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Ministry of Social Affairs
and Employment

Health-based recommended occupational exposure limit for ozone

Dutch expert committee en occupational standards
(met Nederlandse samenvatting)

RA 4/92

Labour Inspectorate

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This is a report of the Dutch Expert Committee on occupational standards (DECOS). The draft-document has been prepared by A.A.E. Wibowo

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NEDERLANDSTALIGE SAMENVATTING
OZON

1. FYSISCHE EN CHEMISCHE EIGENSCHAPPEN

Ozon is een gas, zwaarder dan lucht, met stekende geur. Bij kamertemperatuur ontleedt ozon snel in zuurstof; in een gasfles heeft ozon een halfwaardetijd van 3 dagen bij 20° C en 3 maanden bij -50° C. De stof ontleedt bij verhitting met kans op brand en explosie. De stof is een sterk oxidatiemiddel en reageert heftig met brandbare en reducerende stoffen. Het heeft een kookpunt van -112° C en een smeltpunt van 193° C. De relatieve dichtheid is 1,6 (water = 1) en de relatieve dampdichtheid is 1,7 (lucht = 1).

2. MONITORING

Het NIOSH beschrijft twee methoden voor monitoring van ozon op de werkplek. Bij beide methoden wordt gebruik gemaakt van de spectrofotometrie voor de analyse van de monsters; het verschil ligt in de voorbewerking van de luchtmonsters. Er is geen werkwijze bekend voor biologische monitoring van werknemers die blootgesteld zijn aan ozon.

3. GRENSWAARDEN

De huidige MAC-waarde voor ozon in Nederland is 200 $\mu g/m^3$ (100 ppb), TGG-8 uur. Deze grenswaarde wordt ook gebruikt in Duitsland, het Verenigd Koninkrijk, Zweden en Frankrijk, een waarde oorspronkelijk overgenomen van de TLV-lijst. Anderzijds heeft de ACGIH recentelijk deze grenswaarde van 200 $\mu g/m^3$ tot een plafond-waarde opgewaardeerd.

4. TOXICOKINETIEK

De opname van ozon in de luchtwegen kan beinvloed worden door een aantal factoren: de concentratie van ozon in de inademingslucht, de anatomische structuur van de luchtwegen, de invloed van de slijmvliezen van de bovenste luchtwegen, de luchtstroom in de luchtpassages en de chemische/fysische eigenschappen van de stof zelf.
Ozon is matig oplosbaar in water wat betekent dat een overgroot deel van de geïnhaleerde hoeveelheid de kleinste bronchiën en de alveolen kunnen bereiken. Experimenten met jong-volwassen vrijwilligers tonen aan dat ongeveer 85 % van de ozon die de borstkas binnen dringt opgenomen wordt. Er zijn geen aanwijzingen over de aanwezigheid van ozon in de andere inwendige organen. Bij het metabolisme van ozon is

bekend dat het grote oxidatievermogen ten grondslag ligt aan de capaciteit om nadelige effekten te veroorzaken, o.a. oxidatie van thiolen en aminozuren van eiwitten en peptiden, oxidatie van onverzadigde vetzuren tot hun peroxiden.

5. EFFEKTEN

De luchtwegen vormen het doelorgaan bij blootstelling aan ozon, alle delen van de ademhalingswegen kunnen nadelig beinvloed worden. In de bovenste luchtwegen kan necrose van de epitheelcellen ontstaan. Men schat de NAEL bij de mens voor dit soort effekten op minder dan 800 $\mu g/m^3$ na een twee uur durende blootstelling. In de diepere luchtwegen is het centro-ácinus gebied het meest gevoelig voor ozon. Hierin worden de geciliëerde cellen en de Type I cellen beschadigd. Een ander effekt van ozon is de negatieve beinvloeding van het afweersysteem en het immunologisch systeem van de longen. Zij worden extra gevoelig voor bacteriële/virale infecties. Men schat dat de MAEL voor dit soort effekten bij de mens ligt op ongeveer 200 $\mu g/m^3$ ozon na een blootstellingsperiode van enkele uren.
Vermindering van de longfuncties kan ook vóórkomen, o.a. toename van de ademhalingsfrekwentie, vermindering van het ademvolume en toename van de luchtwegresistentie. Men schat een NAEL van 300 $\mu g/m^3$ ozon gedurende een blootstellingsperiode van 1 tot 2 uur, bij gezonde niet-rokende jong-volwassen personen. Het blijkt dat er een cumulatie van effekten optreedt, die samenhangt met de duur van blootstelling.
Ozon heeft indirekt een nadelige invloed op het prestatievermogen van het individu. Gedurende maximale inspanning van getrainde atleten die blootgesteld zijn aan ozon blijken vermindering van de piek V_E, V_{O2}, tidal volume, werkvermogen en maximale duur van inspanning voor te komen. Voor dit soort effekten wordt de NAEL geschat op 120-240 $\mu g/m^3$ gedurende een aantal uren blootstelling.

Er zijn weinig aanwijzingen naar een direkte mutageniteit/genotoxiciteit van ozon. Ook zijn er geen gegevens over mogelijke kankerverwekkende eigenschappen van ozon in de mens.

6. EVALUATIE EN ADVIES

In de gezondheidskundige evaluatie van blootstelling aan ozon, wordt grotere betekenis gehecht aan de gegevens uit humane studies dan aan proefdierstudies, daar er verschillen zijn in de toxicokinetiek tussen mens en dier.

De meest prominente niet-nadelige effekt-concentratie van ozon bij de mens ligt bij 120-240 $\mu g/m^3$ gedurende een aantal uren blootstelling.

Voor het vaststellen van een gezondheidskundige advieswaarde, stelt de WGD voor een advieswaarde van 120 $\mu g/m^3$ (60 ppb) ozon, TGG-1 uur.

Datum van afsluiting: februari 1992.

INTRODUCTION

This document is based on the report "Ontwerp basisdocument ozon" by the authors W. Sloof, R.M. van Aalst, E. Heijna-Merkus and R. Thomas in September 1987 at the Royal Institute of Public Health and Environmental Hygiene (RIVM). The contents of this document will be supplemented with more recent data as gathered through on-line search programs. A few distinctive reviews were used as overall reference sources, e.g.:

- M. Lippmann (1989) Health effects of ozone. A critical review. J. Air Pollut. Control. Assoc. 39, 672-695

- R.R. Beard (1982) Compounds of oxygen, nitrogen and carbon. In: Patty's Industrial Hygiene and Toxicology, Vol. 2c, pp 4053-4139

- W.C. Adams (1987) Effects of ozone exposure to ambient air pollution episode levels on exercise performance. Sports Medicine 4, 395-424

1. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, MONITORING

1.1 IDENTITY

1.1.1 Structure : O_3

1.1.2 Chemical names and synonyms/registry numbers

Chemical name	:	Ozone
Synonym	:	triatomic oxygen
Registry number	:	10028-15-6 (CAS nr.)
		RS 8225000 (RTECS)

1.2 PHYSICAL AND CHEMICAL PROPERTIES

Boiling point (°C)	-112
Melting point (°C)	-193
Relative density (water = 1)	1.6
Relative vapour density (air = 1)	1.7
Vapour pressure at -12°C (bar)	55
Solubility in water at 25°C (g/100 ml)	0.01
Molecular weight	48.0

Ozone is a triatomic oxygen. It is a bluish gas with a slightly pungent odor, about 1.6 times as heavy as air, and it is chemically highly reactive. At normal room temperature it slowly breaks down to oxygen. For ozone in its container, the half-life at 20°C is 3 days and at -50°C is 3 months.

Conversion factors : 1 mg/m^3 = 0.5 ppm at 20°C, 101 kPa.
1 ppm = 2 mg/m^3 at 20°C, 101 kPa.

1.3. ANALYTICAL METHODS

1.3.1 Environmental monitoring

The NIOSH (1977) recommended two different methods for monitoring ozone in work-room air:

a. In the first method, air containing ozone is drawn through a midget impinger containing 10 ml of 1% potassium iodide in a neutral (pH 6.8) buffer composed 0.1 M disodium hydrogen phosphate and 0.1 M potassium dihydrogen phosphate. The iodide liberated in the absorbing agent is determined spectro-

photometrically by measuring the absorption of the tri-iodide at 352 nm. The analysis must be completed within 30 min to 1 hour after sampling.
The range extends from 0.01 ppm to about 10 ppm. The sensitivity of the method is dependent on the volume of air sampled. The accuracy and precision of this method have not been completely determined.

b. In the second method, air containing ozone is drawn through an alkaline solution of potassium iodide. Ozone reacts to form a stable product that can be stored in solution with little loss for several days. Addition of acid to the solution liberates iodine in proportion to the collected ozone. The absorption of iodine at 352 nm is then measured spectrophotometrically.
This method has been validated over the range of 0.1 to 0.4 mg/m^3. This is the limit of the useful range for a 45-litre sample size. The method is capable of measuring smaller or larger concentrations if the sampling size is adjusted, but it has not been validated for other sample sizes. The detection limit for a 45-litre sample size is estimated to be 0.04 mg/m^3. The coefficient of variation (CV_T) for the total analytical and sampling method in the range of 0.1 to 0.4 mg/m^3 is 0.08. The average recovery of ozone from vapor samples in the range of 0.1 to 0.4 mg/m^3 was 98% for the total analytical and sampling method.

1.3.2 Biological monitoring

No method is available for biological monitoring of exposure to ozone, at present.

2. SOURCES OF EXPOSURE

2.1 NATURAL OCCURRENCE

It occurs naturally in the atmosphere, arising from the action of ultraviolet light upon oxygen at high altitudes. The maximal concentration is observed at an altitude of about 23 km, but it can be detected at all altitudes up to about 90 km. A second major source is the photochemical reaction of oxides of nitrogen and hydrocarbons from natural sources or from human activities. A third, minor source is from natural electrical discharges. The latter is most conspicious as mountain lightning storms (Beard, 1982).

2.2 MAN-MADE SOURCES

2.2.1 Production

In the Netherlands ozone is not produced for commercial purposes (Sloof et al., 1987).

2.2.2 Uses

There was little commercial use of ozone until recently when there has been a surge of interest in using it for water and sewage treatment and for the stabilization of industrial wastes. It is also used as a reactant for sterilisation of products in the pharmaceutical industry and foodproducts industry. In these applications ozone is usually produced locally by using ozonisators. At present there are no data on the magnitude of ozone usage in the Netherlands.

The most likely sources of exposures to ozone in industry are leakage from ozone-using processes and high voltage electrical equipment and from electric arc welding. The latter is more potently a source of nitrogen oxides.

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 ENVIRONMENTAL LEVELS

3.1.1 Water and food

There are no data available on the ozone levels in water and food. The RIVM report on ozone tried to estimate the maximal expected levels in surface water by using the Liss and Slater model (Sloof et al., 1987). They found for the Netherlands as mean maximal concentration of ozone in the first 10 cm surface of sea water a level of 0.8 ng/l and for fresh water a level of 50 ng/l. At deeper levels the concentrations should be lower.

3.1.2 Air (occupational)

In a normal situation the ozone concentration in indoor air is strongly related to that of outdoor air, and is usually much lower. Ozone is strongly absorbed by all kinds of surfaces, mostly by rubber, plastics and textiles; it is therefore that the lifespan of ozone in a closed room is about ten minutes. The levels indoor are strongly dependent on the ventilation. It is reported that the levels indoor are about 5 to 85% of the outdoor concentrations. In office buildings with closed windows and ventilation/recirculation systems the ozone levels are usually 30-70% of the outdoor concentrations. The outdoor concentration pattern is mirrored by the indoor pattern with a time lag of about one hour.

Hansen and Andersen (1986) studied ozone emission from 69 different photocopying machines. They found a mean emission rate of 259 µg/min with a range of 0 to 1350 µg/min. Ozone filters can minimize the ozone emission. The ozone emission from a photocopier is determined by the following factors: (1) increased electrical voltage over the corona wires, (2) AC produces twice the amount of ozone compared to positive DC and (3) increased electrical effect (Watt) results in increased ozone production.

In occupational environment ozone may be produced by electrical discharges as found in electrostatic aircleaners, by welding and cutting of metals and by sources of UV-light, e.g. sterilisation instruments (Hage, 1987).

3.2 HUMAN EXPOSURE

3.2.1 General population

According to the RIVM report, the magnitude of ozone exposure to the general

population can be estimated when some factors are known, e.g. the living place during a certain duration, the ozone ambient levels at designated places and times. On the basis of these data, an exposure model has been elaborated in the US. In this model the general population is not only distinguished according to activity patterns, but also to age, sex and physical activity. For the principal living places are discerned: indoor at home, in a motor-vehicle, outdoor near a thoroughfare or outdoor at other places. Based on these factors and ambient monitoring data it is concluded that the levels of ozone indoors at home are about 50% (35-70%) of the outdoors levels, inside the motor-vehicles are about 0-30%, and outdoors near a thoroughfare are about 10-30%. The data necessary to make such analysis in the Netherlands are not available. Nevertheless, by using an alternative model, the RIVM estimates 75% of the general population in the Netherlands are exposed to an average ozone level of about 10-35 $\mu g/m^3$ (5-18 ppb), dependent on the duration spent outdoors, on the relationship of ozone levels indoors/outdoors and on the influence of ozone emissions by traffic density.

Aircraft flying at altitudes greater than 10000 m may take in significant quantities of atmospheric ozone into their cabin ventilators. Schädell et al. (1987), measured ozone concentrations in the aircraft cabins during the whole flight of flying the Northern Transatlantic route during February to April. These flights may pass the exterior parts of the stratospheric ozone cover. In 22 flights the mean concentration of ozone was 0.59 mg/m^3 air (294 ppb). Concentrations of ozone above 1.00 mg/m^3 (498 ppb) were measured in 3 (of 22) flights lasting 6.5 to 34 minutes. In this study they used the mean value of over 30 minutes for estimating the average exposure to ozone, by using a UV-absorption ozonometer.

3.2.2 Occupational population

Not much data exist for occupational population. Hansen and Andersen (1986) determined the maximum ozone concentration in the breathing zone of 19 operators of photocopying machines. The measurements were carried out by the Technical Institute in Copenhagen, and the photocopy machines were located in 20 different places chosen at random, so as to ensure combinations of different photocopiers, different room sizes, varying degrees of ventilation and similar factors. The ozone concentration was measured after it had reached equilibrium following continued copier operation. They found the levels ranging from $\leq$ 1 ppb to 150 ppb.

Van der Wal (1986) studied the exposure of plasma welders and plasma cutters at

workplaces in the Dutch industries. In microplasma welding high ozone concentrations were found in the breathing zone of some welders. This is due to the very short distance between the plasma torch and the welder's face which was less than 20 cm. The breathing zone levels of ozone on most locations was less than 5 $\mu g/m^3$ (2.5 ppb), but one with an ignited torch was 20-80 $\mu g/m^3$ (10-40 ppb), one breathing zone cutter had 10-30 $\mu g/m^3$ (5-15 ppb) and another had < 5-500 $\mu g/m^3$ (< 2.5-250 ppb) dependent on distance between torch and face.

4. GUIDELINES AND STANDARDS

4.1 GENERAL POPULATION

The Public Health Council of the Netherlands (Gezondheidsraad, 1984) recommended a limit of 120 $\mu g/m^3$ (60 ppb) as a maximal one-hour average. They also noted that the ambient level, at the least, should be lower than 200 $\mu g/m^3$ (100 ppb).

In the Netherlands the (current official) interim limit level of ozone is 240 $\mu g/m^3$ (120 ppb) t.w.a. 1 hour, not to be exceeded for more than 5 days per year. The interim target level is 120 $\mu g/m^3$ (60 ppb) t.w.a. 1 hour, not to be exceeded for more than 1 day per year (IDC, 1985).

The RIVM (1987) in her recent evaluation recommended a standard of 160 $\mu g/m^3$ (80 ppb) as a maximal one-hour average. At the same time they expressed the need to advise also a standard for longer period, resulting in a maximal 8-hour average of 110 $\mu g/m^3$ (55 ppb).

In 1988, based upon evaluation of the RIVM criteria document, the Public Health Council of the Netherlands recommended to retain the "old" advised limit of 120 $\mu g/m^3$ (60 ppm) for one-hour average. In this recommendation the possible effects of mutagenicity and carcinogenicity have not been taken into account.

The WHO (IDC, 1985) recommended the following standards for ozone:
150-200 $\mu g/m^3$ (75-100 ppb) for one-hour average
100-120 $\mu g/m^3$ (50- 60 ppb) for eight-hour average.
These recommendations are also stipulated by the WHO-Europe Air Quality Guidelines in 1987.

4.2 OCCUPATIONAL POPULATION

It should be noted that the standards of ozone in the Netherlands, Germany, United Kingdom, Sweden and France in the category of 8 hour-t.w.a. are the same (200 $\mu g/m^3$ or 100 ppb) and they are derived from the TLV of the ACGIH. On the other hand, at present, the limit recommended by the ACGIH has the same numerical level but should be considered as Ceiling level.

Country	year	µg/m³ (ppb)	comments
The Netherlands	1989	200 (100)	t.w.a.-8 hour
USA-ACGIH	1990	200 (100)	ceiling
Germany	1990	200 (100) 400 (200)	t.w.a.-8 hour short-term limit, with time limit of 8x5 (frequency X duration in min/shift)
United Kingdom	1989	200 (100) 600 (300)	t.w.a.-8 hour short-term limit (10 min reference period)
Sweden	1987	200 (100) 600 (300)	t.w.a.-8 hour short-term limit
France	1986	200 (100) 400 (200)	t.w.a.-8 hour t.w.a.-15 min
USSR	1986	100 (50)	-

5. TOXICOKINETICS

5.1 ABSORPTION

There are a few factors which may be of influence in the respiratory uptake of ozone in mammals, aside from the concentration of the gas in the air: (a) the structure of the respiratory tract, (b) the influence of the mucus that covers the air passages, (c) the flow of air, and (d) the physical and chemical properties of ozone.

Ozone is rather sparcely soluble in water, so a considerable part of the inhaled gas reaches the smallest bronchioles and alveoli. On the other hand ozone is chemically most reactive so that its effects are observed throughout the respiratory tract of man.

The problem of the structure of the respiratory tract arises when we try to extrapolate animal data to humans. Experiments in beagle dogs, rabbits and guinea pigs indicated that more than half the ozone inhaled is taken up by the nasal and pharyngeal mucosa, in exposures to less than 2 ppm (Beard, 1982). Tracheo-bronchial absorption has not been measured, but mathematical modelling predicts that the maximum dose will be taken up by the respiratory bronchioles, a result that agrees well with experimental observations in various animal species.

The RIVM report (1987) gives the following data on the uptake of ozone in the upper respiratory tract (nose and throat):

- the percentage of ozone taken up is inversely proportional to the rate of air-stream in the lungs
- the uptake is larger by mouth breathing than by nose breathing
- the uptake is positively correlated with the ozone levels. It is estimated that at levels of 200-400 $\mu g/m^3$ the uptake would be about 50%. Recent data indicate that the uptake of ozone by young adult males is about 45%.

Estimation of the uptake by the lower respiratory tract is based on models. The RIVM report (1987) cited the following charateristics on the uptake:

- Ozone may penetrate the whole pulmonary area and react directly with lung tissues.
- A maximal ozone level in tissue will exist in the transition zones between the gas-transport and the gas-exchange tissues of the lung.
- A very small percentage of inhaled ozone will be taken up by the blood.
- An increase of the minute-volume has little influence on the tracheobronchial

uptake, but on the other hand, it has a strong positive influence on the uptake in the lower airways. Experimental data on young adult males indicate an uptake of about 85% of the amount of ozone that has entered the thorax.

5.2 DISTRIBUTION

There has been no evidence of the presence of inhaled ozone outside of the respiratory organs, however, its effects are not limited to the lungs and airways. Changes in blood morphology, in central nervous system functions and in liver enzyme concentrations have been reported (Beard, 1982). It should be kept in mind that in the tissues of the lung and in the blood all sorts of oxidized components (e.g. ozonides, epoxides) can be formed, as wel as oxigen in an activated state and other radicals that can be transported by the blood stream.

5.3 METABOLISM/MECHANISM

It is universally accepted that the oxidative capacity of ozone is the basis for its ability to induce toxic effects. The following hypotheses are introduced to explain the molecular workingmechanisms of ozone:

- the oxidation of thiols and aminoacids in proteins and peptides
- the oxidation of unsaturated fatty acids into fatty acid peroxides.

Cells and cell organelles which have specific large surface areas are the target because cell membranes are formed by proteins and fatty acids. Because of the high reactivity of ozone the worst effects are seen in the respiratory airways. Schelegle et al. (1987) studied the mechanism of the ozone-induced pulmonary function decrements in human subjects. Fourteen young adult males completed six 1-h exposure protocols consisting of no drug, placebo or indomethacin (a prostaglandin synthetase inhibitor) pretreatments, with filtered air and O_3 (700 $\mu g/m^3$) exposures within each pretreatment period. Pretreatments were delivered weekly in random order in a double-blind fashion. Exposures consisted of 1-h exercise on a bicycle ergometer with work loads set to elicit a mean minute ventilation of 60 l/min. The results revealed significant effects across pretreatment for FVC and FEV_1, with no drug versus indomethacin and placebo versus indomethacin comparisons being significant. These findings suggests that cyclooxigenase products of arachidonic acid, which are sensitive to inhibition by indomethacin, play a prominent role in the development of pulmonary function decrements consequent to acute ozone exposure.

Kleeberger et al. (1988) also studied the role of mediators on the effects of

ozone on peripheral lung in canine. The results of their experiments suggested that the bronchoconstrictive response to a single ozone exposure (1000 µg/m^3, 5 min) is mediated, in part by histamine and selective metabolites of arachidonic acid. The hypothesis that the surface epithelial cells of the lungs are disrupted, causing subsequent release of bronchoconstriction agents were also offered by Fouke et al. (1988) in their experiments on baboons exposed to 500 µg/m^3 for 5 minutes.

5.4 BIOLOGICAL MONITORING

There are no data available on the applicability of biological monitoring techniques for exposure to ozone in humans.

Tanswell et al. (1989,1990) claimed to have found a "factor" which may be used as a marker of early oxidant lung injury. They found this factor in animal experiments using rats exposed to 1960 µg/m^3 (1000 ppb) ozone continuously for 2 weeks. Heat-activated plasma and lung lavage fluid from the exposed animals for 5 or 7 days has significantly increased DNA synthesis of the lung pneumocyte. Fractionation of the plasma and lavage samples indicated that the factor responsible has an isoelectric point of 6.45-6.75 and a molecular weight of about 38 kDa. This factor has a dose-dependent effect on lung pneumocyte DNA-synthesis in culture. There are no data available to suggest whether this reaction also occurs in humans. It is therefore too early to use it for biological effect monitoring purposes.

6. EFFECTS

In addition to the RIVM report (1987) recent literature data will be forwarded in this document. For the health risk evaluation of workers exposed to ozone the priority lies in the human data. Information on animal experiments is useful to understand the mechanism and sequence of the disease induced by exposure to ozone. There is no doubt that the respiratory system is the crucial target organ of ozone exposure. The effects are discussed according to the subsequent parts of the respiratory tract.

6.1 ANIMAL EXPERIMENTS

6.1.1 Effects on the upper respiratory tract

Data on the effects of ozone on the upper respiratory tract is reported in Table 1. This subject has not been covered in the RIVM report.

The response of the upper respiratory tract to ozone exposure has been less extensively studied. Both short-term and long-term exposure cause ciliated cell necrosis, shortened cilia and secretory cell hyperplasia in the nasal mucosa of monkeys (Harkema et al., 1987A). In the tracheal epithelium of various experimental animals, short-term exposure to ozone causes damage primarily to ciliated cells. Loss of cilia, necrosis of ciliated cells, alterations in secretory cells in some species, and increased cell turnover are the foremost lesions (Nikula et al., 1988). The membranous portion of the trachea demonstrates more ozone-induced injury than the cartilaginous portion. The effect of long-term ozone exposure on the tracheal epithelium of rats and other species and the response to the postexposure period have not been reported much until recently.

It is absolutely clear that the effects of ozone on the upper respiratory tract should not be underestimated. There are indications that the upper respiratory tract may be even more sensitive to ozone than the lower respiratory tract. Hotchkiss et al. (1989) compared the effects of ozone on the upper and lower respiratory tract of rats. They exposed rats to 0, 196, 1294 or 2411 $\mu g/m^3$ ozone for 6 hours (these levels were extrapolated from experimental conditions into concentrations at sea-level, because the experiments were performed in a laboratory located at high altitude). They found that eighteen hours after exposure, increased neutrophils were recovered from the nasal lavage fluid when the rats were exposed to 196 $\mu g/m^3$ ozone. There was no change in the number of neutrophils recovered from the broncho-alveolar lavage fluid at any time after exposure. Since the number of neutrophils reflected the response at sites that were

Table 1. Effects of exposure to ozone on the upper respiratory tract (URT) of experimental animals (n=total number of experimental animals)

Species of animals	Levels of exposure ($\mu g/m^3$)	Duration of exposure	Effects	Comments	Reference
Bonnet monkeys (n=28)	300 600	8 h/d, 6 or 90 d 8 h/d, 6 or 90 d	Changes in nasal transitional and respiratory epithelium. Ciliated cell necrosis; secretory cell hyperplasia.	May impair defence mechanism of URT. Otherwise no gross changes of nasal cavity architecture.	Harkema et al. (1987A)
Bonnet monkeys (n=20)	300	8 h/d, 6 or 90 d	Significant changes in the stored secretory product of nasal epithelium.		Harkema et al. (1987B)
F344/N rats (n=30)	240 800	6 h/d, 7d 6 h/d, 7d	At 240 $\mu g/m^3$ no change within epithelium of nasopharynx, but increased stored mucosubstance in epithelium lining media aspect of nasal turbinate. At 800 $\mu g/m^3$ pathological lesions.	240 $\mu g/m^3$ can be accounted as a NAEL in this respect.	Harkema et al. (1989)
F344/N rats (n=108)	196 1294 2411	6 h 6 h 6 h	Increased neutrophils in nasal lavage fluid. No histologic alterations in the lungs at the lowest dose.	Levels extrapolated into concentrations at sea level. Observed NAEL at 196 $\mu g/m^3$.	Hotchkiss et al. (1989)

S-D rats (5 rats per group)	1920	3 or 60 d, 8 h/d	Ciliary damage, cell necrosis and increased density of intermediate cells in the tracheal epithelium.	There is a certain adaptation in the tracheal epithelium in long-term exposure.	Nikula et al. (1988)
Wistar-rats (10 rats per group)	400 800 1600	22 h/d, 3 d	At 800 and 1600 µg/m^3 enhanced proliferation in nasal respiratory lining, except on the septum. Changes comprised of hyper- and metaplasia, hyperkeratonization and rhinitis.	NAEL is observed at 400 µg/m^3.	Reuzel et al. (1990)

injured by acute ozone exposure, this may show the difference in actual and local concentration between the upper and lower respiratory tract, evoked by sequential "consumption" of O_3, to start with the upper part of the respiratory tract.

From the experimental data it may be concluded that the NAEL of ozone on the upper respiratory tract may figure around 200 µg/m³ for a short-term exposure period.

6.1.2 Effects on the lower respiratory tract and lung

6.1.2.1 Effects on the morphology of the lung

The following characteristics are quoted from the RIVM report (1987): the target area is the transition zone between the air transport and air exchange tissues of the lung, also called the centro-acinar area. It may be affected at exposure to 400 µg/m³ for a few hours. The ciliated cells and type I cells from this zone will be injured and perished. After that it will be followed by hyperplasia of the non-ciliated bronchiolar cells and the non-ciliated type I cells. At the same time inflammation reactions will take place with the converging of white blood cells and macrophages in the alveoles and interalveolar spaces. The collagen content of the lung increases, which results in the thickening of the interalveolar septa.

In sub-chronic exposure (a few weeks to a few months) a dynamic equilibrium may be reached between the ciliated and non-ciliated cells in the bronchioles and type I and type II cells in the alveoli. Although the inflammation reaction is less intense, it does not disappear but seems to be correlated with the structural changes formed in the centro-acinar zone and a further increase of collagen contents of the lung. There are indications of a constriction of the lower airways. More recent animal data are reported in Table 2.

The following sequence of alterations occurred in the lungs after exposure to high level (6000 µg/m³, 4 h) of ozone, as reported by Heroshima et al. (1987):

- At 1 h after exposure, many alveoli were filled by edema fluid, and peribronchial and perivascular lymphatics were greatly distended. In the terminal bronchioles, bronchiolar epithelial necrosis and sloughing were observed.
- At 1d after exposure: accumulation of alveolar macrophages in the centro-acinar area.
- At 2 d after end of exposure: regression of the pulmonary edema, but increase of alveolar macrophages and epithelial hyperplasia of the bronchioles and centroacinar area.
- At 7 d after end of exposure: the accumulation of alveolar macrophages and

mucosal hyperplasia had diminished considerably.

6.1.2.2 Effects on the lung function

Exposure for short duration results in increased breathing frequency, decrease of the tidal volume and increase of airway resistance. Additionally the hypersusceptibility of the airways to bronchoconstrictive agents escalates.

Exposure of ozone for a few weeks induces a decrease of the elasticity of the lungs, leading to enlargement of the lung volume, particularly at high transpulmonary pressure. The increase of the airway resistance and the decrease of the expiratory airflow rate suggest the occurrence of obstruction of the airways in the lower regions of the lungs.

Recently Yokoyama et al. (1989) exposed rabbits intermittently to ozone and the mechanic properties of the lungs were studied in order to know details of ventilatory functions in lung injuries caused by this gas. Exposure to 4000 $\mu g/m^3$ for 6 h/d, 3 d, showed earlier stage of lung edema. In this group of animals, dynamic compliance decreased, pulmonary flow resistance increased, and flow-volume curve obtained by forced deflation showed a definitely altered slope with reduced flows at the latter part of descending line. On the other hand, the significant change observed in rabbits exposed to 2000 $\mu g/m^3$ ozone for 6 h/d, 7 d, was only the increase in pulmonary flow resistance.

6.1.2.3 Biochemical changes in the lungs

Exposure for a few days of ozone induces expansion of the anti-oxidant metabolism and the oxygen consumption in the lungs. The mechanism of this activity is not yet fully understood. It is assumed that the changes occurring in the number of specific cells, e.g. the destruction of type I cells and the proliferation of type II cells, which are rich in anti-oxidant enzymes, may play an important role in the mechanism. Long-term exposure to ozone induces increase of collagen synthetase. More recent data on the influence of exposure to ozone on enzym activity of the lungs are reported in Table 3.

Although this document does not take into consideration the problem of combined exposure, nevertheless two papers are of interest because they compared the effects of exposure to ozone and NO_2. In some instances, such as photochemical smog, these two gasses are present in the ambient air. There are some indications of an antagonistic activity between these two gases when the xenobiotic metabolizing activity in the lung tissues is considered (Takahashi et al., 1989). On the other hand, synergistic or even additive activities are noted in combined ex-

Table 2. Effects of ozone on the general morphology of the lungs of experimental animals

Species of animals	Levels of exposure ($\mu g/m^3$)	Duration of exposure	Effects	Comments	Reference
F344/Nrats	196 1294 2411	6 h	Increased neutrophils in broncheoalveolar lavage fluid at >1294 $\mu g/m^3$. Signs of bronchiolitis and peribronchial alveolitis. Infiltration of macrophages and neutrophils.	See also Table 1 and text. Observed NAEL 196 $\mu g/m^3$, 6 h.	Hotchkiss et al. (1989)
F344 rats	240 500 1000	20 h/d, 1-14 d	Increase of alveolar macrophages as well as type II cells after 2 d exposures.		Wright et al. (1987)
NZ rabbits	200 2400 200	2 h 2 h/d, 13 d	Lowest dose already changes in number and functional properties of alveolar macrophages.	Effects already occur at exposure to 200 $\mu g/m^3$.	Driscoll et al. (1987)
B6C3F1 mice	400 1000 2000	23 h/d, 14 d	Inflammation response immediately after exposure. No histopathological signs of fibrosis.		Sun et al. (1988)

Mongrel dogs	2000	5 min	Increase of polymorpho nuclear leucocytes in the subepithelial tissues.		Kleeberger et al. (1989)
Albino rabbits	2000 4000	6 h/d, 7 d 6 h/d, 3 d	At the highest dose: epithelial damages and submucosal edema. Thickening alveolar walls in proximal portion of alveolar ducts. Lower dose similar effects but less marked.		Yokoyama et al. (1989)
S-D rats	4000	4 h	Increase of neutrophils and myeloperoxidase in the inflammatory cell population.		Esterline et al. (1989)
Wistar rats	6000	4 h	Severe damage on the type I cell of centro-acinar location and bronchiolar cells. Hyperplasia of the type II cells. Ciligenesis of bronchiolar ciliated cells 4 d after exposure.	Injured type I cells are replaced by proliferation of type II cells. Injured bronchiolar ciliated and Clara cells are replaced by proliferation of bronchiolar non-ciliated cells.	Heroshima et al. (1987)

Table 3. Effects of ozone on the enzym activity of the lungs in experimental animals

Species of animals	Levels of exposure ($\mu g/m^3$)	Duration of exposure	Effects	Comments	Reference
Wistar rats	300 1000	continuously, 7 days	Increase in the protein content, lactate dehydrogenase, glucose-6-phosphate dehydrogenase and glutathione peroxidase activities in the lung.	Emphysematous rats are not more susceptible to ozone than non-emphysematous rats.	Dormans et al. (1989)
Wistar rats	400	continuously, 1 and 2 mo	Increase of cytochrome P-450 content in the lungs. Also increase of 7-ethoxy coumarin-o-deethylase activity and benzo-a-pyrene hydroxylase activity. But a decrease of the coumarin hydroxylase activity.	The results showed an increase of xenobiotic metabolizing activity in the lungs by exposures to ozone.	Takahashi and Miura (1989)
S-D rats	600	continuously, 3 days	Increased enzym activities related to NADPH generation, sulfhydryl metabolism and cellular detoxification.	Combined exposure with NO_2 showed synergistic as well as additive effects on some enzym activities.	Lee et al. (1990)

S-D rats	900	continuously, 3 days	Increased activities of glucose-6-phosphate dehydrogenase, ornithine decarboxylase and S-adenosyl-methionine decarboxylase. Polyamine contents were increased. Incorporation of tritiated thymidine into DNA was elevated.		Elsayed et al. (1990)
F344 rats	1140 2200	19 h/d, 11 days	Increased cathepsin D and macrophages elastase activity. Increased lavage fluid hydroxyproline. Increased total lung collagen.	Enzymal changes preceded modest fibroplasia and fibrosis in the alveolar duct regions.	Pickrell et al. (1987A)
F344 rats	1000 2000 3000	continuously, 48 h	Decrease of antiproteinase activities in serum and in lung tissue, at levels up to 2000 $\mu g/m^3$ ozone. Acid proteinase activities increased by exposure to 2000 or 3000 $\mu g/m^3$.	Pulmonary edema occurred at 3000 $\mu g/m^3$ ozone exposure.	Pickrell et al. (1987B)
F344 rats	6000	continuously, 8 h	Decrease of specific enzyme activity of five lamellar body hydrolases. Also total enzym activity was reduced to zero for ß-hexosaminidase and for α-mannosidase and α-L-fucosidase.	May be related to alterations in the storage and and secretions of surfactant.	Glew et al. (1989)

posure when the oxidant effects on the enzym systems of the lungs are noted (Lee et al., 1990). It is assumed that ozone can cause a 15- to 20-fold greater lung injury than NO_2 at the same concentration.

6.1.2.4 Effects on the defence mechanism and immunological system of the lung

Exposure for a few hours to mice increased its susceptibility to bacterial infections. Besides that, there are other changes in the defence mechanism of various experimental animals after short-term exposure to ozone, e.g. a negative influence on the capacity of the lung tissue to abolish bacteriae and viruses, decreases in the mucociliary clearance, suppression of the immune system and decrease in the vitality of the alveolar macrophages. There are indications that ozone influences the severity and duration of bacterial infections. A few recent data on the effects of ozone on the imunologic system are reported in Tabel 4.

Pulmonary immune competence may usually be assessed by measurement of lung (a) interferon production, (b) alveolar macrophage function, (c) natural killer activity, (d) cytotoxic T lymphocyte activity and (e) antibody production. These immunological functions represent a cascade of defence mechanisms important in defence against viral, bacterial and neoplastic diseases (Burleson et al., 1989). Suppression or abrogation of any one of these early defence mechanisms could result in a compromised ability to defend against pulmonary viral, bacterial and neoplastic diseases. It may be concluded that the NAEL for effects on the immunological systems may lie between 200 and 800 $\mu g/m^3$ for a duration of hours and days.

6.1.2.5 Effects on the blood cells

After exposure to ozone in vivo, red blood cells tend to loose their disklike shape and to become spherical. They can be hemolyzed more easily. Hemoglobin characteristics and oxygen transport appear to be unaffected. The acetylcholine-esterase bound to red blood cell membranes is decreased. Glutathione and related enzymes appear to be unaffected (Beard, 1982). Leucocytes appear to be unaffected by ozone exposures up to 4000 $\mu g/m^3$.

6.1.2.6 Other effects on the lung and other organ systems

Short-term exposure of rats to ozone seems to have influence on the pulmonary epithelial permiability. Bhalia and Crocker (1987) studied the transport of small and large molecule compounds, respectively radioactivated diethylene triamine-

Table 4. Effects of ozone on the immunologic system of the lung of experimental animals

Species of animals	Levels of exposure ($\mu g/m^3$)	Duration of exposure	Effects	Comments	Reference
Wistar rats	400 800 1600	continuously, 7 days	Two lower doses cause stimulation, but the highest dose causes depression of the Natular Killer activity in the lymphoid cell suspensions. Body weights of the latter were also lower than controls.	NAEL is observed at 800 $\mu g/m^3$, continuously for 7 days.	van Loveren et al. (1990)
BALB/c mice	1600	continuously, 3-56 days	Lung weights were increased, while the thymus and spleen weights decreased. Antibody response to sheep red blood cells (SRBC) was suppressed.	Comparison was made with exposure to NO_2. It was found that the magnitude of effect was greater for 1600 $\mu g/m^3$ ozone than that of 4 ppm NO_2.	Fujimaki et al. (1989)
F344 rats	200 1000 2000	continuously, 2h continuously, 2h continuously, 1-10 days	Significant decrease of the pulmonary NK activity, but returned to normal values after continued 10 days exposure.	No effect was shown at 200 $\mu g/m^3$, continuously for 2 hours.	Burleson et al. (1989)

Mice	1000 1000 2000	4 h/d, 1 w continuously, 1w continuously, 4w	Decreased ability of the spleen for primary antibody formation. Loss of body weight and thymus weight. Decreased response to SRBC.	Estimated NAEL at 1000 $\mu g/m^3$, 4 h/d, 1 w.	Goodman et al. (1989)
Cynomulgus monkeys	2000	6 h/d, 5 d/w, 12 w	Baseline pulmonary function not affected by ozone, but needed less P_t salt and metacholine in bronchoprovocation challenge. Increased incidence of positive P_t skin test.	This means ozone increased specific as well as non specific bronchial hyperreactivity.	Biagini et al. (1986)

penta-acetate ([^{99m}Tc]DTPA) and ^{125}I-labeled bovine serum albumine, from blood into the alveolar air. The compounds were injected intravenously and the lungs were lavaged 6 minutes later. They found that rats exposed to ozone [600 or 4000 µg/m^3, for two hours) showed increased permiability in a dose-related fashion. The NAEL for this unfavourable phenomenon of increased alveolar permiability for serum components will figure below 600 µg/m^3 for exposures of a few hours.

The influence of exposure of the airways to ozone on acute allergic responsiveness has been investigated by Turner et al. (1989).They reported that in a series of experiments on mongrel dogs it was demonstrated that the number of mast cells at the base of the epithelial region of small subsegmental airways exposed to 2000 µg/m^3 for 5 minutes were significantly increased, three hours following exposure, compared to air exposed or non-exposed controls. In a different series of experiments, they also showed that in dogs with inherent sensitivity to Ascaris suum antigen, simultaneous ozone preexposure of a contralateral lobe completely blocked the late-phase response to antigen. These results showed that the consequences of a single exposure to ozone persist beyond its effects on acute antigen-induced bronchoconstriction and extend to the complex processes involded with the late response.

Umezu et al. (1987) reported that exposure to ozone has a dose-dependent effect on the drinking behaviour of rats. The animals were exposed to concentrations of 400, 800 and 1600 µg/m^3 continuously for 1 week. Drinking decreased considerably on the first day after onset of exposure. On the first day the suppression rate was calculated to be 28, 70 and 93%, respectively, for the three doses.

Uchiyama and Yokoyama (1989) reported the effects on the heart rate and blood pressure of emphysematous rats. The heart rates of both elastase-treated emphysematous and saline-treated control rats decreased to about 50 and 65% at the end of 2000 µg/m^3 ozone for 3 h and 1000 µg/m^3 ozone for 6 h respectively. Mean arterial blood pressure also decreased to about 76 and 82%, respectively. There was no significant difference in these responses between emphysematous and control rats.

6.1.2.7 *Mutagenicity/genotoxicity and carcinogenicity*

Ozone remains one of the three most important world-wide outdoor air pol-

lutants, yet little directly documented evidence of its genotoxicity exists. The interest in the pathology of ozone exposure and the molecular events that underlie its toxicokinetic and toxicodynamic features stems from DNA damage caused by oxygen stress including hydroxyl radicals, superoxide, singlet oxygen and hydrogen peroxide. Although the tissue damage associated with ozone inhalation occurs at both the conducting airway and the alveolus, the cellular and mechanistic processes underlying these events are less well understood. Recently, Steinberg et al. (1990) in their review summarized as follows on ozone-induced damage:

- ozone leads to the oxidative decomposition of poly-unsaturated fatty acids
- ozone depresses DNA replication in V79 Chinese hamster lung fibroblasts in a dose-dependent fashion, which indicates that ozone or its reaction products may interact directly with DNA and inhibit replication.
- ozone also linearizes circular DNA and induces ozone-sensitive mutant and pneumocytes to repair its DNA.

A summary of recent data on the effects of ozone on the DNA metabolism is presented in Table 5.

Last et al. (1987) studied the influence of ozone exposure on the development of lung tumors. Mice from either strain A/J or Swiss Webster were exposed for 18 weeks either to filtered air or to 800 or 1600 $\mu g/m^3$ ozone for 8 hours/day. Subgroups received a single i.p. injection of 1000 mg urethane/kg or 0.9% sodium chloride vehicle/day prior to initiation of the exposure regimen. Exposure to ozone caused a decrease in the number of tumors per lung in urethane-treated mice of both strains in a dose-dependent manner. Most interesting was a significant increase in the number of tumors per lung in A/J mice exposed to 1600 $\mu g/m^3$ ozone without urethane. A similar ozone effect on lung tumor development was not observed in Swiss Webster mice. In strain A/J mice lung tumours can easily be induced by a variety of substances. Therefore, the toxicological relevance of the increase observed in this strain is questionable.

Interaction between ozone and ionizing radiation (Borek et al., 1986) or ultra violet radiation (Borek et al, 1989) on in vitro cellular systems, inducing neoplastic transformation, has been resported. The interpretation of these experiments is difficult to make since it is known that ozone itself is a very reactive substance and these cells have an inherent versatility.

Table 5. Recent data on the effects of ozone on DNA metabolism

Experimental model and method	Dose	Results	Reference
Hamster embryo cells and Mouse C3H/10-½ cells in vitro	10000 μg/m³ (5 ppm), 5 minutes	Enhanced levels of free radical-mediated lipid peroxidation products, and induction of cell transformation.	Borek et al. (1986)
Cultures of human epidermal cell line RHEK in vitro	10000 μg/m³ (5 ppm), 10 minutes	No strand breakage of DNA in Alkaline Sucrose Gradient Analysis. No single strand breaks in Alkaline Elution Analysis.	Borek et al. (1988)
Hamster embryo cells and Mouse C3H/10T-½ cells in vitro	12000 μg/m³ (6 ppm), 10 minutes	Transformation was scored in both systems. It was also found that O_3 acts in additive fashion with ultraviolet light to produce neoplastic transformation. Vit. E inhibits the transformation.	Borek et al. (1989)
Heat inactivated plasma samples of ozone exposed rats were tested in fetal rat lung fibroblasts and cultured pneumocytes in vivo in vitro	2000 μg/m³ continuously for 2 w	A dose-dependent increase in DNA synthesis by lung fibroblasts, but no effect on cultured pneumocytes.	Tanswell et al. (1989)

Heat inactivated plasma and lavage of ozone treated rats tested in fetal rat lung pneumocytes and cultured fibroblasts in vivo in vitro	2000 µg/m³ continuously for 2 w	Increased DNA synthesis by lung pneumocytes, but no effect on the cultured fibroblasts DNA synthesis.	Tanswell et al. (1990)
Study of the epithelium of anterior nasal cavity of ozone exposed rats in vivo	200 µg/m³ 440 µg/m³ 1320 µg/m³ 6 h/d, 7 d	At higher dose there was increase of DNA replication in the non-ciliated cuboidal/ transitional epithelium. On the other hand, in the ciliated respiratory and olfactory epithelia DNA replication was less marked. At this dose it also caused hyperplasia of the cuboidal epithelium.	Johnson et al. (1990)

6.2 OBSERVATION IN MAN

6.2.1 Acute toxicity (incidents and cases)

The acute "local" effects of ozone appear to be almost entirely the consequences of irritation of the respiratory tract. Inasmuch as ozone is highly reactive and only moderately soluble, one might expect to see signs of action at all levels.

The odor of ozone can be detected at 100 $\mu g/m^3$ or possibly at even 40 $\mu g/m^3$, but some apparently normal people do not detect it at 600 $\mu g/m^3$ (Beard, 1982).

Natural human exposure studies are most useful for studying the magnitude and extent of the acute responses to naturally occurring pollutants among people engaged in normal outdoor recreational activities. They provide little information on the possible influence of prior chronic exposures on acute responses to the exposure at the day itself or at immediately preceding days. Also, since ambient mixture contains varying amounts of a variety of pollutants, it may sometimes be difficult to apportion the responses to one or more of the pollutants or to other, uncontrolled variables, such as temperature, humidity and each individual's precise level of exercise or ventilation (Lippmann, 1989).

There is very little information on cases of occupational incidents due to ozone. Recently Lee et al. (1989) reported of a 27-year old man developing frequent episodes of cough, breathlessness and wheezing about three months after starting work as a quality control inspector in a factory manufacturing television tubes. He was admitted to hospital on four occasions for bronchial asthma over a two-month period while working in the inspection section. His symptoms usually started at about 9.00 pm, i.e. after work. He worked a day shift from 8.00 am to 5.00 pm. Symptoms improved on weekends and holidays. Further investigations showed the patient had non-specific bronchial hyperreactivity as assessed by histamine inhalation challenge. Prick tests to metals were negative. His job included working near a conveyor system and high electric charging of the television tubes took place while the tubes were being carried by the overhead conveyor system. Ozone is known to be generated by electric discharges. Environmental measurements showed that the ozone level near the conveyor system was about 180 $\mu g/m^3$ and at the inspection station of the worker the level was 80 $\mu g/m^3$. No known allergens such as Ni and Cr were detected in the air.

6.2.2 Human short-term controlled studies

Controlled human exposure studies are most useful for studying the nature and extent of transient functional changes resulting from one or a brief controlled exposure. They can provide information on chronic effects only to the extent that prior exposures affect the transient response to single exposure challenges. Furthermore, interpretation of results of such tests is limited by our inadequate ability to characterize the nature and/or magnitude of the prior long-term exposures (Lippmann, 1989). For the interpretations of the results of controlled human studies one should understand the limitations inherent to this method: (1) ethical constrains limit the challenges and effect assays that can be performed, (2) the numbers of repetitive challenges and assays are limited by subject tolerance and cooperation and (3) the number of subjects that can be studied is limited by the generally large costs of performing the studies, and/or by the availability of sufficient numbers of subjects with the desired characteristics.

There are four phenomena known as effects in humans exposed intermittently to ozone: (1) effects on the upper respiratory tract, (2) increased prevalence or severity of lung infections due to the influence of ozone on the defence mechanism of the lung, (3) premature loss of lung elasticity possibly associated with small airway changes due to lung remodelling, and (4) increased airway reactivity. Each of these subjects will be discussed in the following paragraphs.

6.2.2.1 Effects on the upper respiratory tract

Carson et al. (1985) studied the morphology of ciliated nasal epithelium obtained from human volunteers exposed under controlled conditions to 800 $\mu g/m^3$ of ozone for 4 hours by transmission electron microscopy. Seventeen healthy young adult males participated in this study over four separate exposure periods. During exposure four subjects engaged in physical exercise while the remaining subjects stayed at rest throughout the exposure period. The results of these experiments indicated that the cell structure is generally retained and no appreciable manifestation of injury is evident in human nasal mucosa. Graham et al. (1988) reported that ozone induces an inflammatory response in the upper respiratory tract of humans. In a double blind design, 41 healthy non-smoking male volunteers aging 18-35 years were exposed randomly to either 1000 $\mu g/m^3$ ozone or filtered air for a 4-hour period on two consecutive days. No exercise was performed during the exposure periods. Nasal lavages (NAL) and blood samples were taken before, immediately after exposure and 22 h after the second exposure. The study

showed an increased number of neutrophils in the nasal lavage by a factor between 3.5 to 6.5 fold over the air exposed group. The total protein levels in the nasal lavage fluid and peripheral blood neutrophil concentrations were not different between the two groups and did not change significantly during the study. It may be concluded that at this level of exposure ozone induces local inflammatory reaction of the nasal mucosa. Using the same technique, Koren et al. (1990) studied the acute effect of 2 hour exposure to ozone at 800 $\mu g/m^3$ on the inflammatory response in the upper airways of 10 normal volunteers (healthy, non-smoking volunteers, 18-35 years of age) and compared the results to those obtained in the lower airways assessed by bronchoalveolar lavage (BAL). The results indicate significant increases in the number of polymorphonuclear neutrophils in NAL immediately post exposure. This increase is still detectable 18 h post exposure (6-fold) which is similar to the increase of PMN in BAL. Tryptase, released by mast cells was also increased in the NAL fluid immediately post exposure. While albumin level, which is an indicator of epithelial cell permiability, was elevated 18 h post exposure, tryptase level was not anymore elevated at that point. Interestingly, several other markers of inflammation such as prostaglandin E_2, C_{3a}, urokinase-type plasminogen activator, which were found to be significantly elevated in the BAL of the same group of subjects (18 h post exposure) were not elevated in the NAL. From this experiment it may be concluded that NAL may serve as a sensitive and reliable technique to detect inflammation in the upper respiratory tract and NAL seems to mirror the inflammatory response in the lower respiratory airways 18 h post exposure, reflected by the number of PMN and albumin levels.

From this study it may also be concluded that exposure of healthy individuals to 800 $\mu g/m^3$ ozone for a few hours may already induce inflammatory reaction to the upper respiratory airways.

6.2.2.2 *Effects on the defence mechanisms of the lower respiratory tract*

From studies on the defence mechanisms of the lower respiratory tract against noxious agents can be concluded that increased permiability of the lung, changes in the number of macrophages, changes in particle clearance and the induction of inflammation of the lower respiratory airways may occur.

As reported in the previous chapter, examination of the BAL is one of the methods for studying the condition whether inflammation took place in the lower respiratory tract.

Koren et al. (1989) studied the BAL of 11 healthy non-smoking male volunteers, 18 to 35 years of age, 18 hours after being exposed to 800 $\mu g/m^3$ ozone for two hours with intermittent exercise. There was an 8.2-fold increase in the percentage of PMN in the total cell population and a small but significant decrease in the percentage of macrophages. Immuno-reactive neutrophil elastase often associated with inflammation and lung damage also increased in the fluid as well as its activity in the lavaged cells. Increases were also found for protein, albumin and IgG suggesting increasing vascular permiability of the lung. The results of this study has been substantiated in a succeeding study by the same authors (Koren et al., 1990) on 11 healthy non-smoking male volunteers. The exposure protocol was the same as performed in the earlier study. They found elevation of the levels of prostaglandin E_2, C_{3a}, urokinase-type plasminogen activator in the BAL 18 hours post exposure.

Kehrl et al. (1987) also reported that ozone exposure increases respiratory epithelial permiability in humans. Their method used tracer-labeled diethylene triamine pentacetic acid (DTPA) taken by inhalation. In a randomized, cross-over double-blind study, 8 healthy non-smoking young men were exposed for 2 hours to purified air or 800 $\mu g/m^3$ ozone while performing intermittent high intensity treadmill exercise (minute ventilation = 66.8 l/min). The results showed that 7 of the 8 subjects displayed increase of DTPA clearance and decrements of the pulmonary function. The effect of ozone on particle clearance has been a subject of discussion in the survey of Lippmann (1989). He cited that exposure of humans to 800 $\mu g/m^3$ produced marked acceleration in particle clearance from both central and peripheral airways as well as a 12% drop in FVC; but exposure to 400 $\mu g/m^3$ ozone for 2 hours produced acceleration of particle clearance in peripheral airways but failed to produce significant drop in FVC. This may suggest that significant changes in the ability of the deep lung to clear deposited particles take place before significant changes in the respiratory function occur. It is not known why animal tests show only retarded mucociliary clearance in response to ozone exposure, while the human tests show accelerated clearance.

Significant alteration of the numbers and functional properties of alveolar macrophages has been reported in experimental animals already at 200 $\mu g/m^3$ ozone (Lippmann, 1989). In humans, a decrease in the number of macrophages was reported at exposure to 800 $\mu g/m^3$ for two hours (Koren et al., 1989). Less available are the data on functional changes in the alveolar macrophages in human exposed to ozone. McGee et al. (1990) reported changes in the genes for the tissue

factor and factor VII proteins in the alveolar macrophages of humans exposed to ozone. They obtained these cells from the alveolar fluid 18 hours after healthy male adults were exposed for two hours during intermittent exercise to either air or air with 800 µg/m³ ozone. They found that tissue factor in RNA concentration in the macrophages was increased about 2.6-fold and factor VII in RNA concentration was reduced to 0.64-fold. The total numbers of macrophages recovered did not change significantly. In the lavage the tissue factor activity was increased with 2.1-fold.

From the accumulated data it may be concluded that the effect of exposure to ozone on the defence mechanisms of the lower respiratory tract may already occur at 800 µg/m³ for 2-hours, with intermittent exercise. The MAEL for this effect is estimated at 200 µg/m³. These levels apply only for healthy non-smoking adults.

6.2.2.3 Effects on the lung function

There are more data on the respiratory function responses than any other coincident responses to short-term ozone inhalation. Such functional responses, can be obtained with non-invasive, readily performed protocols, and can be detected at as low or even lower levels of exposure as any other well established assays. The major debate about very small, but statistically significant, decrements in function from such studies is how to interpret their health significance (Lippmann, 1989). A summary of recent data is reported in Table 6.

It may be concluded from these data that the estimated NAEL for impairment of the ventilatory function of the lung of healthy non-smoking young adults may be in the order of magnitude of 300 µg/m³ ozone during 60-120 minutes with moderate exercise.

With symptoms of irritation the MAEL is about 320 µg/m³ ozone.

The duration of exposure seemes to play an important role on the magnitude of the effects. Folinsbee et al. (1988) performed exposure study in 10 adult male volunteers involving 6.6 hours of ozone exposure at 240 µg/m³. Moderate exercise was performed for 50 min/h for 3 hours in the morning, and again in the afternoon. They found that the functional decrements became progressively greater after each hour of exposure, reaching average values of about 400 ml for FVC and about 540 ml for FEV_1 by the end of the day. The effects were transient in

Table 6. Effects of short-term exposure of ozone on the ventilatory function of the lung in male (M) and female (F) healthy adult volunteers

Number of subjects and gender	Age range (year)	Activity level	Ozone level ($\mu g/m^3$)	Exposure duration (min)	Effects	Reference
24 M	18-33	$\dot{V}$ 68 l/min (15 min every half hour)	160 200 240 280 320	120	For the group as a whole, no meaningful untoward effects even at the highest level, but only irritant response. Measured were SRaw, FEV_1, FVC, PEFR and MMFR MAEL observed at 320 $\mu g/m^3$.	Linn et al. (1986)
10 (gender unknown, athletes)	19-29	86% of $\dot{V}O_2$ max (30 min)	240 360 480	60	Decrease of FVC and FEV_1 at levels of 360 and 480 $\mu g/m^3$. Subjective symptoms also increased at these levels. NAEL below 360 $\mu g/m^3$.	Schelegle and Adams (1986)
19 M 7 F	mean age 20	65% of $\dot{V}O_2$ max, $\dot{V}_E$ 63 l/min	500	60, and then reexposed after 12,24, 48 and 72 h for 60 min	Decrease of FEV_1 after second ozone exposure was larger than that after first exposure for subjects reexposed at 12 or 24 h. Also changes in FVC and MVV.	Folinsbee and Horvath (1986)
14 M	18-34	$\dot{V}_E$ 60 l/min	700	60	Significant decrease of FVC and FEV_1 and increase of the SRaw.	Schelegle et al. (1987)

8 M	20-30	$\dot{V}_E$ 67 l/min	800	120	14% decrement of FVC, 71% increase of SRaw. Respiratory symptoms in all subjects.	Kehrl et al. (1987)
11 M 6 F	18-31	$\dot{V}_E$ 30 l/min	800	30 (either mouth or nose breathing)	Decrements of FEV_1, FVC and FEF_{50}. No difference in effects between nose and mouth breathings.	Hynes et al. (1988)
3 M 5 F	mean age 24	$\dot{V}_E$ 27 l/min (alternate 20 min)	900	120/day, 5 consecutive days	Decrements of FEV_1, FVC and $FEF_{25-75\%}$.	Drechsler-Parks et al. (1987)
8 M 8 W	18-26	$\dot{V}_E$ 25 l/min (alternate 20 min)	900	120	Decrements of FVC, FEV_1 and $FEF_{25-75\%}$. Older subjects had smaller and fewer significant decrements in pulmonary functions.	Drechsler-Parks et al. (1989)
8 M 8 W	51-76	- " -	900	120		
10 F	19-36	$\dot{V}_E$ 25 l/min	960	120	Decrements of the FVC, FEV_1, FEV_2, FEV_3, $FEF_{25-75\%}$, IC, ERV and TLC.	Horvath et al. (1986)

Abbreviations:

FEV_1	Forced Expiratory Volume in 1 sec	IC	Inspiratory Capacity
FVC	Forced Vital Capacity	ERV	Expiratory Reserve Volume
TLC	Total Lung Capacity	FRC	Functional Residual Capacity
MVV	Maximal Voluntary Ventilation	$FEF_{25-75\%}$	Average flow rate between 25 and 75% of vital capacity
SRaw	Specific Air Way Resistance	$\dot{V}_E$	Expired Minute Ventilation
PEFR	Peak Expiratory Flow Rate	$\dot{V}O_2$	Oxigen Uptake
MMFR	Maximal Midexpiratory Flow Rate	$\dot{V}O_2max$	Maximal Oxigen Uptake

that there were no residual functional decrements on the following day. The decrements in FEV_1 after 6.6 hours of exposure at 240 µg/m³ averaged 13.6%.

This means that the NAEL for an individual exposed to ozone for 8 hours should be below 240 µg/m³, and 240 µg/m³ must be classified as the AEL.

6.2.2.4 *Effects on the non-specific responsiveness of the lung*

Exposure to ozone can also alter the responsiveness of the airways to other bronchoconstrictive challenges as measured by changes in the ventilatory capacity. A summary of recent data on this effects is shown in Table 7. As can be seen from the experiment performed by Folinsbee et al. (1988), the mean change in the metacholine dose-response relationship indicated that the dose required to cause a doubling of airway resistance was reduced by approximately 50% (i.e., one metacholine concentration level) following ozone exposure. In this experiment a level of 240 µg/m³ ozone for a duration of 6.6 hours was used, which means that the NAEL for this effect should be lower than 240 µg/m³.

The basis for the effect of ozone on airway reactivity was studied by Gordon et al. (1981) in guinea pigs exposed for 60 min to either 200 or 1600 µg/m³ ozone. Both exposures significantly inhibited lung cholinesterase activity as compared to levels in unexposed animals. But the question remains whether this mechanism also applies to human beings.

6.2.2.5 *Other effects of exposure to ozone*

It is reported that exposure to ozone also impaired individual performance, Gong Jr et al. (1986) evaluated the exercise performance of 17 top-caliber endurance cyclists under conditions simulating competition and realistic temperatures. They were exposed to filtered air, 240 or 400 µg/m³ ozone. During maximal exercise they found no differences at exposure to 240 µg/m³, but significant reduction in peak $\dot{V}_E$, $\dot{V}O_2$, tidal volume, work load and ride time (during maximal exercise) occurred at exposure to 400 µg/m³ compared to filtered air. Linder et al. (1987) also examined 12 healthy women and 12 healthy men on exercise bicycle until exhaustion in a climate chamber at ozone levels of 0, 120 or 240 µg/m³. Under high ozone concentration,a clear decrease of performance was seen at maximal efforts as well as a shift of the aerobic threshold to somewhat lower performance values. The authors suggested that these changes are probably caused by increasingly difficult breathing due to a reflex bronchial constriction.

Table 7. Effects of short-term exposure to ozone on the hyperresponsiveness of the lung in humans

Number of subjects and gender	Ozone level ($\mu g/m^3$)	Exposure duration (min)	Activity level	Challenge	Effects on lung function	Reference
10 M	240	396	$\dot{V}_E$ 40 l/min	metacholine	Airway reactivity doubled following ozone, as seen in the SRaw.	Folinsbee et al. (1988)
15 M 2 F (athletes)	240 400	> 60 > 60	$\dot{V}_E$ 89 l/min $\dot{V}_E$ 89 l/min	histamine histamine	1 subject hyperresponsive 9 subjects hyperresponsive (seen from decrease of FEV_1)	Gong et al. (1986)
14 M 1 F (athletes)	420	> 60	$\dot{V}_E$ 80 l/min	histamine	Positive challenge, no prevention with albuterol.	Gong et al. (1988)
6 M 3 F	600	120	$\dot{V}_E$ 64 l/min	metacholine	No hyperresponsivity. Experimental protocol devaluated due to selection of volunteers.	Chatham et al. (1987)

It may be concluded that the NAEL for this kind of effects will be between 120 and 240 $\mu g/m^3$ for a few hours exposure. It should be noted that those levels are applicable to physically well trained men and women.

Henderson et al. (1988) studied 24 young adult male volunteers experimentally inocculated with type 39 rhinovirus to determine whether the course of viral infection was modified by exposure to moderate levels of ozone (600 $\mu g/m^3$ for 6 h/day) over the 5 days after virus inocculation. In relation to ozone exposure no differences were demonstrated of rhinovirus in nasal secretions, recruitment of neutrophils into nasal secretions, levels of interferon in nasal lavage fluid, in vitro lymphocyte proliferative responses to rhinovirus antigen, or levels of convalescent serum neutralizing antibody to type 39 rhinovirus.

6.2.3. Epidemiological studies

Epidemiologal studies involve realistic pollution mixtures and exposure patterns, and can study large groups of subjects, including the young, old and other potentially susceptible populations. Epidemiological documentation helps determining the public health significance of small, reversible changes in lung function. But in spite of this potential value, epidemiological studies on acute pulmonary function effects have played a limited role in determining the ambient air quality standard for ozone (Kinney et al., 1988), and even much less in occupational standards. This reflects difficulties in the quantitative interpretation of results that are, to some extent, inherent to the epidemiological approach, but it may be partly attributed to design inadequacies in reported studies. Some problems include poor assessment of individual exposures, failures to account for varying activity levels and confounding by temporal covariates such as temperature and pollen. These problems limit somewhat the confidence in results from individual studies.

There are very few epidemiological data available for occupational exposure to ozone. Piere et al. (1988) performed a survey on arc welders, one group consisted of 13 aluminium welders working inside aluminium tanks and 8 welders engaged in the production of vans for dump trucks in non-confined space. The reference group consisted of 26 workers of the same plant who were not exposed to welding fumes. The serum copper and ceruloplasmin of these workers were determined. They found that the mean ceruloplasmin in serum of the confined welders to be significantly lower in comparison with that of the reference group and non-confined welders. The authors attributed the decreased ceruloplasmin level to exposure to ozone. Six-hour sampling of ozone in the helmet of welders working

in the tank indicated levels of 20 to 3000 µg/m³ with occasional values higher than 20000 µg/m³. A shorter sampling time (2 h) using the same procedure at the non-confined welder working area showed concentrations of 200 to 400 µg/m³ ozone. Beard (1982) in his review reported the following summary on the effects of exposure to ozone on welders: there are no effects from short exposures at 400 or 500 µg/m³; sensations of chest constriction and throat irritation at 600 to 1600 µg/m³; dry mouth and throat and irritation of nose and eyes at 1600 to 3400 µg/m³; and severe headaches, throat irritation, cough, choking, painful breathing and signs of pneumonia or pulmonary edema at 18400 µg/m³. An exposure at concentrations as high as 22400 µg/m³ for 2 hours caused sweating, coughing and collaps.

There are no data available to indicate that long-term exposure to ozone may induce any kind of cancer in man.

6.3 SUMMARY

- The effects of ozone on the upper respiratory tract should not be underestimated. The targets are the ciliated cells, inducing loss of cilia, necrosis of ciliated cells. The membranous portion of trachea received more injury than the cartilaginous portion. From the animal experimental data it is assumed that the NAEL of ozone on the upper respiratory tract may figure around 200 µg/m³ for a short-term exposure period.
  Humans seem to be less susceptible to ozone than experimental animals when effects on the upper respiratory tract are considered. Exposure to 800 µg/m³ for 4 h showed the cell structures to stay generally intact and no injury is evident in the nasal mucosa. Signs of inflammation are found at 1000 µg/m³, 4 h, two consecutive days. But in another study, exposure to 800 µg/m³ for two hours resulted in an increase of polymorphonuclear neutrophils in the nasal lavage fluid immediately post exposure. This means that the NAEL of ozone on the upper respiratory tract must be lower than 800 µg/m³ for a two-hours exposure for humans.

- For effects on the morphology of the lower respiratory tract, the target area of destruction is the transition zone between the conducting airways and the gas exchange structures of the lung, also called the centro-acinar area. In experimental animals morphological changes may already be seen at 400 µg/m³ ozone for a few hours. The ciliated cells and type I cells of this region will be

injured and will perish. In long-term exposure (a few weeks to a few months) a dynamic equilibrium may be reached between the ciliated and non-ciliated cels in the bronchioles and type I and type II cells in the alveoli.

- One of the effects of exposure to ozone on the defence mechanism and immunologic system of the lung is the increased susceptibility to bacterial/viral infection as found in experimental animals. There are indications that ozone influences the seriousness and duration of bacterial infection. It is assumed that the NAEL may lie between 200 and 800 µg/m^3 for a duration of hours and days, in experimental animals. In humans, exposure to 800 µg/m^3, 2 h, already showed increased PMN in the broncheo-alveolar lavage fluid and decrease of macrophages, as well as increased vascular permiability of the lung. At 800 µg/m^3 alteration in the numbers and functional properties of macrophages are reported. The MAEL of ozone for effects on the defence mechanism of the lung is estimated at 200 µg/m^3 for a few hours exposure, in humans.

- For effects of ozone on the lung ventilatory function of airways and the lungs the following can be mentioned: a progression in the breathing frequency, decrease of tidal volume and increase of airway resistance. Rabbits exposed to 2000 µg/m^3, 6 h/d, 7 d, showed only increase of the pulmonary flow resistance. At 4000 µg/m^3, 6 h/d, 3 d, the dynamic compliance decreased and there were signs of early lung edema. In man, there are many data available on the effects of ozone on the lung function. The major debate is how to interpret the health significance of very small, but still significant, decrements in the functions from such studies. It is concluded that the estimated NAEL for impairment of the ventilatory function of the lung of healthy non-smoking young adults should be in the order of magnitude of 300 µg/m^3 ozone for exposure duration of 60-120 minutes with moderate exercise. The MAEL is about 320 µg/m^3, for symptoms of irritation.

  The duration of exposure plays an important role in the magnitude of effects. An exposure duration of 6.6 hours showed that the functional decrements become progressively greater after each hour of exposure. This means that in an 8 hour exposure duration, the NAEL will be clearly below 240 µg/m^3 ozone, in man.

- Exposure to ozone can also alter the responsiveness of the airways to non-spe-

cific broncho-constrictive challenges, such as histamine or metacholine. The NAEL for this effect is estimated to be lower than 240 µg/m³ ozone for an exposure duration of 6.6 hours, in man.

- Biochemical changes in the lung of experimental animals are reported after ozone exposure, e.g. boosting of anti-oxidant metabolism and the oxigen consumption. It is probably caused by the destruction of type I cells and proliferation of type II cells, which are rich in anti-oxidant enzymes. Other changes in specific enzym activities in the lung occurred at exposures to 300 µg/m³ continuously 7 d to 6000 µg/m³, 8 h.

- It is also reported that exposure to ozone in experimental animals caused changes in the morphology of red blood cells. They can be hemolyzed more readily. There is also a decrease of the acetylcholine esterase which is bound to red blood cell membranes.

- Increased alveolar permiability for serum components after short-term exposure of rats to ozone was reported. The NAEL for this unfavourable phenomenon will figure below 600 µg/m³ for ozone exposure of a few hours.

- Exposure to ozone seems to change the drinking habits of rats in a dose-dependent manner. A decrease in drinking was reported in exposure at levels of 400-1600 µg/m³, continuously for 1 week. Exposure to ozone also influenced the heart rate and blood pressure of emphysematous rats.

- In man, ozone is reported to impair the individual physical performance. During maximal exercise by trained athletes a reduction of in peak $\dot{V}_E$, $\dot{V}O_2$, tidal volume, work load and maximal duration of the exercise occurred at exposures to 400 µg/m³. It is estimated that the NAEL of ozone for this kind of effects will be between 120 and 240 µg/m³ for a few hours exposure.

- There is little direct documented evidence of the mutagenicity/genotoxicity of ozone. The interest in the pathology of ozone exposure and the molecular events that underlie its course stems from DNA damage caused by oxygen stress including hydroxyl radicals, superoxide, singlet oxygens and hydrogen peroxide. Interaction between ozone and ionizing radiation or ultra violet radiation on in vitro cellular systems has been reported, inducing neoplastic transfor-

mation. But the interpretation of these experiments is difficult.

- Most epidemiological studies have been performed under outdoor environmental conditions in which a mixture of pollutants is present. The target population is formed by specific groups at risk, e.g. children, elderly people, etc. They have a limited role in the risk evaluation to determine occupational standards. There are no data available to indicate that ozone may induce malignancy in man.

7. PREVIOUS EVALUATION BY (INTER)NATIONAL BODIES

The ACGIH (1986) recommended a threshold limit value of 200 µg/m³ as ceiling for ozone. The following aspects have been taken into consideration: (1) whether pulmonary effects are a function of dose and whether exercise potentiates the effects of exposure, (2) whether effects of chronic exposure occur at concentrations below those causing acute effects, and (3) whether workers with chronic obstructive pulmonary disease are at greater risk than workers without pulmonary disease. No STEL has been presented (ACGIH, 1989-1990).

Based on the information from man and animals, it appears that exposures to ozone in the order of 400 µg/m³ produce mild acute, but not cumulative effects. Thus, control of exposure should not be based on the concept of cumulative dose as measured by the eight-hour TWA. It also appears that exposures in the order of 200 µg/m³ will be well tolerated by most workers including asthmatics. Based upon all these information, a ceiling of 200 µg/m³ was recommended.

The DFG recommended in 1973 an occupational limit of 200 µg/m³ ozone as TWA-8 hour. At a later date they supplemented this limit with a short-term limit of 400 µg/m³. They based this earlier recommendation on animal as well as human data. They came to the conclusion that short-term exposure to 200 µg/m³ ozone does not show significant, but otherwise measurable subjective signs of irritations; but a decrement of effects was shown when the exposure duration was extended. It is acknowledged that the safety margin to the recommended MAK level is very small. From animal experimentation data it was postulated that long-term exposure to 400 µg/m³ did not induce functional or structural changes in the lung.

They also cited from industrial experience that, due to the activity pattern, ozone exposure usually does not occur during the whole workshift, but a few, more or less, recovery times are interspaced. It is therefore that a MAK of 200 µg/m³ is found to be justified.

Sweden (1987) has an occupational limit of 200 µg/m³ TWA-8 h and a short-term exposure limit of 600 µg/m³ ozone. In their consensus report for ozone, which is based on a criteria document from the Nordic Expert Group, the following conclusions are made: people seem to vary widely in their sensitivity to ozone, and a dose-effect relationship is therefore difficult to establish. Available data are not sufficient to allow an assessment of dose-response or dose-effect relationships for long-term exposure to ozone. The critical effects of exposure to ozone are irrita-

tion of the respiratory passages and effects on the bronchial resistance. It should be noted that ozone reacts with other irritants such as NO_2 and SO_2, and that persons with lung diseases can suffer exposure to ozone or other oxidants.

There is no documentation for the occupational standards of ozone from United Kingdom, France and USSR.

The Netherlands. The RIVM (1987) recommended a standard of 160 $\mu g/m^3$, 1-hour average for ambient air based on the decreased lung function found in human experiments with an adverse effect level of 240 $\mu g/m^3$ and a safety factor of 1.5. A standard of 110 $\mu g/m^3$, 8-hour average was also recommended, based on effects at 160 $\mu g/m^3$ from epidemiological data and using also a safety factor of 1.5.

The Public Health Council in the Netherlands (1988) recommended to retain the "old" advised limit of 120 $\mu g/m^3$ for 1-hour average. They have acknowledged that there is no fundamental difference in the health-risk assessment with the recommendations from the RIVM. The directive of the Council of 120 $\mu g/m^3$ is based on the assumption that the adverse effect levels (200-240 $\mu g/m^3$) incidentally can be reached in ambient air. They contended that the use of a safety factor of 1.5 did not leave much room for a substantial safety margin. In this recommendation the possible effects of mutagenicity and carcinogenicity have not been taken into account.

8. EVALUATION OF HUMAN HEALTH RISK

8.1 GROUPS AT EXTRA RISK

It is well established that inhalation of ozone causes concentration dependent decrements in volumes and flow rates during forced expiratory manoeuvers, and that the mean decrements increase with increasing minute ventilation, that there is a wide range of reproducible responsiveness among healthy subjects, and that functional responsiveness to ozone, is not greater and usually lower among cigarette smokers and older adults. Asthmatics and patients with allergic rhinitis or chronic obstructive pulmonary diseases (COPD) should be included in the groups at extra risk.

8.2 ASSESSMENT OF HEALTH RISK

The problem of duration of exposure plays a large role in the assessment of effects of ozone. The present occupational standard in the Netherlands for this gas is 200 $\mu g/m^3$ TWA-8 hours. There is no documentation on which this level is based. From historical point of view it is presumed that this standard is adopted from the TLV as recommended by ACGIH. However, there is a great difference in opinion about the sampling duration that should limit the exposure criteria. The present TLV of the ACGIH is 200 $\mu g/m^3$ to be presented as Ceiling. The ACGIH in 1986 stressed the fact that exposure to ozone in the order of 400 $\mu g/m^3$ produced mild acute, but not cumulative effects; therefore a ceiling value was chosen. However, the consideration of no cumulative effects; at low level exposure of ozone has been overhauled by more recent evidence in which cumulation of effects has been proven. Folinsbee et al. (1988) undertook a chamber exposure study of 10 adult male volunteers involving 6.6 hours of ozone exposure at 240 $\mu g/m^3$. They found that functional decrement becomes progressively greater after each hour of exposure. This means that in an occupational situation of an 8-hour workschedule the greatest risk occurs at the end of the workshift.

It is now clear that the respiratory function effects may accumulate over many hours, and that appropriate averaging time for transient functional decrements caused by ozone is $\geq$ 6 hours. Thus there is less scientific basis for the current health based exposure limit with an averaging time of 1 hour than previously believed.

There are no data available on the effects of ozone after long-term exposure. Most epidemiological studies refer to environmental events in which pollution of a

mixture of pollutants plays a role. Therefore the scientific basis for the risk assessment is achieved from effects after short-term exposure.

From the accumulated experimental animal and human data the following conclusions may be summarized:

* For the upper respiratory tract

200 µg/m³, few hours,	NAEL for experimental animals
< 800 µg/m³, 2 hours,	NAEL for humans

* For the lower respiratory tract (lung)

Animal data:

200-800 µg/m³, for hours and days	NAEL on the defence mechanism and immunologic system of the lung
300 µg/m³, continuously 7 d	Biochemical changes in the lungs
400 µg/m³, for a few hours	Morphological changes on the lung epithelium
below 600 µg/m³, few hours	Increased alveolar permiability of serum components
400-1600 µg/m³, continuously 1 w,	Changes in drinking habits
2000 µg/m³, 6 h/d, 7 d,	Increase in pulmonary flow resistance
4000 µg/m³, 6 h/d, 3 d,	Decrease in dynamic compliance of the lung and signs of early lung edema

Human data:

120-240 µg/m³, a few hours exposure,	NAEL for impairment in the individual performance of trained athletes
200 µg/m³, a few hours,	MAEL for effects on the defence mechanism of the lung
240 µg/m³, 6.6 h,	AEL for decrement of the lung function in healthy individuals
240 µg/m³, 6.6 h,	AEL for alteration in the responsiveness of the airways to non-specific broncho-constrictive challenges

800 $\mu g/m^3$, a few hours,	Alteration in the numbers and functional properties of the macro-phages in the lung.

The most convenient and efficient way to study the mechanism and pattern of response to inhaled ozone is by controlled exposures to laboratory animals. Although one can study the transient functional responses to acute exposures and establish the interspecies differences in response among different animal species and between them and humans similarly exposed, there are still limitations to the use of exposure-response data from animal studies in human risk assessment. It is the quite limited ability to interpret the responses in relation to likely responses in humans who might be exposed to the same or lower levels. There is little reason to expect humans to be less sensitive than rats or monkeys. On the contrary, humans have a greater dosage delivered to the respiratory acinus than do rats for the same exposures (Lippmann, 1989). It is therefore that the basis for the occupational standard is taken from the human data.

Human data show that the no-observed adverse effect level is about 120-240 $\mu g/m^3$ ozone during a few hours exposure. Therefore an occupational exposure limit of 120 $\mu g/m^3$ (60 ppb) ozone, TWA-1 hour, is recommended. It is reminded that an 1-hour TWA occupational exposure limit is an extraordinary recommendation by the DECOS since it is outside the customary 8-hour or 15-minute TWA limits. The present recommendation is based on the available data related to health effects. The DECOS has the feeling that a short-term (15-minute) exposure limit may also be needed for ozone, but since no data are available, the DECOS refrains from doing it.

The DECOS has the opinion that the recommended exposure limit would also prevent adverse effects during longer period of exposure, therefore a limit for 8 hour exposure is not necessary.

It should be reminded that for the general population in the Netherlands the recommended ambient air limit as proposed by the Public Health Council was 120 $\mu g/m^3$, TWA-1 hour. A dynamic equilibrium exists between ambient air and air inside buildings.

8.3 RECOMMENDED OCCUPATIONAL EXPOSURE LIMIT

The DECOS recommends a health-based occupational exposure limit for ozone at 120 $\mu g/m^3$ (60 ppb) ozone as TWA of 1 hour.

9. RECOMMENDATIONS FOR RESEARCH

- Health-survey studies of workers exposed to ozone are recommended. The magnitude of exposure should be documented and the monitoring of work-room air should be performed according current standards.

- More data should be gathered for effects after long-term low level exposure to ozone.

- More studies should be performed for the possibility of mutagenic and genotoxic activity of ozone, and whether these activities may lead to the carcinogenicity of the gas in human.

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gezondheidskundige adviezen van de werkgroep van deskundigen ter vaststelling van mac-waarden

Code		*Prijs*
RA 1/80	Fosfine	*f.* 12,=
RA 2/80	Anorganisch Lood	*f.* 18,=
RA 3/80	Carcinogene stoffen	*f.* 16,=
RA 4/80	Tolueen Diisocyanaat	*f.* 7,=
RA 5/80	Cadmium	*f.* 16,=
RA 6/80	Chloor	*f.* 13,=
RA 1/81	n-Heptaan	*f.* 11,=
RA 2/81	Pentaan	*f.* 9,=
RA 3/81	1,1,1-Trichloorethaan	*f.* 18,=
RA 4/81	Formaldehyde niet meer verkrijgbaar (zie RA 3/87)	
RA 5/81	Metallisch Kwik	*f.* 13,=
RA 1/82	Mangaan	*f.* 17,=
RA 2/82	Monochloorethaan	*f.* 11,=
RA 3/82	Anorganische Kwikzouten	*f.* 15,=
RA 4/82	Organische Kwikverbindingen *(Uitsluitend phenylkwik en alkoxyalkylverb.)*	*f.* 13,=
RA 5/82	Kwikalkylverbindingen - Korte keten *(Uitsluitend methylkwik en ethylkwik)*	*f.* 18,=
RA 1/83	Methyleenchloride	*f.* 17,=
RA 2/83	Triethylamine	*f.* 16,=
RA 3/83	Trichloorethyleen	*f.* 18,=
RA 1/84	Asbest	*f.* 28,=
RA 2/84	Anorganische Arseenverbindingen *(Exclusief Arseenwaterstof)*	*f.* 20,=
RA 4/84	Caprolactam	*f.* 17,=
RA 1/85	2-Nitropropaan	*f.* 12,=
RA 2/85	Lachgas	*f.* 21,=

Code		*Prijs*
RA 3/85	Nikkel en nikkelverbindingen	*f.* 21,=
RA 4/85	Zwaveldioxide	*f.* 17,=
RA 5/85	Stikstofdioxide	*f.* 15,=
RA 6/85	Chroom en chroomverbindingen	*f.* 20,=
RA 1/86	Epichloorhydrine	*f.* 19,=
RA 1/87	1,4-Dioxaan	*f.* 13,=
RA 2/87	Hydrazine, dimethylhydrazine, hydroxyethyl-hydrazine en fenylhydrazine	*f.* 21,=
RA 3/87	Formaldehyde *(Engelse uitgave)*	*f.* 22,=
RA 4/87	4,6-Dinitro-ortho-cresol	*f.* 13,=
RA 5/87	Dibroomethaan	*f.* 13,=
RA 6/87	Aflatoxine B1, B2, G1 en G2	*f.* 16,=
RA 7/87	Chloroform	*f.* 18,=
RA 8/87	1,1-Dichloorethaan	*f.* 9,=
RA 9/87	Trimethylamine	*f.* 13,=
RA 10/87	Vanadium metaal en anorganische verbindingen	*f.* 16,=
RA 11/87	n-Hexaan	*f.* 21,=
RA 12/87	2-Propoxyethanol, 2-Propoxyethylacetate, 2-Isopropoxyethanol *(Engelse uitgave)*	*f.* 9,=
RA 13/87	Acrilaten	*f.* 13,=
RA 14/87	Trichlorofluoromethane *(Engelse uitgave)*	*f.* 16,=
RA 15/87	Fluorcarbons(except FC11) *(Engelse uitgave)*	*f.* 21,=
RA 1/88	Para-Dichloorbenzeen	*f.* 15,=
***		
RA 2/88	Hexachlorobenzene	*f.* 24,=
RA 3/88	Carbonylfluoride and PTFE Pyrolysis products	*f.* 11,=
RA 4/88	Beryllium and Beryllium compounds	*f.* 22,=
RA 1/89	Fluorine, Hydrogenfluorine and Inorganic fluorine compounds	*f.* 22,=
RA 2/89	Aniline	*f.* 17,=

Code		*Prijs*
RA 3/89	Phtalic anhydride	*f.* 12,=
RA 4/89	Ethyl Methanesulphonate (EMS) Methyl Methanesulphonate (MMS)	*f.* 22,=
RA 5/89	Benzeen *	*f.* 10,=
RA 6/89	Ethyleenoxide *	*f.* 13,=
RA 7/89	Selenium en verbindingen *	*f.* 18,=
RA 8/89	Styreen *	*f.* 17,=
RA 9/89	Evaluatie van risico op kanker bij beroepshalve blootstelling aan asbest (aanvullend op RA 1/84) *	*f.* 12,=
RA 1/90	Methyl acrylate	*f.* 14,=
RA 2/90	2-Hexanone	*f.* 17,=
RA 3/90	Cyclohexanol	*f.* 16,=
RA 4/90	Amyl acetate	*f.* 11,=
RA 5/90	1,3-Butadiene	*f.* 17,=
RA 6/90	Ethyl acrylate	*f.* 15,=
RA 7/90	Ethyl amine	*f.* 13,-
RA 8/90	Gezondheidskundige aspecten van het begrip Blootstelling en van het meten/schatten ervan *	*f.* 26,-
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RA 10/90	Dimethylamine	*f.* 16,-
RA 11/90	Thiourea	*f.* 11,-
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RA 13/90	Methylbromide	*f.* 18,-
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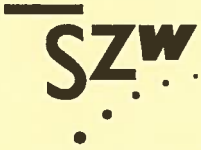
RA 16/90	Methyl ethyl ketone	*f.* 17,-

Code		*Prijs*
RA 1/91	Tetrahydrofuran	*f*. 18,-
RA 2/91	Tolueen *	*f*. 21,-
RA 3/91	Diisocyanates	*f*. 22,-
RA 4/91	Methyl isobutyl ketone	*f*. 17,-
RA 5/91	Xylene	*f*. 27,-
RA 6/91	Talc dusts	*f*. 19,-
RA 7/91	Piperazine	*f*. 16,-
RA 8/91	Wood dust	*f*. 23,-
RA 9/91	Ethylbenzene	*f*. 21,-
RA 10/91	Ethyl acetate	*f*. 18,-
RA 1/92	Allyl- and Isopropyl-glycidyl ether	*f*.
RA 2/92	Nitrous oxide (Lachgas)	*f*.
RA 3/92	Gasoline	*f*.

*** Alle rapporten vanaf RA 2/88 zijn Engelstalige uitgaven voorzien van een Nederlandstalige samenvatting uitgezonderd de rapporten voorzien van *, deze zijn Nederlandstalig.



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