# Chapter 7.2   Ozone and other photochemical oxidants

General description

Sources

Ozone (O_3) is a strong oxidizing agent. In the troposphere, it is formed through a complex series of reactions involving the action of sunlight on nitrogen dioxide (NO_2) and hydrocarbons. There are no significant anthropogenic emissions of ozone. Ozone-producing processes, which involve absorption of solar radiation ($h\nu$) by nitrogen dioxide and ozone scavenging by nitric oxide (NO), can be characterized by the following reactions:

$$NO_2 + h\nu \xrightarrow{J_{NO_2}} NO + O(^3P)$$
$$O(^3P) + O_2 \rightarrow O_3$$

$$O_3 + NO \xrightarrow{h\nu} NO_2 + O_2$$
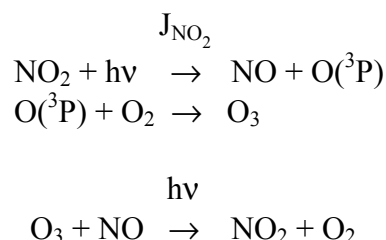
In its steady state, the ozone concentration can be described thus:

$$O_3 \text{ concentration} = J_{NO_2} [NO_2] / k_3 [NO]$$

$$O_3 + h\nu \xrightarrow{< 320 \text{ nm}} O_2 + O(^1D)$$
$$O(^1D) + H_2O \rightarrow 2OH$$
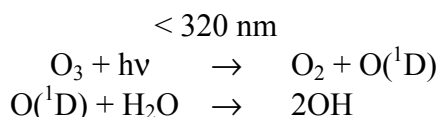
The presence of hydroxyl radicals and volatile organic compounds in the atmosphere, of either natural or anthropogenic, causes a shift in the equilibrium towards much higher concentrations of ozone. In addition to ozone, other products are formed during the photochemical processes, such as the peroxyacyl nitrates, nitric acid and hydrogen peroxide, all of which are atmospheric oxidants, as well as secondary aldehydes, organic acids, fine particulates and an array of short-lived radicals.

The maximum ozone concentration that can be reached in a polluted atmosphere depends not only on the absolute concentrations of volatile organic compounds and nitrogen oxides (NO_x) but also on their ratio *(1)*. At intermediate ratios (4:1 to 10:1), conditions are favourable for the formation of appreciable concentrations of ozone. In rural areas, ozone production is usually limited by the availability of nitrogen oxides. Summer conditions favour the formation of ozone primarily because of increased ultraviolet radiation, temperature and low wind speeds with stagnation conditions, and also because of increased precursor emissions, including nitrogen oxides from soils and increased levels of volatile organic compounds. Natural sources account for about 15% of nitrogen oxide levels in the summer but may account for a larger proportion in some rural areas.

Because the ratio of volatile organic compounds to nitrogen oxides is not prone to large shifts in the densely populated and heavily industrialized European Region, meteorological conditions appear to be the rate-limiting factor in photochemical processes and the year-to-year variability in ozone concentrations in this area *(1–3)*. In 10 major cities in the north-east and mid-west of the USA, ratios of volatile organic compounds to nitrogen oxides ranged from 5.8 to 11.5, but were generally below 10 *(4)*. The ratios in four of these 10 cities have shown a downward trend over the last decade or so *(4,5)*, presumably as a result of ozone control measures taken, because all four cities are part of the north-eastern corridor and have similar meteorological conditions.

Occurrence in air

Ozone

Tropospheric background ozone concentrations, caused primarily by stratospheric intrusions and photochemical reactions of biogenic and geogenic precursors, have been measured in places far from sources of air pollution. Natural levels also vary with altitude. The tropospheric background is derived from both natural and man-made sources; a range of annual average values of 40–70 $\mu g/m^3$ is a reasonable estimate of the level. The typical range of daily maximal 1-hour concentrations in clean nonurban areas in the USA is 60–100 $\mu g/m^3$, with summer-time highest 1-hour averages of 120–200 $\mu g/m^3$. Summer-time 7-hour daily averages range from 40 to 100 $\mu g/m^3$ in isolated areas with no ozone source in the USA, Canada and Germany *(1)*. It is reasonable to assume that, under circumstances of increased probability of oxidant scavenging by nitric oxide in urban areas, the 24-hour background ozone concentration does not exceed 120 $\mu g/m^3$.

Elevated ozone concentrations have been measured in rural areas where local anthropogenic sources of ozone precursors are insignificant. The long-range transport of ozone and its precursors from upwind source areas (or possibly ozone from a stratospheric origin) is thought to be responsible for the high concentrations found. Maximal hourly ozone concentrations exceeding 200 $\mu g/m^3$ and 300 $\mu g/m^3$ have been observed in rural areas of Norway and Sweden and in rural areas of the USA, respectively *(1)*. Maximal hourly ozone values of 430 and 520 $\mu g/m^3$ were measured in the Netherlands and the United Kingdom, respectively *(6)*.

In certain parts of Europe, urban 1-hour mean concentrations exceed 350 $\mu g/m^3$, whereas in the USA, 1-hour mean concentrations only occasionally exceed 400 $\mu g/m^3$, except for the Los Angeles area where this level is exceeded frequently *(1)*. Generally, concentrations in city centres are lower than those in suburbs, mainly as a result of the scavenging of ozone by nitric oxide originating from traffic.

Diurnal patterns of ozone vary according to location, depending on the balance of the factors affecting its formation, transport and destruction. From the minimal levels of early morning, levels rise as a result of photochemical processes, peaking in the early afternoon. Peak 1-hour concentrations in excess of 500 $\mu g/m^3$ are reached in parts of Southern California and in Mexico City. Mean hourly concentrations may exceed values of 240 $\mu g/m^3$ for 10 hours or more in the eastern USA and Southern California *(1)*, and in the Netherlands *(7)*. In the Netherlands, maximal 1-hour averages range from 227 to 431 $\mu g/m^3$ at different sites; maximal 8-hour averages range from 191 to 350 $\mu g/m^3$ *(6)*. During the night, ozone is scavenged by nitric oxide. Other removal processes include transport by wind and vertical

mixing of the air mass. It should be noted that several of these typical days with increased photochemical activity can occur consecutively during an episode. The length of the recovery period between two successive episodes and the number of episodes in a season may also be important factors in the nature and magnitude of health and vegetation effects.

Seasonal variations in ozone concentrations occur and are caused mainly by changes in meteorological processes and insolation. Quarterly mean ozone concentrations are typically highest during the summer. Seasonal average ozone levels are associated with mean temperatures, and there is some evidence of a day-to-day association.

Ozone is a highly reactive pollutant, and for this reason indoor:outdoor ratios vary according to air exchange. Indoor:outdoor ratios may be 0.6 to 0.8 for interiors with ventilation systems having a large volume exchange with outdoor air, 0.3 to 0.4 with conventional air conditioning systems, and as low as 0.02 to 0.2 with restricted ventilation or charcoal filter systems *(8)*.

Peroxyacetyl nitrate
Data gathered in the Netherlands and the USA indicate that the diurnal variation of peroxyacetyl nitrate concentrations is qualitatively similar to the diurnal ozone cycle *(9)*. In Sweden, on the other hand, peroxyacetyl nitrate has been observed to peak about 5 hours ahead of the ozone peak *(3)*.

The peroxyacetyl nitrate:ozone ratio is not constant and is, moreover, season-dependent. The ratio varies from 0.04 to 0.20 for mean daily averages in Los Angeles but is usually less than 0.05 in other cities. The peroxyacetyl nitrate concentrations reach maximal values of 100–150 $\mu g/m^3$ in Southern California, 90 $\mu g/m^3$ in the Netherlands, 100 $\mu g/m^3$ in Paris, and 15–30 $\mu g/m^3$ in other cities worldwide *(1)*. It is also clear that in the Netherlands an increase in peroxyacetyl nitrate concentrations has been observed during the last decade. The indoor:outdoor ratios for peroxyacetyl nitrate are higher than those for ozone. Measured values range from 0.90 to 1.50, depending primarily on the hour of the day.

Ozone-aerosol relationships
Ozone contributes to the formation of significant amounts of organic and inorganic aerosols. Correlations between levels of ozone and sulfuric acid, nitric acid, sulfates and nitrates have been observed *(1,3)*. Recent information obtained during summer smog episodes revealed a correlation of ozone and acid sulfate *(10,11)*.

Conversion factors
Ozone (O_3):
     1 ppm = 2 mg/m^3
     1 mg/m^3 = 0.5 ppm
Peroxyacetyl nitrate:
     1 ppm = 5 mg/m^3
     1 mg/m^3 = 0.2 ppm

Routes of exposure

The chemical reactivity of ozone and peroxyacetyl nitrate is so high that their half-time in solid and liquid media is virtually negligible. Thus, ozone exposure will not occur via

ingestion or transdermal absorption. The uptake of either gas into the body by routes other than inhalation is unlikely.

Toxicokinetics

Knowledge of the dosimetry of ozone (i.e. the mass of ozone that is absorbed per unit of tissue area at a particular site) is essential for quantitative extrapolation of experimental results from experimental animals to humans and for understanding phenomena such as the effects of exercise. Dosimetry has been studied by quantitative uptake measurements in animals and humans and by mathematical modelling *(1)*.

In studies of total respiratory tract uptake, approximately 50% of inhaled ozone is deposited in the respiratory tract of rats; about half of that (i.e. 25%) is removed by the supralaryngeal airways *(12)*. In humans, the total respiratory tract uptake is 80–95%, the efficiency being inversely proportional to flow rates and directly proportional to tidal volume. However, the ozone uptake calculations are not equivalent in the rat and human studies and the actual differences between rats and humans are probably less than have been reported. Uptake is similar in the nasal and oral airways in humans, accounting for about 30–40% of the respiratory tract uptake. The respiratory responses of humans exposed to ozone while breathing orally or nasally are similar, and this is consistent with these uptake observations *(1)*. The recent observations of Gerrity et al. *(13)* and Hu et al. *(14)* indicate that ozone uptake in the larger airways is greater than previously thought; although this is difficult to estimate precisely, some 20% of ozone inspired at rest may be removed in the larger airways.

Mathematical models *(1)* predict that the dose to the airway lining fluid and airway tissue gradually increases from the trachea to the end of the tracheobronchial region of the lung. Increased ventilation associated with exercise causes a shift of the net ozone dose toward the lung periphery. Ozone dose drops off considerably in the gas exchange region. Models also predict that the centriacinar region receives higher ozone doses than other local regions of the lower respiratory tract. This may help to explain why greater morphological effects in animals are observed here.

Improvements in model estimates of tissue dose and better data on regional ozone uptake efficiency have improved interspecies comparisons, which can now be made on the basis of delivered rather than exposure dose. Animal-to-human extrapolation requires an integration of dosimetry and species sensitivity. Factors such as species sensitivity of specific tissue sites and differences in pulmonary defence mechanisms (e.g. antioxidant levels) may be important modifiers of responses in different species, even when the same dose of ozone is delivered to the same site in the respiratory tract. Another important question is whether the animal responses represent the same biological response in humans. Comparisons based on dose–response characteristics show that rats have a greater tachypnoeic response but a lesser spirometric response than humans, while the inflammatory responses across species appear similar *(1)*.

Health effects

Ozone is a powerful oxidant, and, as such, it can react with a wide range of cellular components and biological materials. Ozone exerts its action through several mechanisms:

1. reactions with sulfhydryl groups, aldehydes, and amino groups of low molecular weight;

2. reactions with antioxidants such as vitamins E and C; other direct scavengers include bronchoalveolar lavage (BAL) uric acid and intracellular taurine; and

3. reactions with polyunsaturated fatty acids, the stable reaction products of which include hydrogen peroxide and aldehydes with some ozonides and lipid hydroperoxides; these reactions may lead to the formation of free radicals.

Ozone is not thought to penetrate through cell membranes or even the surfactant layer. Thus, the biological effects are probably caused by intermediates such as free radicals, lipid hydroperoxides, aldehydes, hydrogen peroxide, etc. *(15)*. Hatch et al. *(16)* have shown that ^{18}O from $^{18}O_3$ accumulates in the airway lining layers, suggesting that ozone reacts with components of these layers.

Effects on experimental animals and *in vitro* test systems
Damage to all parts of the respiratory tract can occur, and the extent of damage is dependent on the ozone concentration, exposure duration, exposure pattern and ventilation. Major classes of effects observed in the respiratory tract of animals include increases in permeability and inflammation; morphological, biochemical and functional changes; and decreases in host defence functions. Lung inflammation, marked by increased levels of protein and polymorphonuclear leukocytes and elaboration of leukotrienes and prostaglandins by alveolar macrophages, is a characteristic response to ozone exposure and has been observed in all animal species examined, from mice to monkeys *(1)*. The polymorphonuclear leukocyte and protein responses appear to peak some 6–18 hours after exposure, but the pattern is not the same for all inflammatory markers. Acute proinflammatory mediators such as prostaglandin E_2 and interleukin-6 are elevated immediately after exposure, whereas mediators that may be important in resolving inflammation such as fibronectin and plasminogen activator are elevated 18 hours after exposure. After acute exposure, the lowest concentration that increases the number of polymorphonuclear leukocytes and protein in the BAL fluid is 240 µg/m^3 (24 hours) in mice *(17)*. Two major studies which used BAL protein as an indicator of effects showed that concentration (C) had a greater influence than time (T), except at the lowest $C \times T$ products, at which their influence was similar *(18, 19)*. However, as concentration increased, the influence of time increased also. The contribution of the inflammatory cells to subsequent long-term effects of ozone has not been studied in detail, but should receive more attention, because apparently reversible alterations of this nature may ultimately result in irreversible effects.

Host defences are altered by ozone *(1)*. Mucociliary clearance is slowed by acute exposure, but longer exposures have no such effects. Alveolar macrophages, which are responsible for clearing the pulmonary region and participating in immune responses, can show decreased phagocytosis and antimicrobial metabolic activity, increased release of prostaglandins E_2 and F_2 , and alterations in numbers. For example, exposure to ozone at a concentration of 200 µg/m^3 for 2 or 6 days (2 hours/day) decreased the phagocytic capacity of rabbit macrophages *(20)*. Ozone-exposed lungs are less able to kill bacteria. It should be noted that ozone is used commercially as a bacteriostatic agent. Although both major components of the pulmonary immune system are affected, T-cell-dependent immunity appears to be more susceptible *(1)*.The effects on these and other host defence mechanisms result in an increased susceptibility to respiratory infection, as indicated by the increase in bacterial-induced

mortality in mice exposed to ozone concentrations as low as 160 μg/m³ for 3 hours *(21–23)*. However, prolonged exposure does not increase the magnitude of this response *(24)*. Research to date does not show an effect of ozone on acute viral infection in animals, but postinfluenzal alveolitis can be enhanced *(1)*.

The cell types that appear to be most sensitive to ozone are the type I alveolar epithelial cells, across which gas exchange takes place, and the ciliated epithelial cells, which function in particle clearance (see Tables 1 and 2 for examples of the types of structural changes caused by ozone). At relatively low concentrations, the centriacinar region (the junction between the alveoli and the conducting airways) is particularly affected by ozone, perhaps because, according to models, it receives a relatively large dose of ozone and because it has a large surface area covered by susceptible type I cells. After cessation of exposure and even during exposure, type I cells and ciliated cells are replaced by proliferating type II cells and nonciliated secretory cells, respectively. Complete evolution of type II cells to type I cells, or of nonciliated cells to ciliated cells, does not occur during ozone exposure, regardless of the exposure period *(1)*. A rise in antioxidant enzyme activities accompanies the hyperplasia of type II cells, which are rich in these enzymes. These epithelial changes are preceded by an inflammatory response marked by increased numbers of polymorphonuclear leukocytes and alveolar macrophages. As exposure continues, bronchiolarization occurs, which consists of the replacement of the cells in the alveolar ducts with bronchiolar epithelium; this has been observed at exposure levels of 500 μg/m³ for 8 hours/day for 18 months *(43)*. Alveolar septa thicken owing to increased matrix, basement membrane, collagen and fibroblasts, and a thicker alveolar epithelium. The nasal epithelium is also susceptible. Cilia are damaged and the transitional epithelium is altered *(49–51)*. These types of changes are observed in all animal species studied, including rodents and nonhuman primates, even though there are significant interspecies differences in lung structure *(1)*. However, the intensity of the response differs, with monkeys being more affected than rats *(52)*.

The responses of rats and monkeys that are exposed intermittently appear to be more pronounced than for animals exposed continuously *(1)*. For example, monkeys exposed to 500 μg/m³ "seasonally" (8 hours/day, 1 month of ozone followed by 1 month of air alternating for 18 months) had more alterations than monkeys exposed daily over this period *(43)*. Both groups had respiratory bronchiolitis, but only the seasonal group had increased lung collagen content, increased chest wall compliance and increased inspiratory capacity.

There is no conclusive evidence that ozone causes emphysema, although it does cause fibrotic changes in animals *(1)*. At low ozone levels (less than 0.50 ppm), frank pulmonary fibrosis does not occur. However there is mild, local fibrosis, primarily demonstrable as a local increase in collagen in the interalveolar septa of the centriacinar region *(31,34,42,47,53,54)*. Even after exposure ceases, the increased collagen content can persist; "abnormal collagen" cross-links were persistent in monkeys *(1,48)*.

The time course of these morphological changes is complex, as shown schematically in Fig. 1. During the first few days of exposure, inflammation occurs and then persists at an attenuated level. At the same time, epithelial hyperplasia progresses, reaching a plateau after about one week of exposure. Interstitial fibrosis, in contrast, increases slowly and can persist even after exposure ceases.

Table 1. Examples of short-term effects of ozone on lung structure

Concentration (µg/m^3)	Exposure duration	Species	Procedure	Effect	Reference
300	8 hours/day, 6 days	Monkey	LM, SEM, TEM	Nasal epithelium: ciliated cell necrosis, shortened cilia, and increased small mucous granule cells.	(25,26)
400, 200, 1000 and 1600	8 hours/day, 7 days	Monkey (rhesus and bonnet)	LM, EM	Increased respiratory bronchiolitis at all concentrations. Increased AMs. Bronchiolar epithelium both hyperplastic and hypertrophic. Increased type II cells. Random foci of short, blunt cilia or absence of cilia.	(27)
400 and 700	8 hours/day, 7 days	Monkey (bonnet)	LM, EM	All exposed monkeys had lesions. Trachea and bronchi had areas of shortened or less dense cilia. RBs had AM accumulation and cuboidal cell hyperplasia. Alveoli of RBs had increased AMs and type II cells. RB walls of the 700-µg/m^3 group were often thickened.	(28)
400, 1000 and 1600	8 hours/day or 24 hours/day, 7 days	Rat	LM, EM	Focal areas of missing or damaged cilia in trachea and bronchi. TB nonciliated (Clara) cells were shorter and had increased surface granularity and less smooth endoplasmic reticulum. TB ciliated cells had fewer cilia and focal blebs. Centriacinus had clusters of AMs and PMNs. Type I cells were swollen and fragmented and type II cells were frequently in pairs or clusters. Proximal IAS were minimally thickened. Lesions in the 400-µg/m^3 group were mild. Only slight differences between rats exposed continuously for 24 hours/day and those exposed for only 8 hours/day.	(29)
1000	2 to 6 hours	Rat (young males)	LM, EM	Centriacinar type I cells were swollen, then sloughed. Type II cells were not damaged and spread over the denuded basement membrane. Damage was most severe only in the most central two to three alveoli. Interstitial oedema.	(30)

Concentration (μg/m^3)	Exposure duration	Species	Procedure	Effect	Reference
1000–4000	24 hours/day, for 7 days	Rat	LM Biochemical analyses	Elevated collagen synthesis rates and histologically discernible fibrosis in the 1000-μg/m^3 group. At 1000 μg/m^3: minimal or no thickening of walls or evidence of fibrosis; increased number of cuboidal cells and macrophages present. At 1600–4000 μg/m^3: moderate thickening of alveolar duct walls and associated IAS by fibroblasts, reticulum and collagen, with narrowing of the ducts and alveoli; the thickening decreased with increased length of exposure.	(31)
1000–3000	24 hours/day, for 14 and 21 days			At 1000 μg/m^3: sometimes minimal thickening of alveolar duct walls with mildly increased reticulum and collagen.	
7200	24 hours/day, for 1, 2, and 3 days	Rat (1, 5, 10, 15, 20, 25, 30, 35, and 40 days old)	LM, EM	Birth to weaning at day 20: very little indication of epithelial changes in TB or alveoli or development of tissue nodules. 21 or 22 to 35 days old: changes progressive with age included loss of cilia, hypertrophy of TB cells, tendency towards flattening of luminal epithelial surface and alveolar injury, including sloughing of type I cells resulting in bare basal lamina. 35 days old: response plateau is reached.	(32)

Source: Modified from Graham et al. *(33)*.

Abbreviations: AM, alveolar macrophage; EM, electron microscopy; IAS, interalveolar septum; LM, light microscopy; PMN, polymorphonuclear leukocyte; RB, respiratory bronchioles; SEM, scanning electron microscopy; TB, terminal bronchioles; TEM, transmission electron microscopy

Table 2. Examples of the subchronic and chronic effects of ozone

Concentration (μg/m^3)	Exposure duration	Species	Procedure	Effect	Reference
120 and 500	120 μg/m^3 for 13 hours/day; slow 9-hour peak rising to 500 μg/m^3 for 5 days/week; 1, 3, 13 and 78 weeks, recovery for 6 weeks	Rat	TEM PFT	Shift from acute inflammatory phase to a more chronic character. Changes in the proximal alveolar region. Type I cells: increased number and volume at 1 week; increased number and volume at 13 and 78 weeks, with decreased surface area at 78 weeks; still altered 6 weeks after exposure. Type II cells: biphasic response – changes at 1 week and 3 and 20 months only. Total interstitium increased at 78 weeks and noncellular interstitium increased at 13 and 78 weeks. Some changes (increased volume of type II cells and thickened basement membrane) did not completely return to normal 6 weeks after exposure. Increased collagen observed. Increased AMs at 1 week only. Increased expiratory resistance at all times, but mostly at 78 weeks.	(34)
240, 500 and 1000	21 hours/day for 6, 12 and 18 months	Rat	Bio-chemical analyses	No change in total lung collagen.	(35)
240 and 500	12 hours/day for 6 weeks	Rat (neonates and young adults)	TEM PFT	At 500 μg/m^3 in the proximal alveolar region: increased number, surface area and thickness of type I cells; increased number of type II cells and AMs; noncellular interstitium suggested fibrotic reactions; increased tissue thickness, which increased the barrier for gas diffusion. Similar, but smaller changes at 240 μg/m^3. No significant differences between neonates and young adults. Increased lung volumes at high distending pressures at 500 μg/m^3; increased peak inspiratory flow.	(36–38)
240, 500 and 1000	21 hours/day for 3–12 months	Rat	Bio-chemical analyses	Turnover rate of lung collagen.	(39)
300 and 600	8 hours/day for 6 or 90 days	Monkey	LM, EM	Respiratory bronchiolitis at 6 days, persisting to 90 days of exposure; nonciliated bronchiolar cells were hypertrophied and increased in number.	(40)
300 and 600	8 hours/day for 6 or 90 days	Monkey	TEM SEM	Epithelial hyperplasia; RB epithelium and interstitium thickened. No inflammatory cell infiltration other than increased AMs in RBs.	(41)

Concentration (μg/m^3)	Exposure duration	Species	Procedure	Effect	Reference
400, 1000 and 1600	8 hours/day for 20, 50 or 90 days	Rat	LM, EM	Epithelial changes and AM accumulations at 90 days similar to 7-day exposures, but less severe. The 1000- and 1600-μg/m^3 groups had centriacinar AMs at all times. No effect at 400 μg/m^3. The 90-day 1600-μg/m^3 group had changes in the terminal bronchiole-alveolar duct junctions. TBs had loss of or shortened cilia. Nonciliated cells were flattened. Proximal alveoli in the 20- and 90-day 1600-μg/m^3 groups had thicker blood/air barriers.	*(42)*
500	Continuous (8 hours/day for 18 months) and seasonal (1 month ozone then 1 month air, repeated for 18 months)	Monkey	LM	Both groups: increased respiratory bronchiolitis and increased number of RBs and alterations in lung growth. Continuous group: increased inflammatory cells in lumen and interstitium. Seasonal group: increased total lung collagen, chest wall compliance and inspiratory capacity.	*(43)*
500	12 hours/day for 6 weeks	Rat (neonates and young adults)	EM	Effects on the terminal bronchiolar region. Decreased ciliated surface of Clara cells and number of brush cells per square millimetre of terminal bronchiolar basement membrane.	*(44)*
800 and 130	8 hours/day for 90 days	Monkey	LM, EM	Changes in respiratory bronchioles: thicker walls, narrower lumens; more cuboidal, fewer squamous cells; thicker interstitium; and more cellular organelles associated with protein synthesis.	*(45)*
1000	20 hours/day for 52 weeks	Rat	LM	At 6 and 12 months: increased functional reserve capacity and residual volume, diffusion capacity for carbon dioxide, and inflammation. Recovery by 3 months after exposure.	*(46)*
1000, 1600, 2200 and 3000	24 hours/day for 7, 14 and 21 days	Rat	Bio-chemical analyses	Increased collagen synthesis rate at all exposures; correlated with fibrosis (histological) of alveolar duct walls after 14 or 21 days. Effects concentration-dependant; for duration, 7 days < 14–21 days.	*(31)*

Concentration (μg/m^3)	Exposure duration	Species	Procedure	Effect	Reference
1140 and 2200	19 hours/day for 11 days	Rat	EM	At day 12, concentration-dependent inflammation, type II cell hyperplasia. Increased elastolytic/collagenolytic activities. Reduced intracellular collagenolysis. At 60 days after exposure, increased total collagen and modest alveolar duct fibrosis.	(47)
1220	8 hours/day for 1 year	Monkey	Bio-chemical analyses	Increased lung collagen with altered cross-linking; "abnormal" collagen deposited and the change was irreversible 6 months after exposure.	(48)

Source: Graham et al. *(33).*

Abbreviations: AM = alveolar macrophage; EM = electron microscopy; LM = light microscopy; PFT = pulmonary function tests; PMN = polymorphonuclear leukocyte; RB = respiratory bronchioles; SEM = scanning electron microscopy; TB = terminal bronchioles; TEM = transmission electron microscopy.
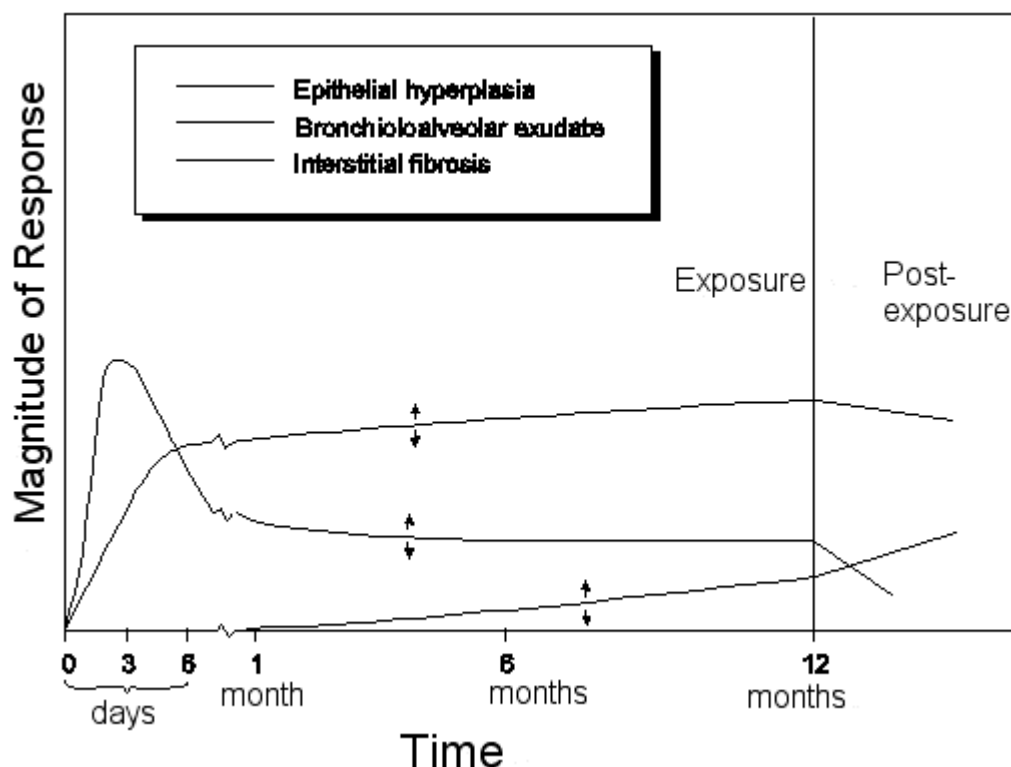
Fig. 1. Schematic comparison of the influence of the duration of exposure to ozone on the morphology of the centriacinar region *(55)*

For a number of species, acute exposure to ozone concentrations of $> 400\ \mu g/m^3$ for 2–3 hours resulted in tachypnoea (increased breathing rate and decreased tidal volume) increased pulmonary resistance, decreased lung volumes (total lung capacity and vital capacity), decreased dynamic pulmonary compliance, decreased diffusion capacity, and increased airway responsiveness *(1)*. The latter response is induced only at relatively high ozone concentrations (typically $> 2000\ \mu g/m^3$) and appears not to be dependent upon the presence of polymorphonuclear leukocytes or their products (e.g. prostaglandins, leukotrienes, etc.), although it may be related to elevated responses to endogenous tachykinins (e.g. substance P). These responses are generally resolved rapidly and disappear within 2 weeks after cessation of exposure *(1,2)*. Repeated acute exposure results in attenuation of some pulmonary function responses over several days of exposure, but morphological changes progress and BAL protein levels remain persistently elevated for all 5 days of exposure.

A wide range of extrapulmonary effects has been identified following ozone exposure *(1)*. Whether these effects are caused by ozone itself or by reactive intermediates or biogenic compounds formed in the respiratory tract, or whether they are an expression of secondary reactions to pulmonary injury is unknown. Ozone exposure causes alterations in circulating red cells and in various components of the serum. Biochemical and morphological changes in red cells have been observed in several animal species after exposure to $400\ \mu g/m^3$ for 4 hours. Changes in enzyme activities, proteins and peptides have been reported at ozone concentrations of $400\ \mu g/m^3$ for 4 hours *(56)*. Ozone exposure decreases the activity level of experimental animals at levels of $240\ \mu g/m^3$ for 6 hours *(57)*. It is unknown whether indirect effects, such as response to lung irritation or reaction to the odour of ozone, or a direct effect

on the central nervous system cause this alteration. Morphological effects on the thyroid and parathyroid gland have been reported *(1)*. No significant teratogenic effects have been observed in offspring from pregnant female rats exposed to 880–3900 µg/m³ for 8 hours. Some delay in developmental behaviours was seen in rat pups from ozone-exposed mothers *(58,59)*. Ozone may alter xenobiotic metabolism in the liver as evidenced by a sex-specific increase in drug-induced sleeping time in female, but not male, animals of several species after exposure to ozone concentrations of 2000 µg/m³ for 5 hours *(1)*.

In vitro studies using high concentrations of ozone (> 10 mg/m³) suggest that ozone has a weak or no potential to cause mutagenic, cytogenetic or cellular transformation effects *(1)*. In a recent cancer bioassay study *(60)*, no evidence of carcinogenicity was found in rats exposed to up to 2000 µg/m³ for 6 hours/day, 5 days/week for life. In female, but not male, mice, some evidence of carcinogenesis was found when the data for animals exposed to 2000 µg/m³ for 2 years were combined with data for animals exposed for their lifetime. Results in male mice were equivocal. There was no concentration–response relationship; there was no evidence of carcinogenesis in animals exposed to 1000 or 240 µg/m³ for 2 years. This study also showed that ozone was not a tumour promoter or co-carcinogen in male rats treated with a tobacco carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and exposed to ozone at a concentration of 1000 µg/m³ (0.5 ppm) for 2 years. Thus, only chronic exposure to a high concentration (2000 µg/m³) has been shown to evoke a limited degree of carcinogenic activity in one sex of one strain of mice *(1)*.

Peroxyacetyl nitrate is far less toxic than ozone with respect to its effect on lethality, behaviour, morphology and the pulmonary defence system *(61,62)*. The concentrations of peroxyacetyl nitrate used in these studies (25–750 mg/m³) are considerably higher than maximal concentrations of peroxyacetyl nitrate in the ambient air in regions with high oxidant levels (0.09 mg/m³).

Effects on Humans

Human clinical studies
In a large number of controlled human studies, significant impairment of pulmonary function has been reported, usually accompanied by respiratory and other symptoms *(1,63)* Single acute ozone exposure studies have lasted from 1 to 8 hours with exposure concentrations ranging from 160 to 1000 µg/m³. (Some of the older literature reports exposure to higher concentrations, but recent studies have used ozone levels of 1000 µg/m³) *(1)*. In addition to healthy young Caucasian male adults (the most studied group), men and women of several races, older adults and children, and people with asthma, chronic obstructive lung disease and cardiovascular disease have been exposed. In many of the initial studies, a pattern of 15 minutes of intermittent exercise alternating with 15 minutes of rest was employed for the duration of the exposure, the intent being to mimic outdoor activity during a brief ozone episode. Many other exposure patterns have been utilized, including continuous exercise for periods of up to 90 minutes and intermittent activity varying from 15 to 50 minutes of exercise per hour for periods of up to 8 hours. The level of minute ventilation has an important influence on the onset and magnitude of the response to ozone exposure. An increased level of exercise results in increases in the volume of inhaled ozone and the increased delivery of ozone to the peripheral airways of the lung *(1)*. Pulmonary function measurements have been made before, during, and directly after exposure *(1,63–70)*, as well as for several days following exposure. The studies are summarized briefly below.

With 1–3 hours of ozone exposure in normal subjects during moderate-to-heavy exercise (ventilation > 45 litres/minute), changes in pulmonary function have been reported for the following tests (lowest-observed-effect levels under conditions of strenuous exercise):

1. forced expiratory volume in 1 second (FEV$_1$) (240 µg/m^3) *(71–73)*

2. airway resistance (360 µg/m^3) *(74)*

3. forced vital capacity (FVC) (240 µg/m^3) *(71,72)*

4. increased respiratory frequency (400 µg/m^3) *(72)*.

With 4–8 hours of ozone exposure in healthy young adults engaged in moderate exercise, the following changes in pulmonary function tests have been reported *(73)*:

1. FEV$_1$, 160 µg/m^3

2. airway resistance, 160 µg/m^3

3. FVC, 200 µg/m^3

4. increased airway responsiveness, 160 µg/m^3.

Fig. 2 presents a model based on the study of Horstman et al. *(73)* indicating the fraction of the exposed population who would be predicted to experience 5%, 10% and 15% decrements in FEV$_1$ for various combinations of ozone concentration and duration expressed as the CT exposure dose (ozone concentration (µg/m^3) × hours of exposure) *(75)*. From this figure, it can be estimated that the most sensitive 10% of subjects, while engaged in moderately strenuous activity during ozone exposure, would experience a 10% decrement in FEV$_1$ with an exposure dose of approximately 600 µg/m^3 × hours (e.g. 200 µg/m^3 for 3 hours). The determinants of the ozone response include not only the CT product but also the dose-rate (the concentration–ventilation product, CV$_E$). This is illustrated in the study by Hazucha et al. *(76)* which demonstrated greater responses to ozone at a higher dose rate even though the overall CT exposure was the same. This study also demonstrated that prolonged exposure (8 hours) to a low concentration (240 µg/m^3) resulted in a plateau of pulmonary function response after 5 or 6 hours, indicating that these responses do not continue to decline with increasing duration of exposure. Nevertheless it must be recognized that active outdoor exposures of an hour or so would be experienced by no more than 2–3% of the general population.

The severity of respiratory and other symptoms parallels the impairment of pulmonary function both in magnitude and time-course *(1)*. Nevertheless, pulmonary function and symptom responses are not highly correlated on an individual basis. Symptoms that have been reported include cough, throat irritation, pain on deep breath, chest tightness, substernal pain and, rarely, headache and nausea. In addition to causing functional changes and symptoms, ozone is capable of inducing increased nonspecific airway responsiveness to acetylcholine, methacholine, and histamine *(1,66,67)*. Ozone has more recently been implicated in increased airway reactivity to antigen challenge *(77,78)*, although these data are just emerging and exposure–response relationships have not been established.
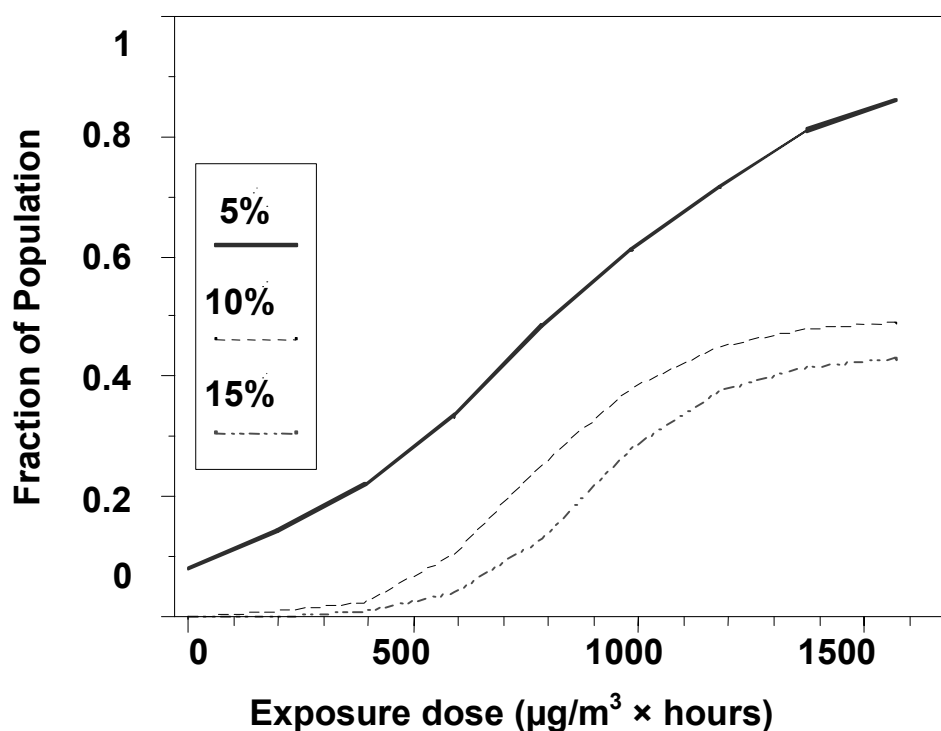
Fig. 2. Proportion of moderately exercising young adults exposed to ozone for 6.6 hours predicted to experience 5%, 10% or 15% decrements in forced expired volume in 1 second as a function of exposure dose expressed as $\mu g/m^3$ × hours *(72)*

Ozone causes a mild acute inflammatory response in the lung, as shown by several recent studies employing BAL. Ozone-induced damage of type I alveolar epithelial cells and ciliated airway epithelial cells results in release of proinflammatory mediators such as interleukins 6 and 8 and prostaglandin E_2. Release of these and other mediators leads to an influx of polymorphonuclear leukocytes, activation of alveolar macrophages, inflammation, and increased epithelial permeability. The inflammation is characterized by erythema of the airways, accumulation of polymorphonuclear leukocytes, and increased levels of protein and various inflammatory mediators. Some measures of the phagocytic capacity of alveolar macrophages also decline with ozone exposure. The elaboration of the response mechanism and meaning of changes in all mediators is not fully understood. With exposures of 1–3 hours with heavy exercise, these responses have been observed at ozone levels as low as 400 $\mu g/m^3$, but results at lower levels have not been reported. With exposures of 6–8 hours including moderate exercise, modest responses are observed at 160 $\mu g/m^3$. Inflammatory responses are also observed in the nasal airway; the lowest concentration at which this response is seen is 800 $\mu g/m^3$ in resting subjects *(79)*. At outdoor ozone levels of > 180 $\mu g/m^3$ (maximum level 263 $\mu g/m^3$), evidence suggests that schoolchildren in Germany (Freiburg) may experience nasal airway inflammation *(80)*, indicating that people engaged in recreational activity outdoors may show ozone responses.

The inflammatory response develops within an hour after exposure and persists over at least 20 hours, although the pattern of response changes over time. Elevated levels of acute proinflammatory mediators (such as prostaglandin E_2 and interleukin-6) are most pronounced

immediately after exposure, whereas polymorphonuclear leukocyte levels peak some 6–12 hours later; mediators that are thought to be involved in the repair processes (e.g. fibronectin) are most elevated after 18–20 hours. The duration and time-course of the acute inflammatory response probably vary from subject to subject and under different exposure conditions, and have not been studied in sufficient detail to describe with any certainty at present *(1)*.

Functional recovery from a single exposure is not linear with respect to time. Initially, there is a rapid improvement of pulmonary function and symptoms; typically a 50% improvement within 1–3 hours and a return to pre-exposure values within 24–48 hours. Recovery of other regulatory systems does not necessarily parallel the functional and symptomatic recovery, and effects may persist for longer than 48 hours.

Repeated daily short-term chamber exposures result in an altered pattern of response to ozone. With repeated exposure to relatively high ozone concentrations, the decrements in pulmonary function are larger after the second exposure day than after the first *(1,81)*. This enhanced responsiveness may persist for up to 48 hours, depending on the level of exposure. With continuing exposures after a second day, responsiveness to ozone eventually attenuates and minimal changes are typically observed after the fourth or fifth exposure days. With exposure to lower ozone concentrations or exposure regimens inducing smaller functional responses, the first day response is maximal and attenuation of response begins with the second exposure *(82)*. Attenuation of respiratory symptoms follows a similar time-course to that in pulmonary function responses. Such attenuation as a result of repeated chamber exposures apparently occurs only when the initial exposure is sufficient to cause functional changes *(1,68)* and persists for only 4–7 days. Some elements of the inflammatory response are still detectable after 5 days of exposure, but the overall pattern of cells and mediators is considerably modified from that seen immediately after a single acute exposure *(83)*. Animal studies indicate that cellular damage does not attenuate *(84)*, a finding supported by the elevated level of lactate dehydrogenase observed after 5 days of chamber exposure of humans.

A number of early studies of patients with chronic obstructive lung disease and asthma suggested that these subjects were similar to healthy subjects in their spirometric responses to ozone *(1,65,69)*. More recently it has been shown that asthmatics have a similar "restrictive" response (i.e. decreased FVC) but a greater bronchoconstrictive response (i.e. increased airway resistance) than nonasthmatics *(85)*. Ozone can also increase maximal response to a bronchoconstrictor 12 hours after ozone exposure of both healthy and asthmatic subjects, the effect being greater in healthy subjects *(86)*. In another study, Scannell et al *(87)* studied the response of a group of asthmatic subjects exposed to ozone using the same protocol previously used for healthy subjects and found no significant differences in lung function responses and a nonsignificant trend toward higher airway resistance. The asthmatic subjects had significantly greater ozone-induced increases in inflammatory endpoints (percentage of neutrophils + total protein) in BAL fluid.

The responses of chronic obstructive pulmonary disease patients, who were middle-aged and older adults, were not compared to those in age-matched healthy controls, thus their relative responsiveness is unknown. However, it appears that older adults are less responsive than young adults *(88)*. Cigarette smokers are apparently less responsive to ozone than nonsmokers, and their responsiveness may return after a period of smoking cessation *(1,89)*.

Patients with lung disease and smokers are thought to be at increased risk from ozone-induced decrements in lung function since any decrement will have more serious health consequences because of their already compromised lung function. There are insufficient data to determine whether males or females are more responsive to ozone, though differences are likely to be small, if they exist *(1)*. The possibility of racial differences in sensitivity has not been extensively investigated, but there is no evidence of clear differences in response between Americans of European descent and those of African descent *(74)*. Within an apparently normal population, there is a broad range of responsiveness to ozone among healthy young adults. Responses within individuals appear to be reproducible over a period of several months (i.e. an individual who is highly responsive remains highly responsive). The reproducibility of responses among children and persons with respiratory disease is not established, but the responses of older subjects, which are generally smaller, may be less reproducible than those of young adults *(1)*.

At peroxyacetyl nitrate levels (1350 or 650 μg/m^3) much higher than typical maximal ambient levels (100–150 μg/m^3), no significant effects on pulmonary function were observed. Peroxyacetyl nitrates may act additively with ozone at these high concentrations. However, even at maximal ambient levels, little effect would be expected *(1,90,91)*.

Field and epidemiological studies
Field and epidemiological studies have indicated a number of acute health effects that are associated with ambient levels of ozone or oxidants. Associations have been demonstrated between daily ozone levels and mortality, hospital admissions for respiratory disease, and emergency room visits. Kinney and Ozkaynak *(92,93)* indicated that an increase of 0.4–0.8 deaths per day per million persons was associated with an increase of 200 μg/m^3 in the concentration of ozone, although this relationship was no longer present when total suspended particulate levels were subsequently accounted for. Anderson et al. *(94)* reported a 3.5% increase in all-cause mortality associated with a 57 μg/m^3 increase in ozone concentration. The association was stronger in the summer than in the winter. The limited number and inconsistent outcomes of studies (see also *95–97*) do not provide a strong consensus that ozone is causally related to mortality. The strongest and most consistent association is with hospital admissions for respiratory causes in a variety of North American locations (e.g. southern Ontario, Canada; New York, New Jersey and Atlanta, GA, USA) *(98–103)* and in some cities in Europe (e.g. London, Helsinki) *(104,105)* Ozone is significantly associated with medical treatment for asthma (i.e. hospital admissions, emergency room visits) especially in eastern North America *(99–103)* but also in Helsinki *(105)* and Rotterdam *(106)*, positively but not significantly associated in Amsterdam *(106)* and not significantly in Paris *(107)* and Seattle *(108)*. It has been estimated that ambient ozone accounts for one to three excess respiratory hospital admissions per million population for each 200 μg/m^3 increase in concentration *(1)*.

A series of field studies, commonly referred to as "camp studies", using children and adolescents exposed to ambient air while attending summer camps, provides an extensive database from which to estimate spirometric responses to ambient ozone. A key measurement is the slope of the relationship between FEV$_1$ and the ozone concentration during the previous hour (even though exposures have occurred over multiple hours). The average slope from six studies was 0.32 ml per μg/m^3 (0.64 ml/ppb) within an ozone concentration range of 20–320 μg/m^3 *(1)*. For an exposure to 200 μg/m^3, this corresponds to a decrease in FEV$_1$ of 64 ml from a base level of approximately 2000–2500 ml, a decrease of 2.5–3.5%. This is

comparable to the findings of McDonnell et al. *(69)* for boys aged 8–11years exposed to 240 μg/m^3 for 2 hours; they found a 3.4 % decrease in FEV_1. However, the latter children performed heavy intermittent exercise during 60 minutes of their exposure. Thus the exposures are dissimilar in both activity level and overall duration of exposure. Recent studies have shown an association between decreased spirometry in adults performing outdoor exercise and increased ambient ozone levels *(109–111)*. In one of these studies *(111)* the FEV_1 decrements averaged about 1 ml per μg/m^3, corresponding to average changes of up to 3.5%. Such responses are similar to changes that have been observed in subjects exposed to comparable levels of ozone (in terms of concentration, duration and exercise intensity) in controlled environmental chambers.

Ambient oxidant levels have been associated with respiratory symptoms, especially cough, beginning at exposures of about 300–400 μg/m^3 *(1)*. In asthmatics exposed to ozone in their daily lives, an increased incidence of asthmatic attacks and respiratory symptoms has been associated with increased ozone levels although this effect is often difficult to separate from other cofactors (temperature, biocontaminants, other pollutants).

A new finding, not yet corroborated, found associations between an annual average increase in ozone concentration of 10 ppb and development of asthma in men, but not women *(112)*. Apparently, men were more affected because they spent more time outdoors.

In contrast to all of the previously cited studies of healthy subjects, Thurston et al. *(113)* studied the responses of a group of children with moderate to severe asthma to summer-time haze pollution at summer camp in rural Connecticut. The responses measured were changes in peak expiratory flowrate (PEFR), symptom frequency and unscheduled medication usage approved by an on-site physician as a function of daily measurements of pollutants, pollen and ambient temperature. Significant concentration-related changes were reported for ozone and for the hydrogen ion and sulfur oxide content of fine particles in respect of PEFR, lower respiratory symptoms and unscheduled physician approved medication usage (both with and without adjustment for the effects of temperature).

Comparable studies in healthy children by the same group of investigators *(11, 110)* found no symptom responses or medication usage. PEFR responses to ozone concentrations were similar in magnitude, but the healthy children were much more physically active and therefore had higher doses to airway surfaces. Thus, the asthmatic children had greater dose-related function changes which, when considered in relation to their reduced functional capacity, represent a greater health stress. Furthermore, these responses were occurring at relatively low ambient ozone concentrations. The highest peak daily ozone concentration was 300 μg/m^3, but the responses were still statistically significant when days with peak concentrations of > 180 μg/m^3 were excluded.

The greater responsiveness of asthmatic children to ambient ozone suggests that subjects with asthma may be expected to seek acute care services from private physicians, clinics and hospitals. This hypothesis is supported by findings reported for ozone-associated clinic visits *(102)*, hospital emergency room visits *(103)* and hospital admissions for asthma and other respiratory disease *(99–101,114)*.

An early observation with respect to ambient oxidant exposure was that the performance of runners exposed to oxidants was impaired when the oxidant concentration was in the range 240–740 µg/m^3 *(115)*. Chamber exposures have also shown an effect of ozone on exercise performance *(1)*. A 16% reduction of maximal oxygen uptake has been observed with 1-hour heavy-exercise exposures at ozone levels as low as 400 µg/m^3. Exercise performance is clearly impaired at exposure levels of 320–480 µg/m^3 *(1)* and possibly as low as 120 µg/m^3 *(116)*.

Using a movable chamber in a highly polluted area, it was shown that the effect of ambient air containing ozone was similar to that of the same level of ozone generated in purified air *(117–124)*. Human clinical studies have shown few and variable interactions with other pollutants (e.g. nitrogen dioxide, sulfur dioxide, sulfuric acid, etc.) but typically no more than additive responses with respiratory symptoms or spirometry as an endpoint *(1)*. In one study, ozone exposure increased airway responsiveness to sulfur dioxide in asthmatics *(125)*.

There is limited information linking long-term ozone exposure to chronic health effects. In comparisons between residents of communities with "high" and "low" ozone/oxidant levels, differences have been observed in airway responsiveness *(126)* and, possibly, pulmonary lesions *(127)*. The latter observations are based on limited autopsy data and do not include exposure assessment for ozone, smoking or occupation. Although there is a suggestion that cumulative ozone exposures may be linked with increasing asthma severity and the possibility of increased risk of new asthma *(128)*, this association is not clearly established. A persistent problem in the analyses of associations between acute and chronic health indices and ambient ozone levels is the strong association with particulate levels in many studies, making it difficult to assess the role of ozone *per se*. Nevertheless, the evidence provided by studies of health effects that relate to chronic ambient ozone exposure is consistent in indicating chronic effects on the lung *(1)*.

Photochemical air pollution is a causative factor in eye irritation. This is due to non-ozone components (e.g. peroxyacetyl nitrate) of the photochemical mixture and occurs when ozone levels are above 200 µg/m^3.

Evaluation of human health risks

Exposure
Ozone and other photochemical oxidants are formed by the action of short-wavelength radiation from the sun on nitrogen dioxide. In the presence of volatile organic compounds, the equilibrium favours the formation of higher levels of ozone. Background levels of ozone, mainly of anthropogenic origin, range from 40 to 70 µg/m^3 (0.02–0.035 ppm) but can be as high as 120–140 µg/m^3 (0.06–0.07 ppm) for 1 hour. In Europe, maximum hourly ozone concentrations may exceed 300 µg/m^3 (0.15 ppm) in rural areas and 350 µg/m^3 (0.18 ppm) in urbanized regions. Submaximal levels (80–90 % of maximum) can occur for 8–12 hours a day, for many consecutive days.

Health risk evaluation
Ozone toxicity occurs in a continuum in which higher concentrations, longer exposure duration and greater activity levels during exposure cause greater effects. Short-term acute effects include respiratory symptoms, pulmonary function changes, increased airway

responsiveness and airway inflammation. These health effects are statistically significant at a concentration of 160 μg/m^3 (0.08 ppm) for 6.6-hour exposures in a group of healthy exercising adults, with the most sensitive subjects experiencing functional decrements of >10% within 4–5 hours. Controlled exposures of heavily exercising adults or children to an ozone concentration of 240 μg/m^3 (0.l2 ppm) for 2 hours have also been observed to produce decrements in pulmonary function. There is no question that substantial acute adverse effects occur with 1 hour of exercising exposure at concentrations of 500 μg/m^3 or higher levels, particularly in susceptible individuals or subgroups.

Field studies in children, adolescents and young adults have indicated that pulmonary function decrements can occur as a result of short-term exposure to ozone concentrations in the range 120–240 μg/m^3 and higher. Mobile laboratory studies using ambient air containing ozone have observed associations between changes in pulmonary function in children or asthmatics and ozone concentrations of 280–340 μg/m^3 (0.14–0.17 ppm) with exposures lasting several hours. Respiratory symptoms, especially cough have been associated with ozone concentrations as low as 300 μg/m^3 (0.15 ppm). Ozone exposure has also been reported to be associated with increased hospital admissions for respiratory causes and exacerbation of asthma. That these effects are observed both with exposures to ambient ozone (and co-pollutants) and with controlled exposures to ozone alone demonstrates that the functional and symptomatic responses can be attributed primarily to ozone.

A number of studies evaluating animals (rats and monkeys) exposed to ozone for a few hours or days have shown alterations in the respiratory tract in which the lowest-observed-effect levels were in the range of 160–400 μg/m^3 (0.08–0.2 ppm). These included the potentiation of bacterial lung infections, inflammation, morphological alterations in the lung, increases in the function of certain lung enzymes active in oxidant defences, and increases in collagen content. Long-term exposure to ozone in the range 240–500 μg/m^3 (0.12–0.25 ppm) causes morphological changes in the epithelium and interstitium of the centriacinar region of the lung, including fibrotic changes.

Guidelines

The selection of guidelines for ambient ozone concentrations is complicated by the fact that detectable responses occur at or close to the upper limits of background concentrations. At ozone levels of 200 μg/m^3 and lower (for exposure periods of 1–8 hours), there are statistically significant decrements in lung function, airway inflammatory changes, exacerbations of respiratory symptoms and symptomatic and functional exacerbations of asthma in exercising susceptible people. Functional changes and symptoms as well as increased hospital admissions for respiratory causes are also observed in population studies. Thus it is not possible to base the guidelines on a no-observed-adverse-effect level or a lowest-observed-adverse-effect level with an uncertainty factor of more than a small percentage. Thus, selection of a guideline has to be based on the premise that some detectable functional responses are of little or no health concern, and that the number of responders to effects of concern are too few to represent a group warranting protection from exposures to ambient ozone.

In the case of respiratory function responses, a judgement could be made that ozone-related reductions in FEV$_1$, for example, of < 10% were of no clinical concern. In the case of clinic visits, emergency room visits or hospital admissions for respiratory diseases, it would be necessary to determine how many cases per million of population would be needed to

constitute a group warranting societal protection. In the case of asthmatic children needing extra medication in response to elevated ozone concentrations, it would be necessary to conclude that medication will be available to sufficiently ameliorate their distress and thereby prevent more serious consequences. On such a basis, a guideline value for ambient air of 120 $\mu g/m^3$ for a maximum period of 8 hours/day is established as a level at which acute effects on public health are likely to be small.

For those public health authorities that cannot accept such levels of health risk, an alternative is to select explicitly some other level of acceptable exposure and associated risk. Tables 3 and 4 summarize the ambient ozone concentrations that are associated with specific levels of responses among specified population subgroups. Although chronic exposure to ozone can cause effects, quantitative information from humans is inadequate to estimate the degree of protection from chronic effects offered by this guideline. In any case, the ozone concentration at which any adverse health outcome is expected will vary with the duration of the exposure and the volume of air that is inhaled during the exposure.

Table 3. Health outcomes associated with controlled ozone exposures

Health outcome	Ozone concentration ($\mu g/m^3$) at which the health effect is expected	
	Averaging time 1 hour	Averaging time 8 hours
Change in FEV_1 (active, healthy, outdoors, most sensitive 10% of young adults and children): 5% 10% 20%	250 350 500	120 160 240
Increase in inflammatory changes (neutrophil influx) (healthy young adults at >40 litres/minute outdoors) 2-fold 4-fold 8-fold	400 600 800	180 250 320

Thus, the amount of time spent outdoors and the typical level of activity are factors that should be considered in risk evaluation. Table 3 summarizes the ozone levels at which two representative adverse health outcomes, based on controlled exposure experiments, may be expected. The concentrations presented in this table have been established by experts on the basis of collective evidence from numerous studies and linear extrapolation in a few cases where data were limited. The studies on which this expert judgement was based have been cited above.

Epidemiological data show relationships between changes in various health outcomes and changes in the peak daily ambient ozone concentration. Two examples of such relationships are shown in Table 4. Short-term increases in levels of ambient ozone are associated both

with increased hospital admissions with a respiratory diagnosis and respiratory symptom exacerbations both in healthy people and in asthmatics. These observations may be used to quantify expected improvements in health outcomes that may be associated with lowering the ambient ozone concentration. The values presented in the table assume a linear relationship between ozone concentration and health outcome. However, uncertainties exist concerning the forms of these relationships and it is unclear whether similar response slopes can be expected at widely different ambient ozone levels. In the event that such relationships are curvilinear (i.e. concave), the benefits of lowering the ozone concentration are likely to be greater when the average ambient level is higher. Consequently, if the ambient ozone concentration is already low, the benefits of lowering the concentration may be less than would be suggested by Table 4. Another important area of uncertainty is the degree to which other pollutants influence these relationships.

Table 4. Health outcomes associated with changes in ambient ozone concentration in epidemiological studies

Health outcome	Change in ozone concentration ($\mu g/m^3$)	
	Averaging time 1 hour	Averaging time 8 hours
Increase in symptom exacerbations among adults or asthmatics (normal activity) 25% 50% 100%	200 400 800	100 200 300
Increase in hospital admissions for respiratory conditions: [a] 5% 10% 20%	30 60 120	25 50 100

[a] Given the high degree of correlation between the 1-hour and 8-hour ozone concentration in field studies, the reduction in health risk associated with decreasing 1-hour or 8-hour ozone levels should be almost identical.

The first edition of *Air quality guidelines for Europe (129)* recommended a 1-hour guideline value of 150–200 $\mu g/m^3$. Although recent research does not indicate that this guideline would necessarily be erroneous, the 8-hour guideline would protect against acute 1-hour exposures in this range and thus it is concluded that a 1-hour guideline is not necessary. Furthermore, the health problems of greatest concern (increased hospital admissions, exacerbations of asthma, inflammatory changes in the lung, and structural alterations in the lung) are more appropriately addressed by a guideline value which limits average daily exposure, and consequently inhaled dose and dose rate, rather than one designed to cover the rare short-duration deteriorations in air quality that may be associated with unusual meteorological conditions.

A guideline for peroxyacetyl nitrate is not warranted at present since it does not seem to pose a significant health problem at the levels that are observed in the environment.

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