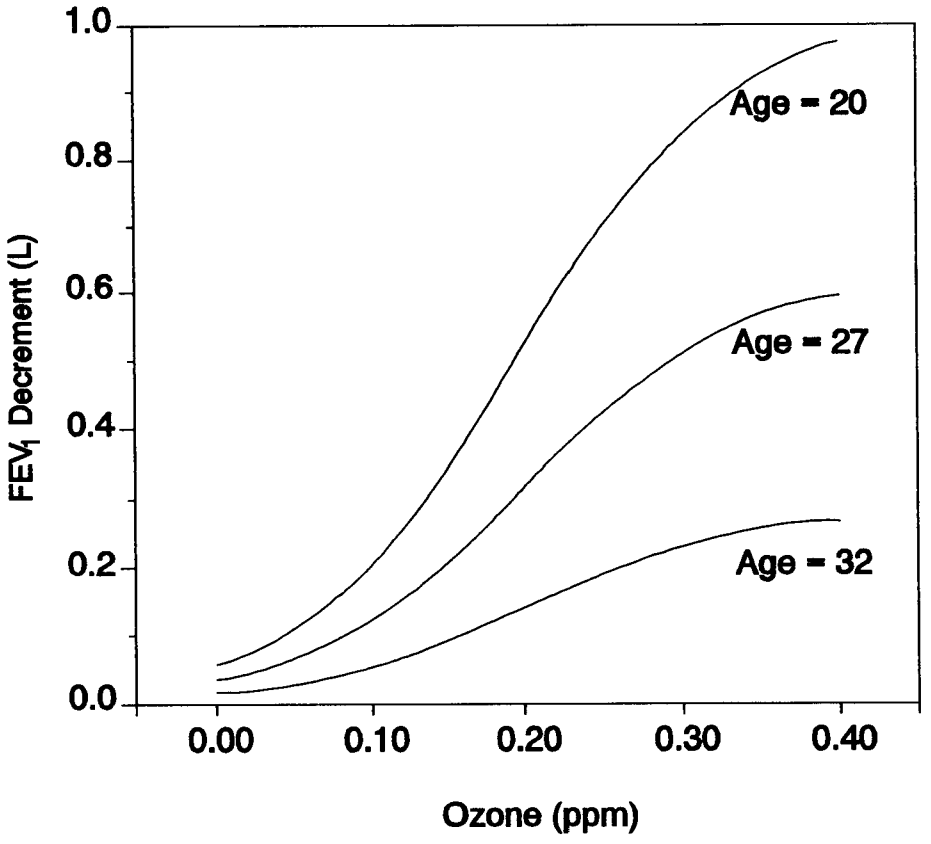

Figure 9-5. Predicted mean decrements in forced expiratory volume in 1 s following 2-h exposures to ozone while undergoing heavy intermittent exercise for three age groups.

Source: McDonnell et al. (1993).

Calculation of group mean responses for a population that includes both more and less responsive individuals is useful for making inferences regarding the probability that a population effect is present or absent for a given exposure. Since the frequency distribution of individual responses to O_3 changes with changing exposure conditions, however, knowledge of the mean and variance of population responses does not provide reliable information on the distribution of individual responses for a given exposure, and hence, is not particularly useful for estimating risks to members of the population. One method of presenting individual data is illustrated in Figure 9-6 in which histograms are presented for individual responses of subjects participating in four 6.6-h studies of low-levels O_3 exposure.

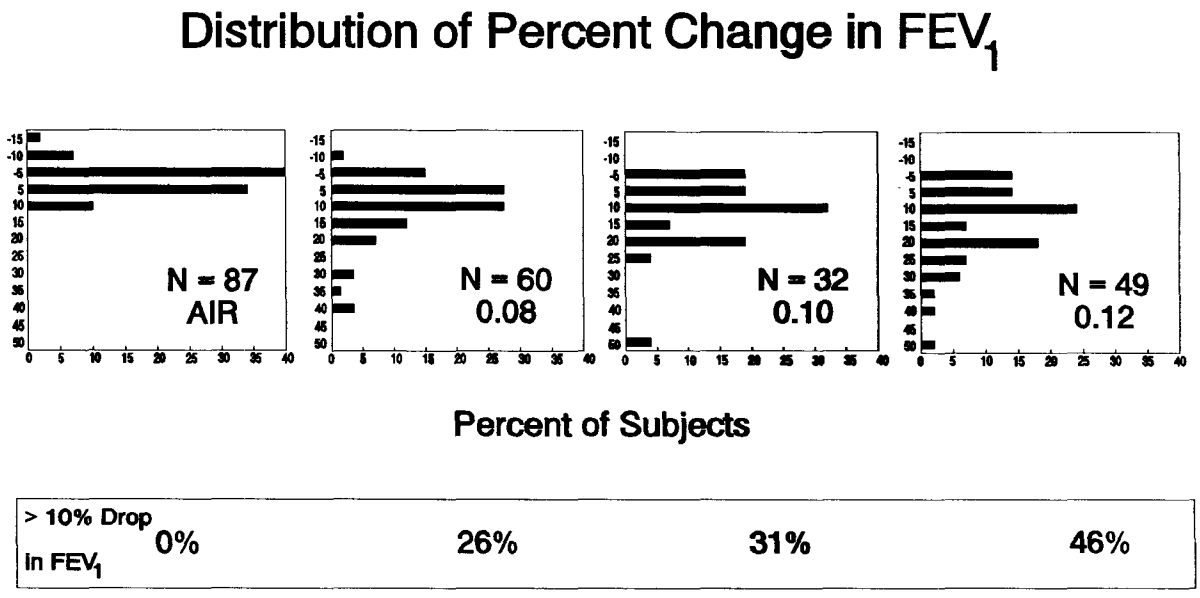

Figure 9-6. The distribution of response for 87 subjects exposed to clean air and at least one of 0.08, 0.10, or 0.12 ppm O_3 is shown here. The O_3 exposures lasted 6.6 h, during which time the subjects exercised for 50 min of each hour with a 35-min rest period at the end of the third hour. The abscissa indicates the number of subjects. The bar labels on the ordinate indicate decreases in FEV_1, expressed as percent change from baseline. For example, the bar labeled 10 indicates the number of subjects with a decrease in FEV_1 of $>5\%$ but $\leq 10\%$; the bar labeled -5 indicates improvement in FEV_1 of $>0\%$ but $\leq 5\%$. The rectangle across the bottom of the graph indicates the percentage of subjects at each O_3 concentration with a decrease of FEV_1 in excess of 10%.

Source: Folinsbee et al. (1991).

Another method that allows interpolation between observed data points involves definition of the effect of interest (e.g., a 10% decrement in FEV_1) and modeling of the proportion of individuals who experience such an effect as a function of exposure conditions. For example, Figure 9-7 shows the prediction of the proportion of individuals (humans) experiencing 10% FEV_1 decrements and respiratory symptom responses (Figure 9-8) as a function of C (0.0 to 0.4 ppm O_3) for three studies conducted at either 1 or 2 h of exposure with heavy exercise.

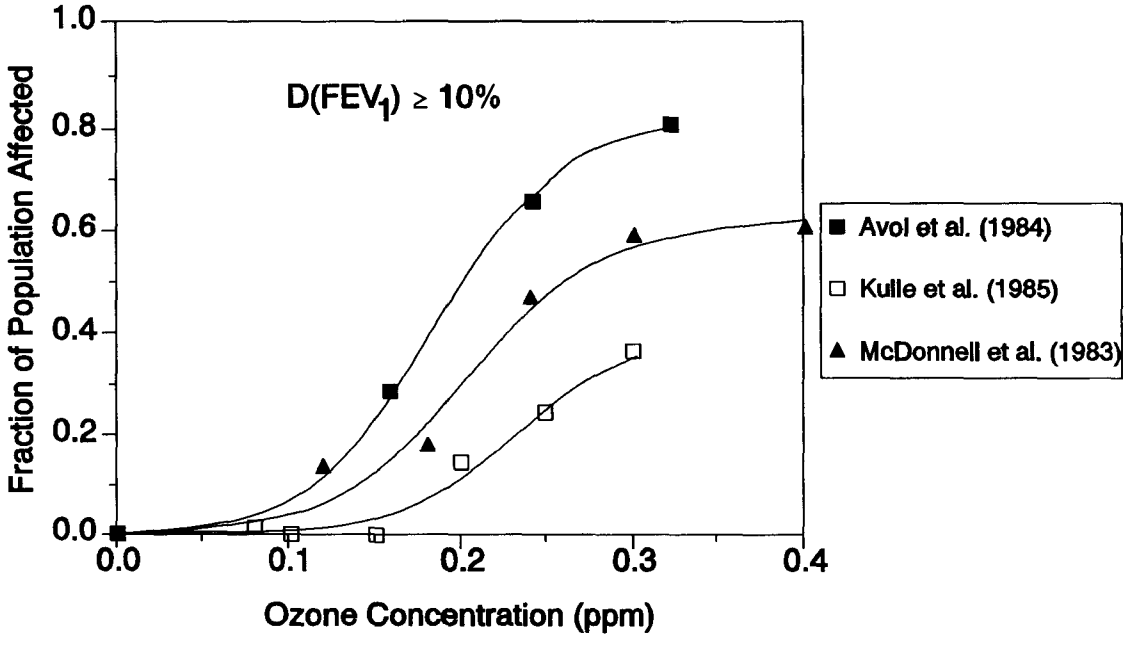

Figure 9-7. Proportion of heavily exercising individuals predicted to experience a 10% decrement in forced expiratory volume in 1 s following a 1- or 2-h exposure to ozone.

Source: U.S. Environmental Protection Agency (1989).

Predictions of the proportion of individuals experiencing a 5, 10, or 15% FEV_1 decrement as functions of C (0.0 to 0.12 ppm), T (1 to 6.6 h), and age (18 to 34 years) for exposures with moderate exercise are shown in Figure 9-9.

As an example of differences between the mean and individual responses, it was stated earlier that exposure for 5.6 h to 0.08 ppm was the shortest duration for which a 5% mean

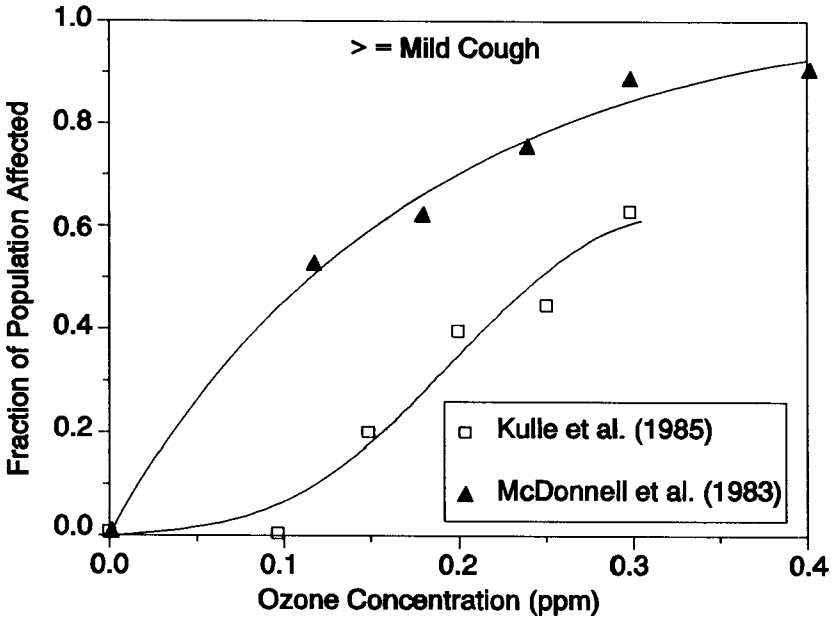

Figure 9-8. Proportion of heavily exercising individuals predicted to experience mild cough following a 2-h ozone exposure.

Source: U.S. Environmental Protection Agency (1989).

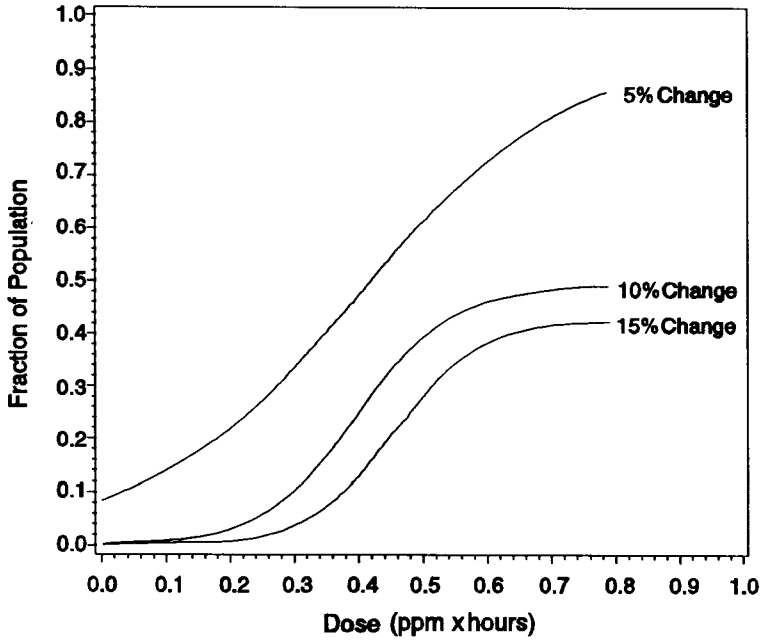

Figure 9-9. Proportion of moderately exercising individuals exposed to ozone for 6.6 h predicted to experience 5, 10, or 15% decrements in forced expiratory volume in 1 s as a function of C×T for age = 24 years.

Source: McDonnell et al. (1994).

decrement in FEV_1 was observed. For those same exposure conditions, 41, 17, and 10% of the subjects studied experienced FEV_1 decrements larger than 5, 10, and 15%, respectively.

The clinical significance of individual responses to O_3 exposure depends on the magnitude of the changes in spirometry (e.g., FEV_1, FVC) and airway responsiveness to nonspecific stimuli, the severity of respiratory symptoms (e.g., cough and pain on deep breath), and the duration of the response. In nonasthmatic individuals, O_3-induced changes in specific airway resistance (SR_{aw}), a measure of large airway narrowing, are small and of minimal significance. Asthmatics, however, often have baseline airway narrowing and experience larger changes in SR_{aw} upon exposure to O_3 than do nonasthmatics. Because of these baseline differences, the clinical significance of increases in SR_{aw} depends both upon percent changes from baseline and absolute increases in SR_{aw}. Table 9-1 categorizes these physiological responses to O_3 exposure as normal (or none), mild, moderate, or severe. Qualitative relationships among the categories provide an indication of the severity of the response.

TABLE 9-1. GRADATION OF PHYSIOLOGICAL RESPONSES TO SHORT-TERM OZONE EXPOSURE[a]

Response	None/Normal	Mild	Moderate	Severe
Cough symptom	Infrequent cough	Cough with deep breath or FVC test	Frequent spontaneous cough	Persistent uncontrollable cough
Pain on deep breath symptom	None	Discomfort just noticeable on FVC test	Marked discomfort on exercise or FVC test	Exercise or breathing tests cause chest pain; FVC tests cannot be performed properly
FEV_1 (also FVC)	Within normal range (±3%)	FEV_1 decreased less than 10%	FEV_1 decreased more than 10% but less than 20%	FEV_1 decreased more than 20%
SR_{aw} (asthmatics)	Within normal range (±20%)	Increase less than 100%	Increase up to 200% or up to 15 cm H_2O/s	Increase greater than 200% or more than 15 cm H_2O/s
Airway responsiveness	Within person's normal range	Increase less than 100%	Increase up to 300%	Increase greater than 300%
Duration of response	None	Less than 4 h	Less than 24 h	Longer than 24 h

[a]See text for discussion.

9.3 HEALTH EFFECTS OF LONG-TERM EXPOSURES

In both humans and test animals, the response to a single O_3 exposure can nominally be characterized by lung dysfunction, lung cell injury and inflammation, and leakage of plasma proteins into the airspace lumen. However, when such an exposure is repeated for several consecutive days, these effects appear to wane, suggesting adaptation or the development of tolerance to the continued intermittent challenge. In spite of this apparent state of tolerance, long-term O_3 exposures have been linked to subtle pulmonary effects, some of which have irreversible components, thereby enhancing concern about chronic effects. The following section will provide an overview attempting to synthesize the current understanding of the phenomenon of adaptation during brief repeated exposures and the evidence for potential health impairments resulting from protracted exposures to this oxidant.

9.3.1 Repeated Exposures

It is well established that a brief exposure of laboratory rodents to a minimally toxic concentration of O_3 will protect the animals from a subsequent lethal challenge of O_3 a week later. This phenomenon, called tolerance, bears a similarity to the pattern of attenuated nonlethal effects (sometimes referred to as "adaptation") observed in both human volunteers and animals when exposed to episodic levels of O_3 ($\leq$0.5 ppm) for 1 to 7 h/day over a succession of 5 or more days. Generally, over a 5-day exposure period, the effects of Day 1 are accentuated on Day 2 and diminish thereafter. Attenuation of the functional effects include spirometric deficits and associated symptoms as well as irritative alterations of breathing; nonspecific airway responsiveness, however, does not revert to normal levels. Measures of tissue effects which attenuate include inflammation and impaired phagocytic capabilities of alveolar macrophages. However, some evidence from animal studies suggests that tissue alterations persist, although the observed changes may be part of a transition to a chronically affected state of the lung. Thus, in general, cell associated indicators of injury or damage within the lung appear to diminish in spite of the continued O_3 exposure.

A number of mechanisms have been shown to be involved in the evolution of this "adapted" state. These mechanisms range from the replacement of sensitive cells in the alveolar lining (epithelium) by more resistant cells (with or without a thickened fluid barrier on the lumenal surface) to the enhancement of antioxidant metabolism providing cell

resistance and more biochemical defenses at the lung surface. However, controlled human studies show that after a one-week period without O_3 exposure, subjects regain their spirometric responsiveness to O_3 challenge, although this abrupt transition between unresponsiveness and responsiveness appears less distinct in field-related studies. For example, studies of Southern Californians suggest that they are significantly less responsive to the spirometric effects of an acute episodic-like controlled challenge with O_3 when studied for a period after the "high" O_3 season than after the relatively "low" O_3 season. Likewise, there is some evidence that O_3-exposed urban populations are also somewhat more resistant to the oxidant than populations that receive minimal exposure. This would appear to be in conflict with hospital admissions data suggesting the aggravation of respiratory diseases, like asthma, within such populations. It remains to be shown whether these latter data reflect the responsiveness of a sensitive subpopulation, perhaps less adapted or having less reserve function.

9.3.2 Prolonged Exposures

Most long-term exposure studies in animals have evaluated structural and functional changes. In the few investigations of the immune system or antibacterial host defenses, prolonged exposures of animals either caused no effects or did not increase the magnitude of effects observed after acute exposures. Thus, the following discussion centers on the larger body of knowledge on other endpoints.

Epidemiologic studies attempting to associate chronic lung effects in humans with long-term O_3 exposure have yet to provide unequivocal evidence that such a linkage exists. Most studies have been cross-sectional in design and have been compromised by incomplete control of confounding variables and inadequate exposure information. Other studies have attempted to follow variably exposed groups prospectively. Studies of such design have been conducted in communities of the Southwest Air Basin as well as in Canada where comparisons could be drawn between lung function changes over several years in populations from high or low oxidant pollution. The findings suggest small, but consistent decrements in lung function among inhabitants of the more highly polluted communities. However, associations between O_3 and other copollutants and, in some cases, problems with study population loss undermine the confidence in the study conclusions. Likewise, recent

associations found between O_3 and the incidence/severity of asthma over a decade of study, though derived from well-designed studies, also tend to be weakened by colinearity of O_3 with other air pollutants. Nevertheless, in all of the studies assessing lung function, the pattern of dysfunction associated with the long-term exposure has been consistent with the small airway lesions seen in animal studies.

The advantage of animal studies is the ability to examine closely the distribution and intensity of the O_3-induced lesions throughout the respiratory tract. Indeed, cells of the nose like the distal lung are clearly affected by O_3. Perhaps of greater health concern would be the lesions that occur in the centriacinar regions of the lung where the alveoli meet the end-airways. Altered function of the distal airways, the proximal conduits of air to the gas-exchange regions, can result in reduced communication of fresh air with the alveoli, air-trapping, and reduced oxygenation of the blood. In fact, chronic O_3 lesions as found in animal studies are reminiscent of the earliest lesions found in autopsied cigarette smokers, many of whom would have theoretically progressed to chronic obstructive lung diseases.

As shown in Figure 9-10, the temporal pattern of effects during and after a chronic exposure is complex. During the early days of exposure, the end-airway lumenal and interstitial inflammation peaks, and thereafter appears to subside at a lower plateau of activity sometimes referred to as a "smoldering" lesion. Several cytokines remain elevated beyond the apparent adaptation phase of the response and may be conceptually linked to the development of chronic lesions in the distal lung. To date, however, a clear association of these BAL-derived mediators and cells with long-term toxicity has not been demonstrated. Some evidence of molecular changes within the matrix of the lung may also link to the chronic effects, but these too remain poorly defined. When exposures to O_3 continue for weeks or months, the diminished O_3-induced exudative response in the distal bronchoalveolar areas is supplanted by hyperplastic epithelia in the alveoli and end-airways. Damaged cells in centriacinar alveoli are replaced by metabolically active progenitor cells that are more resistant to oxidant challenge. Junctional areas between conducting and gas exchange regions, where the O_3 changes are typically most intense, also undergo epithelial hyperplasia, giving the appearance that airway cells are extending into the mouth of the alveolus, hence the term "bronchiolization". The functional result of this concentration-dependent process is the effective elongation of distal bronchioles, which functionally may alter air distribution

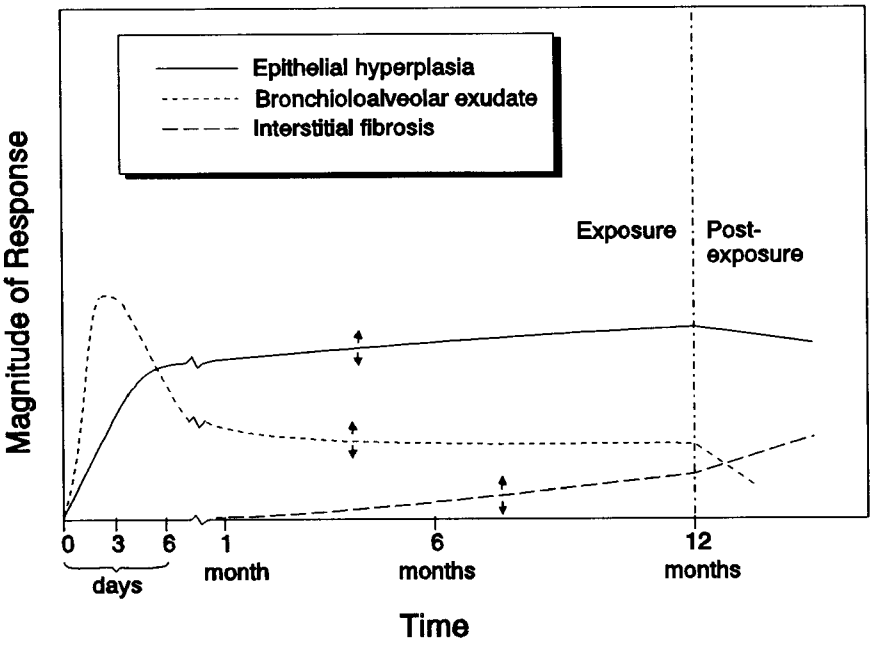

Figure 9-10. Schematic comparison of the duration-response profiles for epithelial hyperplasia, bronchioloalveolar exudation, and interstitial fibrosis in the centriacinar region of lung exposed to a constant low concentration of ozone.

Source: Dungworth (1989).

within the lung during breathing. These hyperplastic cells are also believed to be more resistant to O_3. When exposure to O_3 ceases, most, but not all, of the hyperplasia appears to reverse with time.

In contrast, within the underlying interstitium (tissue between blood and air spaces) of the affected centriacinar region, proliferating fibroblasts appear to evolve excess noncellular fibrous matrix, which may be only partially reversible and may, in fact, progress after removal from O_3 exposure. This would suggest that O_3 can lead to fibrosis of the lung at the regions where O_3 causes epithelial cell damage as a prelude to chronic degenerative lung disease. The crucial question, then, is whether this latter irreversible process, which clearly occurs at relatively high O_3 concentrations, occurs at ambient levels to which humans are typically exposed, in many cases over a lifetime. Unfortunately, comparable morphologic data from humans residing in O_3 polluted areas are lacking; however, anecdotal reports from autopsy examinations of young Los Angelenos following sudden death provide a suggestion

that similar end-airway lesions result from ambient O_3 exposure in areas with high oxidant exposures.

Studies of prolonged exposures in monkeys and rats reveal generally similar morphologic responses, although it appears that the monkey exhibits somewhat more tissue injury than does the rat under roughly similar exposure conditions. Although adequate dosimetric data are not yet available for a direct comparison of interspecies sensitivity, the monkey, with its similarity in distal airway structure relative to the human, provides data that may best reflect the potential effects in humans. As such, monkeys exposed to O_3 at 0.15 ppm for 8 h each day for 6 to 90 days exhibit significant distal airway remodeling. Rats show similar but more modest changes at 0.25 ppm after exposures of longer duration, up to 18 mo and beyond in both species (near-lifetime in the case of the rat). The chronic distal lung and airway alterations appear consistent with incipient peribronchiolar fibrogenesis within the interstitium. Attempts to correlate functional deficits have been variable, perhaps due in part to the degree and distribution of the lesions and the general insensitivity of most measures of the distal lung function. The interstitial changes may progress, however. Moreover, one recent primate study revealed evidence that intermittent challenge with a pattern of O_3 exposure more reflective of seasonal episodes, with extended periods of clean air in between extended periods of O_3, actually leads to greater injury. The reasons for this are unclear, but may relate to the known loss of tolerance which occurs in both humans and animal test species with removal of the oxidant burden.

In conclusion, the collective toxicologic data on chronic exposure to O_3 garnered in animal exposure and human population studies have some ambiguities. What is clear is that the distribution of the O_3 lesions is roughly similar across species, is, in part, concentration dependent (and perhaps time or exposure pattern dependent), and, under certain conditions, has irreversible structural attributes. What is unclear is whether ambient exposure scenarios encountered by humans result in similar lesions and whether there are resultant functional or impaired health outcomes, particularly since the human exposure scenario may involve much longer exposures than can be studied in the laboratory. The epidemiologic lung function data generally parallel those of the animal studies, but they lack the confidence of O_3 exposure history and are frequently confounded by personal or copollutant variables.

9.3.3 Genotoxicity and Carcinogenicity of Ozone

Numerous in vitro exposure studies suggest that O_3 either has a weak or no potential to cause mutagenic, cytogenetic, or cellular transformation effects. Most of these experiments utilized high concentrations of O_3 (>5.0 ppm). Because of the exposure systems used, there are unknowns about the formation of artifacts and the dose of O_3. Therefore, these studies are not very useful in health assessment. Cytogenetic effects have been observed in some, but not all, laboratory animal and human studies of short-term O_3 exposure. However, well-designed human clinical cytogenetic studies were negative.

Until recently, in vivo exposure studies of carcinogenicity, with and without co-exposure to known carcinogens, were either negative or ambiguous. A well-designed cancer bioassay study has recently been completed by the National Toxicology Program (NTP) using male and female F344/N rats and B6C3F$_1$ mice. Animals were exposed for 2 years to 0.12, 0.5, and 1.0 ppm O_3 (6 h/day, 5 days/week). A similar lifetime exposure was conducted, but 0.12 ppm was not used. The NTP evaluated the weight-of-evidence for this study. They found "no evidence" of carcinogenicity in rats. They reported "equivocal evidence" of carcinogenicity in O_3-exposed male mice and "some evidence" of carcinogenic activity in O_3-exposed female mice. The increases in adenomas and carcinomas were only observed in the lungs. There was no concentration response. In the male mice, the incidence of neoplasms in the 2-year study was not significantly elevated by O_3 and was within the range of historical controls. Also, the lifetime exposure did not significantly increase the incidence of neoplasms, even though the incidence of carcinomas was increased. In the female mice, a 2-year (but not lifetime) exposure to 1.0 ppm only increased the incidence of animals with neoplasms. When the female mouse data from the two exposure regimens (at 1.0 ppm) were combined, there was a statistically significant increase (about a doubling) in neoplasms. In a companion 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.

In summary, only chronic exposure to a high concentration of O_3 (1.0 ppm) has been shown to evoke a limited degree of carcinogenic activity in one strain of mice. Rats were not affected. Furthermore, there was no concentration response, and there is inadequate

information from other research to provide a mechanistic support for the finding in mice. Thus, it is not justified to extrapolate these mouse data to humans at the present time.

9.4 COMBINED POLLUTANT EXPOSURES

In the ambient air, people are exposed to mixtures of pollutants, making it important to understand interactions. Epidemiological studies, which inherently evaluate O_3 as part of complex mixtures, are discussed in other subsections dealing with classes of effects. In the laboratory it becomes possible to sort out the role of O_3 in simple mixtures. Complex mixtures are typically not investigated in the laboratory because even if only six pollutants were involved, the experimental design required to unequivocally sort out which pollutant or pollutant interactions were responsible for the responses or portions of the responses could require as many as 719 additional separate experiments, and this would be true only if the concentrations of the six pollutants remained the same.

The summary will focus only on binary mixtures since these are by far the predominant type of experiments. Responses to a binary pollutant mixture may represent the sum of the independent responses to the two chemicals (i.e., an additive response). If there is some interaction between either the two responses or the two pollutants, the resultant response could be larger than additive (synergism) or smaller than additive (antagonism). Interaction between pollutants could result in the production of a more or less toxic byproduct. Alternatively, the response to one pollutant could magnify the response to the other pollutant or could interfere with or block the action of the other pollutant. Binary mixture studies fall into two categories, simultaneous and sequential exposures. In the simultaneous exposures, both the responses and the pollutants can interact. In the sequential exposures, it is primarily the responses that would interact.

In general, controlled human studies of O_3 mixed with other pollutants show no more than an additive response with symptoms or spirometry as an endpoint. This applies to O_3 in combination with NO_2, SO_2, H_2SO_4, HNO_3, or CO. Indeed, at the levels of copollutants used in human exposure studies, the responses can be attributed primarily to O_3. In one study, exposure to O_3 increased airway responsiveness to SO_2 in asthmatics. Similarly, other

pollutants that may increase airway responsiveness could augment the effect of O_3 on airway responsiveness.

The relatively large number of animal studies of O_3 in mixture with NO_2 and H_2SO_4 show that additivity, synergism, and antagonism can result, depending upon the exposure regimen and the endpoint studied. The numerous observations of synergism are of concern, but the interpretation of most of these studies relative to the real world is confounded by unrealistic exposure designs. For example, often ambient concentrations of O_3 were combined with levels of copollutants substantially higher than ambient, creating the possibility that mechanisms of toxicity unlikely in the real world contributed to the experimental outcome. Nevertheless, the data support a hypothesis that coexposure to pollutants, each at innocuous or low-effect levels, may result in effects of significance.

9.5 CONCLUSIONS

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

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

Acute 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. Recovery of pulmonary function and the absence of O_3-induced symptoms is usually complete within 24 h of the end of exposure, although other responses may persist somewhat longer.

- Pulmonary function decrements are generally 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 >0.5 ppm when at rest,
  (2) at >0.37 ppm with light exercise (slow walking),
  (3) at >0.30 ppm with moderate exercise (brisk walking),
  (4) at >0.18 ppm with heavy exercise (easy jogging), and
  (5) at >0.16 ppm with very heavy exercise (running).

  For a number of studies, small group mean changes (e.g., <5%) in FEV_1, the medical significance of which is a matter of controversy, have been observed at lower O_3 concentrations than those listed above. For example, data from one specific study indicate that FEV_1 decrements occur with very heavy exercise in healthy adults at 0.15 to 0.16 ppm O_3, and data from two studies indicate that such effects may occur in healthy 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. Pulmonary function decrements were observed at 0.12 ppm O_3 in healthy young adults undergoing heavy exercise in a recent study. 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

have also 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 have been observed after 1 to 3 h of exposure to 0.40 ppm, but not 0.20 ppm, O_3 at rest, and have been observed at concentrations as low as 0.18 ppm, 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.

Acute 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 neutrophils and protein in lung lavage fluid have been observed following exposure of humans 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 protein and/or neutrophils have also 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.

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

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

During repeated acute 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., neutrophil influx) also attenuate by the fifth day of exposure, but markers of cell damage (e.g., lactate dehydrogenase enzyme activity) do not attenuate and continue to increase. Attenuation of lung function decrements is reversed following 7 to 10 days without O_3. Some inflammatory markers are also 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 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., neutrophil influx in response to inhaled microorganisms).

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

Exposure to O_3 for months and years causes structural changes in several regions of the respiratory tract, but effects may be of the greatest importance in the centriacinar regions where the alveoli and conducting airways meet because this region is typically affected in most chronic diseases of the human lung. This information on O_3 effects in the distal lung is derived from animal toxicological studies because, to date, such data are not available in humans. Epidemiological studies attempting to associate chronic health effects in humans with long-term O_3 exposure have yet to provide unequivocal evidence that such a linkage exists.

Chronic 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 qualitatively extrapolated to humans. Ozone did not show tumor-promoting activity in a chronic rat study (at 0.5 ppm O_3).

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

Combined data from laboratory animal and controlled human exposure studies on 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, sulfuric acid, nitric acid, 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 sulfuric acid show that effects can be additive, synergistic, or even antagonistic, depending upon the exposure regimen and the endpoint studied. This issue of exposure to copollutants remains poorly understood, especially with regard to chronic effects.

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

Identification of population groups that may show increased susceptibility to O_3 are based on their (1) biological responses to O_3; (2) physiological status (e.g., preexisting lung disease); (3) activity patterns; (4) personal exposure history; and (5) personal factors (e.g., age, nutritional status).

The predominant information on the health effects of O_3 noted above comes from 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 may also 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 may be due to the dosimetry of O_3 in the respiratory tract, available data show little effect on O_3 deposition after inhalation through the nose or mouth.

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 they may have greater lung volume responses than nonasthmatics. 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 are confounded by concurrent 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.

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 on personal factors or personal exposure history known or suspected of influencing responses to O_3 are the following.

- 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 conclusively demonstrated 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.

- There is no compelling evidence to date to suggest that any ethnic or racial group has a different distribution of responsiveness to O_3. However, data are not adequate to rule out the possibility of such differences.

- 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 effects 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 responsiveness to ambient concentrations of O_3 consist of exercising healthy and asthmatic individuals, including children, adolescents, and adults.

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