Environmental Health Criteria 55

ETHYLENE OXIDE

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World Health Organization

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

ENVIRONMENTAL HEALTH CRITERIA 55

ETHYLENE OXIDE

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PREFACE

Although only key references essential for the evaluation of the risks for human health and the environment are cited, this document is based on a comprehensive search of the available, original scientific literature, while valuable information has also been obtained from various reviews.

A detailed data profile on ethylene oxide can be obtained from the International Register of Potentially Toxic Chemicals (UNEP/IRPTC, Palais des Nations, CH-1211 Geneva 10, Switzerland, telephone number 988400 - 985850).

The document focuses on describing and evaluating the risks of ethylene oxide for human health and the environment.

Every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors, which may have occurred, to the Manager, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

ENVIRONMENTAL HEALTH CRITERIA FOR ETHYLENE OXIDE

The WHO Task Group for the Environmental Health Criteria for Ethylene Oxide met at the Institute of Hygiene and Epidemiology, in Brussels, Belgium, on 21 - 26 October 1985. Dr G. Thiers, who opened the meeting, welcomed the participants on behalf of the host government, and Dr F. Valic welcomed them on behalf of the heads of the three IPCS co-sponsoring organizations (ILO/WHO/UNEP). The Group reviewed and revised the second draft criteria document and made an evaluation of the health risks of exposure to ethylene oxide.

The efforts of DR T. VERMEIRE, of the NATIONAL INSTITUTE OF PUBLIC HEALTH AND ENVIRONMENTAL HYGIENE, Bilthoven, the Netherlands, who was responsible for the preparation of the draft, and of all who helped in the preparation and the finalization of the document are gratefully acknowledged.

* * *

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1. SUMMARY

Ethylene oxide is a colourless, highly reactive, and flammable gas at room temperature and ambient pressure. The current world production is greater than 5.5 million tonnes. Its major use is as an intermediate in the production of various chemicals. Since ethylene oxide is a reactive epoxide and potent biocide, a small quantity (less than 1%) is used for the fumigation and sterilization of foodstuffs and medical equipment. Because of its high odour threshold (900 - 1260 mg/m^3), sensory recognition does not offer adequate warning of a health hazard.

Detection limits of 0.024 mg/m^3, 2 mg/litre, and 0.15 mg/kg have been reported for gas chromatographic determinations in air, water, and food, respectively. A total loss to the atmosphere of 1 - 2% of production occurs during its manufacture and use. Its removal from the atmosphere and neutral water is slow, but it is more rapid under acidic or basic catalysis. Aerobic biodegradation is slow.

Human exposure mainly occurs through inhalation in sterilization facilities and in production plants. In sterilization facilities, 8-h time-weighted average levels have usually been below 36 mg/m^3, with short-term exposures of about 100 mg/m^3, and peak levels of up to 1800 mg/m^3. In production plants, the time-weighted average has usually been below 4 mg/m^3. Ambient levels at a distance from point sources of emission have been estimated to be below the limit of detection.

Exposure to residues of ethylene oxide or its reaction products, halohydrins and ethylene glycol, also occurs from fumigated foods, pharmaceutical products, and sterilized medical equipment. 2-Chloroethanol levels as high as several g/kg have been measured in food and levels of several hundred mg/kg in medical equipment.

Ethylene oxide is not expected to bioaccumulate in the environment. Fish are the most susceptible aquatic organisms. An LC_{50} of 90 mg/litre was observed for goldfish exposed for 24 h. 2-Chloroethanol, a degradation product in saline water, is equally toxic but, 1,2-ethanediol, a major degradation product, is much less toxic.

When inhaled, ethylene oxide is readily absorbed, distributed throughout the body, and rapidly metabolized. Accordingly, most organs receive equivalent doses of the chemical and its metabolites. The degree of alkylation of proteins and DNA varies slightly between the different organs and blood. In man and rodents, the half-life of the compound in tissues has been estimated to be 9 - 10 min. Two metabolic pathways have been identified including hydrolysis to 1,2-ethanediol and conjugation with glutathione. Excretion is primarily via the urine.

Ethylene oxide is moderately toxic for mammals (the LD_{50} for the rat is 280 - 365 mg/kg body weight; the 4-h LC_{50} is 2630 mg/m^3). Both experimental animal and human data show that aqueous solutions of ethylene oxide are irritating for the skin and eyes; the irritant effects of ethylene oxide vapour or residues in medical equipment on the eyes and the respiratory tract have also been observed. These effects are often delayed. Severe skin irritation is characterized by the formation of vesicles. A concentration of 10 mg/litre produced mild irritation of the human skin; a concentration of 500 g/litre was most injurious to the human skin. Allergic contact dermatitis has been reported; systemic immunologically mediated allergy is considered rare. Respiratory tract irritation increases with inhaled vapour concentration and may result in severe life-threatening pulmonary disease. Repeated exposure (2 - 8 weeks) to ethylene oxide vapour at or above 900 mg/m^3 produced sensory and motor neurological impairment and may result in a peripheral neuropathy. In animals, the latter was often accompanied by muscular atrophy. Lesions in the medulla oblongata of monkeys, following 2 years of intermittent exposure (7 h/day, 5 days/week) to 90 and 180 mg/m^3 indicated neuropathy in the brain, which may be related to the neuropathies observed in man and other animal species. Cardiovascular collapse and renal failure have been attributed to residues of ethylene oxide in medical equipment.

Ethylene oxide alkylates DNA and is mutagenic for plants, microorganisms, insects, and mammals. Cytogenetic studies on man have shown dose-related increased frequencies of both sister chromatid exchanges (SCEs) and chromosomal aberrations; in one

study, SCEs developed following daily exposure for less than 5 min per day.

The evidence that ethylene oxide is a reproductive toxin is less conclusive. Where fetal developmental effects have occurred, the doses of ethylene oxide approached or equalled those producing maternal toxicity. To date, impaired male reproductive function in animals has been demonstrated only at concentrations of 90 mg/m^3 or more in long-term intermittent exposures or at higher air concentrations for brief exposures. In pregnant women, the results of one study suggest that occupational exposure estimated to be an 8-h time-weighted average of 0.18 - 0.90 mg/m^3, with peak concentrations up to 450 mg/m^3, was associated with spontaneous abortions. However, limited exposure data prevents the establishment of a relationship between abortion rates and exposure levels.

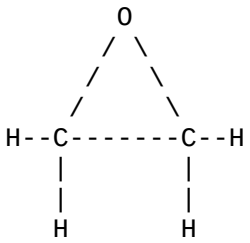
Ethylene oxide is carcinogenic for animals when administered by the intragastric, subcutaneous injection, and inhalation routes of exposure. In man, 2 studies have shown an association between ethylene oxide exposure and an excess risk of cancer, but both studies have limitations. Airborne concentrations of ethylene oxide in the 2 studies were reported to be time-weighted averages of 36 ± 18 mg/m^3 and 10 - 50 mg/m^3, with occasional brief exposures in excess of the odour threshold (900 - 1260 mg/m^3).

Taking into account available data concerning the alkylating nature of ethylene oxide, the demonstration of DNA adducts, and the overwhelmingly positive *in vivo* responses in mutagenic and clastogenic assays, the reproducible positive carcinogenic findings in animals, and the epidemiological findings suggesting an increase in the incidence of human cancer, ethylene oxide should be considered as a probable human carcinogen, and its levels in the environment should be kept as low as feasible.

2. PROPERTIES AND ANALYTICAL METHODS

2.1. Identity

Structural formula:



Molecular formula: C_2H_4O

Abbreviation: EO, ETO

Common synonyms: dihydrooxirene; dimethylene oxide; 1,2-epoxyethane; ethene oxide; oxane; alpha, beta-oxidoethane; oxirane (CAS and IUPAC name)

Common trade names: Anprolene; Melgas; Merpal; Sterigas P (pure products); Carboxide; Cartox; Etox; Oxyfume 20; Oxyfume 30; Sterigas 90/10; Steroxide 20; T-gas (formulations with carbon dioxide); Oxyfume 12; Sterigas 12/88; Steroxide 12/88 (formulations

with fluorocarbons); Etoxiat

CAS registry number: 75-21-8

RTECS registry number: KX 2450000

2.2. Chemical and Physical Properties of Ethylene Oxide

Ethylene oxide is a gas at room temperature and normal atmospheric pressure. It condenses to a liquid at 10 °C. The vapour is highly flammable and subject to explosive decomposition. The liquid is stable to common detonating agents, but may polymerize violently after initiation by acids, bases, or heat. Polymerization is catalysed by metal chlorides and oxides. Ethylene oxide is very reactive in both the liquid and vapour phase. Ring opening readily occurs with release of energy, particularly in reactions with nucleophiles such as water, alcohols, halides, amines, and sulfhydryl compounds.

Some physical and chemical data on ethylene oxide are given in Table 1.

Table 1. Some physical and chemical data on ethylene oxide

Physical state	gas
Colour	colourless
Odour	ethereal
Odour threshold	470 mg/m^3 for perception and 900 - 1260 mg/m^3 for recognition[a]
Relative molecular mass	44.05
Melting point	-111 °C
Boiling point	10.4 °C
Water solubility	infinitely soluble
log *n*-Octanol-water partition coefficient	-0.30
Density	0.87 g/ml, 20 °C
Relative vapour density	1.5
Vapour pressure	146 kPa (1095 mm Hg), 20 °C
Flash point	< -18 °C (open-cup)
Flammable limits	3 - 100% by volume

[a] From: Jacobson et al. (1956) and Hellman & Small (1974).

Conversion factor

ethylene oxide 1 ppm = 1.80 mg/m^3 air at 25 °C and 101.3 kPa (760 mm Hg)

2.3. Analytical Methods

Methods for the sampling and determination of ethylene oxide in

air, water, food, plastic materials, blood, and urine are summarized in Table 2. Some methods are also suitable for measuring important reaction products such as 2-chloroethanol (ethylene chlorohydrin) and 1,2-ethanediol (monoethylene glycol).

Table 2. Sampling, preparation, analysis

Medium	Sampling method	Analytical method	Detection limit	Comments
Air	sampling on charcoal; desorption with carbon disulfide	gas chromatography with electron capture detection after derivatization with hydrogen bromide	0.024 mg/m^3	sample size 1 suitable for and area mon
Air	sampling on charcoal; desorption with carbon disulfide	gas chromatography with flame ionization detection	0.27 mg/m^3	sample size < litre; suita personal and monitoring
Air	trapping in dilute sulfuric acid using a microimpinger	gas chromatography with flame ionization detection	1.8 mg/m^3 (99-litre sample)	sample size 1 litre; suita personal and monitoring
Air		infrared spectroscopy	1.8 mg/m^3	direct analys for instanta continuous a ing; limited
Air		colorimetric direct reading indicator tubes	18 mg/m^3	simple, cheap giving a goo with gas chr analysis; su short-term a ments; limit
Water		gas chromatography with flame ionization detection	2 mg/litre	direct analy suitable for main reactio drugs and fo can be analy extraction w

Table 2. (contd.)

Medium	Sampling method	Analytical method	Detection limit	Comments
Food	extraction by 5:1 acetone-water (by volume) for 24 h	gas chromatography with flame ionization detection	0.15 mg/kg wet weight	sample size also suitabl uring reacti
Food	thermal desorption in an airtight bottle at 40 °C for 30 min	colorimetry using paper strips with sodium sulfite and thymol blue-phenolphthalein indicator	0.7 mg/kg wet weight	simple, chea headspace an sample size alkene oxide hydes may in
Plastic material	thermal desorption in an airtight vial at	gas chromatography with flame ionization detection	0.1 mg/kg	headspace an

	100°C for 15 min	
Blood, Urine	gas chromatography with flame ionization detection	direct analy centrifugati tight vials; able for mea metabolites

Instantaneous gas chromatographic measurements of ethylene oxide in air can be performed after taking grab samples (Mouilleseaux et al., 1983). The rather complex gas chromatographic procedure of Scudamore & Heuser (1971) for the determination of ethylene oxide and reaction products in food could be replaced by a simpler procedure, using temperature programming (Pfeilsticker et al., 1975). Titrimetric or colorimetric methods are available, but these methods are not specific, are often subject to systematic errors, and are not applicable for continuous monitoring.

In studies on mice and rats, the degree of alkylation of amino acids, particulary of histidine, in haemoglobin can be used for monitoring the tissue doses of ethylene oxide. Assuming even distribution, tissue dose is defined as the integral of the calculated concentration of free ethylene oxide in the tissues over a specified period of time (Ehrenberg et al., 1974; Osterman-Golkar et al., 1983; Segerbäck, 1983). A sensitive method, based on derivatization with heptafluorobutyric anhydride followed by gas chromatography and mass spectrometry was developed to measure the amount of N^3-(2-hydroxyethyl)histidine in haemoglobin (Calleman et al., 1978). This method has a detection limit of 0.004 µg/g haemoglobin. It was used in industrial workers by Calleman et al. (1978) and van Sittert (1985). Human haemoglobin has a life span of about 4 months and, therefore, may integrate the dose of ethylene oxide over a long period (Osterman-Golkar et al., 1976). The resolving power of detection of haemoglobin alkylation due to exposure to ethylene oxide appears to be limited by the occurrence of background alkylations. It was estimated that exposures of less than 9 mg/m^3 could be masked by these background alkylations (Osterman-Golkar, 1983). More validation work in human beings is still needed.

3. SOURCES IN THE ENVIRONMENT, ENVIRONMENTAL TRANSPORT AND DISTRIBUTION

3.1. Production, Uses, Disposal of Wastes

3.1.1. Production levels and processes

In 1978, world production of ethylene oxide was estimated to be 4540 kilotonnes (Clayton & Clayton, 1981). The USA production, which roughly accounted for half of this figure, rose from 1750 kilotonnes in 1970 to 2400 kilotonnes in 1980 (USITC, 1971, 1981). For 1983, USA production was estimated to be 2540 kilotonnes (Webber, 1984). In western Europe, 865 kilotonnes were produced in 1972 (Glaser, 1979), while for 1981, production was estimated to be 1370 kilotonnes (IARC, 1985). In Japan, 470 kilotonnes were produced in 1982 (IARC, 1985). Ethylene oxide is also produced in Australia, Brazil, Bulgaria, Canada, China, Czechoslovakia, the German Democratic Republic, India, the Republic of Korea, Mexico, Poland, Romania, and the USSR (IARC, 1985). From the above data, it can be derived that the current world production will be far above 5500 kilotonnes per year.

Ethylene oxide is chiefly produced by the oxidation of ethene

with air or oxygen in the presence of a silver oxide catalyst. This process has virtually replaced the chlorohydrin process in which 2-chloroethanol (ethylene chlorohydrin) reacts with potassium hydroxide or calcium oxide. Common impurities in the oxidation process are water, acetic acid, acetaldehyde, and organic and inorganic chlorides (WHO, 1978). Common impurities in the chlorohydrin process are vinyl chloride, 1,2-dichloroethane, chloroethane, and ethylene chlorohydrin.

3.1.2. Uses

Virtually all the ethylene oxide produced is used as an intermediate in the production of various chemicals. In order of importance in the USA, the principal chemicals are: the antifreeze 1,2-ethanediol; polyethylene terephthalate polyester for fibres, films, and bottles; non-ionic surface active agents; glycol ethers; ethanolamines; and choline. A small fraction of the total consumption (about 1% in the USA in 1976) was used as an antimicrobial sterilant or as an insecticidal fumigant (WHO, 1978; Glaser, 1979). Less than 0.02% of this production (500 000 kg) was used for sterilization in hospitals (Glaser, 1979). In Belgium, an estimated 0.07% of the total consumption of ethylene oxide (120 000 kg) was used in the health care and medical products industries in 1980 (Wolfs et al., 1983).

3.1.3. Disposal of wastes

Escape through air vents during production and sterilization appears to be the most important source of release of ethylene oxide into the environment. The waste gas can be removed from the air by scrubbing. Emission control of liquid wastes mainly occurs by incineration in liquid-burning hazardous waste incinerators. Process waters for the manufacture and use of ethylene oxide are a minor problem with respect to waste management. Conventional effluent water treatment including biological treatment is reported to be sufficient. No specific solid wastes are associated with the manufacture of ethylene oxide (Bogyo et al., 1980).

3.2. Transport and Fate in the Environment

The main pathway of entry of ethylene oxide into the environment is through its escape into the atmosphere due to evaporation and with vented gases during production, handling, storage, transport, and use. Most of the ethylene oxide applied as a sterilant or fumigant will enter the atmosphere (Bogyo et al., 1980). In the USA, production losses were estimated at 13 kg per tonne of ethylene oxide produced by catalytic oxidation. Sterilization and fumigation processes were estimated to account for a loss of 9 kg per tonne of ethylene oxide produced or approximately 1% of the total consumption (WHO, 1978). In 1980, this would have meant a combined loss of 53 kilotonnes of ethylene oxide into the atmosphere in the USA, which is approximately 2% of the total production in the USA.

At ambient levels, ethylene oxide will be removed from the atmosphere via oxidation by hydroxyl radicals. On the basis of a theoretical rate constant for this reaction, the atmospheric residence time of ethylene oxide was estimated to be 5.8 days (Cupitt, 1980). However, experimental data have shown the residence time to be 100 - 215 days, depending on the hydroxyl radical concentration and the ambient temperature (US EPA, 1985). Because of its high water solubility, ethylene oxide levels in air will also be reduced through washout by rain (Conway et al., 1983). The photochemical reactivity of ethylene oxide, in terms of its

ozone-forming ability, is low (Joshi et al., 1982). Evaporation from water is a significant removal process. Under specific conditions, Conway et al. (1983) found a half-life of 1 h for the evaporation of ethylene oxide from water. In the environment, chemical degradation in water through ionic reactions appears to be comparatively slow. In neutral, fresh water at 25 °C, ethylene oxide is broken down to form 1,2-ethanediol with a half-life of 14 days (Conway et al., 1983). At 0 °C, the half-life is 309 days. The reaction is acid- and base-catalysed (Virtanen, 1963). In the presence of halide ions, 2-haloethanol will also be formed. In neutral water of 3% salinity, at 25 °C, 77% of ethylene oxide was found to react to form 1,2-ethanediol and 23%, to form 2-chloroethanol with a half-life of 9 days (Conway et al., 1983).

Ethylene oxide and its possible metabolites can be biodegraded slowly by aerobic microorganisms. Biological oxygen demands of 3 - 5% and 52% of the theoretical oxygen demand were determined for ethylene oxide after 5 and 20 days, respectively, using a domestic sewage seed (Bridié et al., 1979b; Conway et al., 1983).

4.ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

4.1. Occurrence in the Environment

No data are available concerning levels of ethylene oxide in air, water, or soil, following emission from production plants, and there are no data indicating that ethylene oxide occurs as a natural product. Most of the ethylene oxide used for fumigation or sterilization finally enters the environment, mainly the air. Uncontrolled emission of ethylene oxide from a hospital sterilization chamber led to high levels of the sterilant in the immediate surroundings. Concentrations of between 7700 and 12 000 mg/m^3 were measured, 2 - 3 m from an exhaust pipe on the outside wall (Dunkelberg & Hartmetz, 1977).

4.2. General Population Exposure

4.2.1. Exposure via food and tobacco

Residue levels, after fumigation or sterilization using ethylene oxide, depend on a number of factors, such as the concentration of ethylene oxide, the composition of the gas, temperature, aeration, and storage conditions after treatment, the type of commodity and its moisture and lipid content, pH, permeability, particle size, and packaging. Absorbed ethylene oxide disappears rapidly. In a variety of commodities, concentrations between 32 and 7000 mg/kg wet weight, found 1 h after treatment, dropped to below 1 mg/kg within 14 days of storage, at ambient conditions. However, sealed storage or storage at low temperatures will impede desorption considerably (Scudamore & Heuser, 1971). In spices, ethylene oxide at concentrations of 53 - 116 mg/kg wet weight, measured 2 days after fumigation, fell to less than 25 mg/kg within another 24 days (Gerhardt & Ladd Effio, 1983).

Ethylene oxide will react with chloride and bromide ions in commodities to form 2-chloroethanol and 2-bromoethanol, respectively. This reaction can continue after treatment. Levels of 2-chloroethanol of up to several thousands of mg/kg wet weight have been measured, depending on, among other factors, the chloride content and pH of the commodity, and the concentration of ethylene oxide (Wesley et al., 1965; Ragelis et al., 1968; Buquet & Manchon, 1970; Scudamore & Heuser, 1971; Gerhardt & Ladd Effio, 1983). Under unfavourable (e.g., air-tight) conditions, 2-chloroethanol

can persist much longer than residues of ethylene oxide, even longer than one year after treatment. 2-Chloroethanol will disappear rapidly from freely-aerated and finely-divided commodities. However, 2-bromoethanol decomposes slowly (Scudamore & Heuser, 1971; Stijve et al., 1976).

The formation of 1,2-ethanediol (monoethylene glycol) and 2,2'oxybisethanol (diethylene glycol) from water and ethylene oxide are competitive reactions (Gordon & Thornburg, 1959; Buquet & Manchon, 1970; Scudamore & Heuser, 1971). Levels in food up to 2420 mg/kg wet weight have been reported for 1,2-ethanediol and up to 65 mg/kg wet weight for 2,2'-oxybisethanol, 6 - 12 months after sterilization (Scudamore & Heuser, 1971). Food constituents can also be alkylated. Hydroxyethylated derivatives of amino acids, vitamins, alkaloids, and sugars have been identified that might affect the nutritive value of food. A change in organoleptic properties has been reported for a variety of foodstuffs (Oser & Hall, 1956; Gordon & Thornburg, 1959; Windmueller et al., 1959; Kröller, 1966; Pfeilsticker & Siddiqui, 1976).

2-Chloroethanol was detected in cigarette smoke at levels of 350 and 82 mg/m^3 trapped smoke, 1 and 49 days, respectively, after fumigation of the tobacco (Chaigneau & Muraz, 1981).

4.2.2. Exposure via medical equipment

Ethylene oxide may also be absorbed by medical equipment during sterilization and may remain in the materials for some time, as the unchanged compound or as its reaction products. Factors affecting residue levels are similar to those mentioned in section 4.2.1 for food. Aeration and storage conditions are very important, particularly with respect to possible worker exposure.

Other conditions being equal, the removal of ethylene oxide residues by aeration takes longer in plastics such as polyvinyl chloride, polyether-polyurethane, polyglycolic acid, and glassy polymers. Desorption periods for ethylene oxide in polyethylene and rubber materials and textiles are shorter (McGunnigle et al., 1975; Gillespie et al., 1979; Gilding et al., 1980; Star, 1980b,c,d; Dauvois et al., 1982). Star (1980b) sterilized polyvinyl chloride and rubber tubes and found that initial residues of ethylene oxide in polyvinyl chloride tubes of between 3510 and 7300 mg/kg dropped to between 3 and 443 mg/kg after 7 days of aeration at room temperature. In rubber tubes, ethylene oxide residues dropped from 291 and 858 mg/kg after sterilization to levels of between 2 and 24 mg/kg, after 24 h of aeration at room temperature. Using the same sterilization method, similar levels in polyvinyl chloride and rubber tubes were reached after 24 and 4 h of aeration, at 62 °C, respectively (Star, 1980c). Ethylene oxide residues in sterilized cotton wool, adhesive dressings, and compresses dropped from between 270 and 3600 mg/kg to 2 mg/kg or less, in 7 - 8 days of storage. In sanitary pads, the latter residue level was only reached after 14 - 32 days of storage (Dauvois et al., 1982). In sterilized pharmaceutical products, ethylene oxide levels ranging from the detection limit up to 16 300 mg/kg wet weight were measured after 2 - 8 h of vacuum treatment; 1,2-ethanediol was also identified (Adler, 1965). Ethylene oxide levels in water eluates from hollow-fibre dialysers corresponded to a theoretical residue of 1 mg of ethylene oxide per dialyser (50 mg/kg) after an aeration period of 60 days. During 6 h of elution, the concentration of ethylene oxide in the hourly water eluates did not change substantially (Henne et al., 1984).

Maximum residues of 2-chloroethanol in polyvinyl chloride tubes, ranging between 20 and 40 mg/kg, dropped to below the detection limit, within 4 days (Star, 1980d; Jordy, 1983). In rubber, however, the 2-chloroethanol level rose from 300 mg/kg, directly after sterilization, to a maximum of 800 mg/kg, 3 h later; desorption was slow (Jordy, 1983). Gamma-irradiaton before sterilization of polyvinyl chloride by ethylene oxide can increase the 2-chloroethanol residues considerably (Star, 1980d). For the toxicology of 2-chloroethanol, see Vettorazzi (1979).

4.3. Occupational Exposure

In a total of 8 production plants, the levels of worker exposure to ethylene oxide, in recent years, were reported generally to be below 18 mg/m^3 (Hogstedt et al., 1979b; Morgan et al., 1981; Thiess et al., 1981b). In a modern production plant in western Europe, the geometric mean of 0.5 hour-samples, taken in 1974, was less than 0.02 mg/m^3. The geometric mean of 8-h samples was less than 0.02 mg/m^3 in 1978 and 1980, and 0.22 mg/m^3 in 1981. In 89% of the total of 273 samples, the concentration of ethylene oxide was less than 0.2 mg/m^3. In the remaining samples, concentrations of up to 11.6 mg/m^3 were found (van Sittert et al., 1985). In a plant in the USA, typical average daily exposures were reported to be 0.3 - 4.0 mg/m^3 in 1979 (Flores, 1983). Occasionally, higher values can occur. Thiess et al. (1981a) reported a maximum of 3420 mg/m^3, during a plant breakdown. Flores (1983) reported worst-case peak exposures of up to 17 000 mg/m^3. In the past, exposure levels were higher (Joyner, 1964; Hogstedt et al., 1979b).

Although the volume of ethylene oxide used for sterilization is relatively small, many workers are involved. In the USA, approximately 75 000 health-care workers were estimated to be potentially exposed in 1977 (Glaser, 1979). Peak concentrations of up to 1800 mg/m^3 have been measured and occurred mainly when the sterilization chambers were opened. Exposure levels very much depend on the scale and techniques of the process used.

In 4 hospital sterilization units in France, in 1980, concentrations of between 0.9 and 410 mg/m^3 were measured, after sampling for several minutes. During the loading of the sterilizers, the average levels per unit ranged from 3 to 45 mg/m^3. During unloading, averages of 8 - 97 mg/m^3 were measured. In a desorption room, 1- or 2-h time-weighted average levels of between 18 and 173 mg/m^3 were measured; at other sites, time-weighted averages were less than 17 mg/m^3 (Mouilleseaux et al., 1983). Exposures, after the opening of sterilizers, ranging from less than 0.2 to 111 mg/m^3 were found by personal sampling over several minutes in 16 hospitals, in Belgium, in 1981 - 83. In one other hospital, an average of 477 mg/m^3 was measured by personal sampling. In the desorption rooms of a total of 19 hospitals in Belgium, the time-weighted average concentrations, over 30 min, ranged from less than 0.02 mg/m^3 up to 120.6 mg/m^3. In nearby rooms of several hospitals, average 30-min exposure levels of up to 15 mg/m^3 were measured (Lahaye et al., 1984). In 6 hospital sterilization units in Italy, using pure ethylene oxide, the 8-h time-weighted average concentrations were 6.7 - 36 mg/m^3 with an average of 19.3 mg/m^3. Continuous sampling during the 5-min interval following the opening of sterilizers revealed time-

weighted average concentrations of 18 - 288 mg/m^3 (average 112.5 mg/m^3). In 2 other hospitals in Italy, using 11% ethylene oxide in freon, the 8-h time-weighted average levels were 0.36 - 0.90 mg/m^3 with an average of 0.63 mg/m^3, and the 5-min exposure levels were 9 - 47 mg/m^3 (average 15.5 mg/m^3) (Sarto et al., 1984). Time-weighted average exposures of Swedish personnel involved in sterilizing medical equipment in 1975 were 14 mg/m^3, when the sterilizer door was open, and 2.3 mg/m^3, when the door was closed. Before working routines were changed, these levels had been 52 and 16 mg/m^3, respectively. Instantaneous peak levels had reached 94 mg/m^3. In another Swedish factory, in 1978, the time-weighted average personal exposure, during a total shift, was 4.3 mg/m^3 (Högstedt et al., 1983). Pero et al. (1981) reported 1-h time-weighted average personal exposures of up to 18 mg/m^3 for a sterilization facility in Sweden.

Data from the USA agree with the data from Europe. For workers in 5 sterilization rooms of a hospital in the USA, 15-min exposures of up to 86 mg/m^3 were found with 8-h time-weighted averages ranging from less than 0.13 to 7.7 mg/m^3 and instantaneous peaks of up to 1430 mg/m^3 (Hansen et al., 1984). At 3 work-sites in the sterilization facilities of a plant manufacturing health-care products, 8-h time-weighted averages of 0.9, 9 - 18, and 9 - 36 mg/m^3 were measured prior to 1980, but from that year onwards, the 8-h time-weighted averages were below 1.8 mg/m^3 (Stolley et al., 1984).

5. KINETICS AND METABOLISM

5.1. Absorption

Ethylene oxide is very soluble in blood. Therefore, pulmonary uptake is expected to be fast and to depend only on the alveolar ventilation rate and the concentration of ethylene oxide in the inspired air. Ehrenberg et al. (1974) came to such a conclusion after inhalation studies on mice. The rate of uptake of ethylene oxide was 1.1 µg/kg body weight, per min, at an exposure level of 1 mg/m^3. This corresponds to nearly 100% absorption of ethylene oxide from 1.1 litre of air per min and per kg body weight, which is the reported rate of alveolar ventilation in resting mice (Altman & Dittmer, 1974). No specific information pertaining to skin absorption is available, but accidental exposure of the skin of 3 industrial workers to 1% aqueous solution of ethylene oxide was reported to have resulted in marked nausea and profuse vomiting (Sexton & Henson, 1949).

5.2. Distribution

Ethylene oxide is rapidly distributed throughout the body. In mice, body autoradiography, 2 min after intravenous injection, showed that concentrations of ethylene oxide in the liver, kidneys, and pancreas were 3 - 4 times those in the blood. Between 20 min and 4 h after exposure, radioactivity was distributed throughout the body (Appelgren et al., 1977). Directly after inhalation by mice, the highest concentrations of labelled ethylene oxide or its metabolites were found in the liver, kidney, and lung. The radioactivity in the liver and kidney dropped exponentially and approached the levels in the lung, testes, spleen, and brain within 4 h, indicating rapid metabolism and excretion (Ehrenberg et al., 1974). On the basis of tissue alkylation data (Ehrenberg et al., 1974) or haemoglobin alkylation data (Osterman-Golkar et al., 1976, 1983), a half-life of approximately 10 min was estimated for the

first-order clearance of ethylene oxide from mouse or rat tissues. A similar value for man was estimated on the basis of haemoglobin alkylation data (Calleman et al., 1978). In dogs, intravenously-administered ethylene oxide cleared from plasma with a mean half-life of 33 min, which was independent of the dose levels of 25 and 75 mg/kg body weight. Clearance of the confirmed metabolite 1,2-ethanediol from plasma, following intravenous administration, was slower with a half-life of between 3 and 4.4 h (Martis et al., 1982).

When the degree of protein and DNA alkylation was investigated in mice and rats, only small variations were observed between the different tissues in the species. Apparently, most organs receive a more or less equal dose of ethylene oxide after distribution throughout the body. The extent of protein alkylation was approximately equal in the lung, liver, kidney, and spleen of mice, 120 min after inhalation of 2 mg ethylene oxide/m^3 air, for 75 min, but in the testes, it was about 50% lower. When the vapour concentration was increased (up to 59 mg/m^3), the degree of protein alkylation in the liver increased relative to that in the other tissues. In all the tissues investigated, protein alkylation increased linearly with the dose up to an exposure level of 59 mg/m^3, and was relatively constant for at least 3.5 h following exposure (Ehrenberg et al., 1974). Haemoglobin alkylation was previously discussed in section 2.3.

When 0.4 mg ethylene oxide/kg body weight was administered intraperitoneally to mice, DNA alkylation in the testes and spleen was, respectively, 50 and 40% of that in the liver, 5 h after exposure. The approximate half-lives of the alkylation products were 24 h in the spleen, 10 h in the testes, and 12 h in the liver. For the spleen, this half-life was found to be shorter *in vivo* than *in vitro,* indicating active removal (Segerbäck, 1983). In a similar study on rats receiving 0.1 or 0.9 mg ethylene oxide/kg body weight, DNA alkylation in the testes was about one-third of that in the liver (Osterman-Golkar et al., 1983). So far, N^7-(2-hydroxyethyl)guanine is the only DNA alkylation product that has been found *in vivo* (Ehrenberg et al., 1974; Segerbäck, 1983). This reaction product has also been identified *in vitro* (Brookes & Lawley, 1961). In addition, adenosine also reacted *in vitro* with ethylene oxide to form N^1-(2-hydroxyethyl)-adenosine (Windmueller & Kaplan, 1961). When ethylene oxide reacted *in vitro* with uridine, N^3-(2-hydroxyethyl)uridine was the only product found, but in the reaction with uridine-5-phosphate, phosphodiester formation was observed (Ukita et al., 1963).

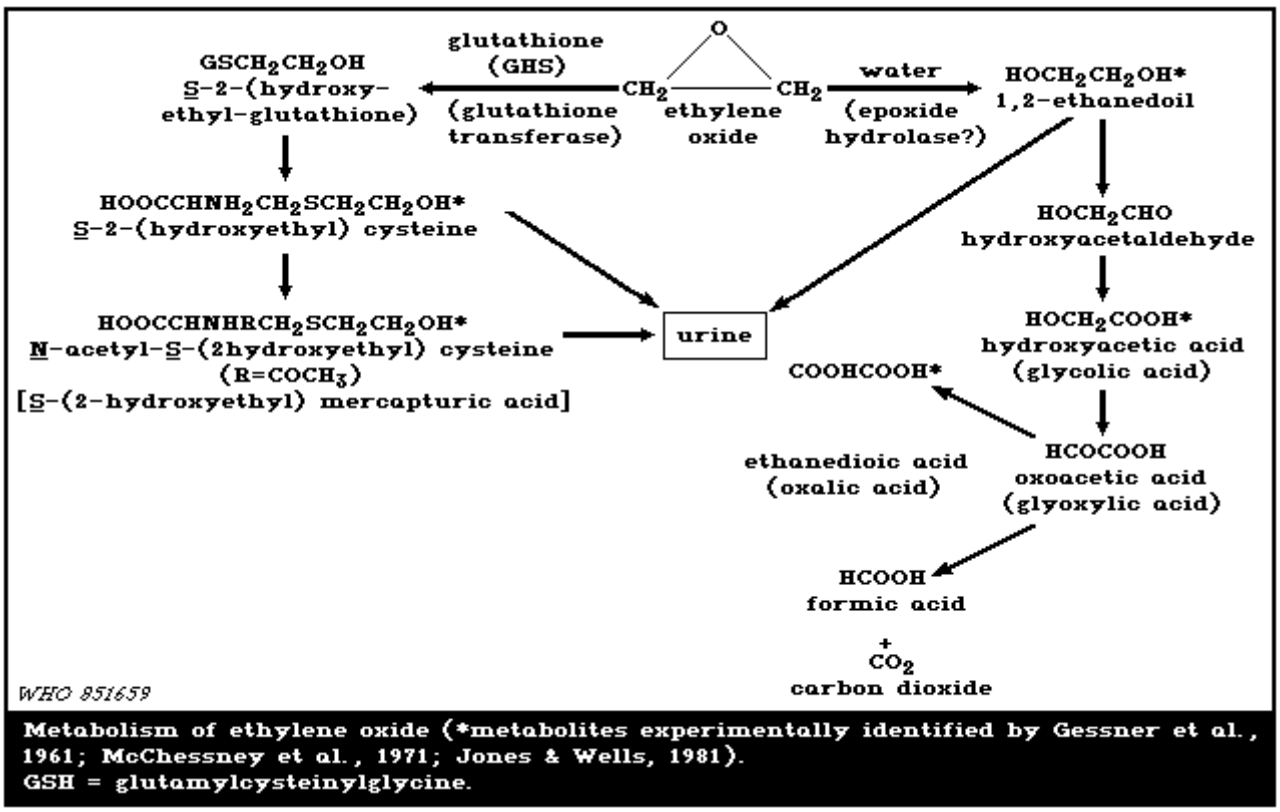
5.3. Metabolic Transformation and Excretion

Available animal data indicate 2 possible pathways for the metabolism of ethylene oxide, i.e., hydrolysis and glutathione conjugation (Fig. 1).

In dogs, peak levels of 13 and 33 mg 1,2-ethanediol/litre blood-plasma were measured between 1 and 3 h after intravenous administration of 25 or 75 mg ethylene oxide in water/kg body weight, respectively. As the half-life for hydrolysis is about 60 h at 40 °C in neutral fresh water (Virtanen, 1963), the involvement of an epoxide hydrolase (EC 3.3.2.3) has been suggested, but this has not yet been confirmed. The peak concentration of 1,2-ethanediol at 25 mg ethylene oxide/kg body weight represented approximately 25% of the dose of ethylene oxide. Within 24 h, 7 - 24% of the dose was excreted in the urine as 1,2-

ethanediol. No other compound-related metabolites were identified (Martis et al., 1982). In the serum of 18 workers occupationally exposed to ethylene oxide (range 0.54 - 27 mg/m^3; average 7.56 mg/m^3), for an average of 5.3 years, the blood concentration of 1,2-ethanediol was found to be elevated compared with that in unexposed controls (Wolfs et al., 1983).

The results of studies on rats, rabbits, and monkeys have shown that some 1,2-ethanediol is metabolized but that most of it is excreted unchanged in the urine (Gessner et al., 1961; McChessney et al., 1971).



Metabolism of ethylene oxide (*metabolites experimentally identified by Gessner et al., 1961; McChessney et al., 1971; Jones & Wells, 1981).
GSH = glutamylcysteinylglycine.

When a single dose of 2 mg labelled ethylene oxide in propanediol/kg body weight was applied intraperitoneally to rats, 43% of the administered radioactivity was excreted in the urine within 50 h (41% within 24 h) of exposure, 9% as *S*-(2-hydroxyethyl)cysteine and 33% as *N*-acetyl- *S*-(2-hydroxyethyl) cysteine, both products of glutathione conjugation. Via the lungs, 1.5% was excreted as carbon dioxide and 1% as unmetabolized ethylene oxide (Jones & Wells, 1981). The involvement of glutathione-epoxide- *S*-transferase (EC 4.4.1.7) has not been investigated further. *In vitro* glutathione conjugation of the homologue propylene oxide was shown to proceed only in the presence of an enzyme (Fjellstedt et al., 1973). In rabbits, no effect was found on liver- and blood-glutathione levels, after 12 weeks of exposure to concentrations of ethylene oxide at 18, 90, or 450 mg/m^3, for 5 days per week, 6 h per day (Yager & Benz, 1982).

As ethylene oxide can react with chloride ions, and this reaction is acid catalysed, 2-chloroethanol might be expected to be a metabolite, especially after oral administration. However, neither 2-chloroethanol, nor its metabolites (Johnson, 1967; Grunow & Altman, 1982) have been found in the plasma, tissues, or urine of species exposed to ethylene oxide.

Ehrenberg et al. (1974) found that an average of 74% of

labelled ethylene oxide, inhaled by mice, was excreted in the urine within 24 h in the form of unidentified metabolites, and only 4% within the next 24 h. Thus, on the basis of this and previously-presented excretion data, excretion of metabolites of ethylene oxide mainly takes place via the urine, within 24 h following exposure.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

A summary of the acute toxicity of ethylene oxide for aquatic organisms is presented in Table 3. Data on the most likely reaction products, 1,2-ethanediol and 2-chloroethanol, are included.

LC_{50}s of ethylene oxide for aquatic species have been reported to range from 90 mg/litre (goldfish, 24-h exposure) to 745 mg/litre (brine shrimp, 48-h exposure). Microorganisms in activated sludge showed 50% inhibition at concentrations between 10 and 100 mg/litre. Hydrolysis to 1,2-ethanediol results in detoxification. The toxicity of 2-chloroethanol for aquatic organisms resembles that of ethylene oxide, though 2-chloroethanol seems to be more toxic for *Daphnia magna*. Nevertheless, under environmental conditions, the conversion of ethylene oxide to 2-chloroethanol or 1,2-ethanediol will be slow.

In a study on the albino guppy, *Poecilia reticulata*, desorption of ethylene oxide or its reaction products from non-aerated plastic materials into water can lead to behavioural disturbances in the fish almost immediately, and to death within about one h. No such toxicity was found when the materials were aerated for 24 h (O'Leary et al., 1969).

Ethylene oxide is very soluble in aqueous media and evaporates from water to a significant degree. The log *n*-octanol water-partition coefficient was reported to be -0.30 (Radding et al., 1977). Thus, ethylene oxide will not bioaccumulate.

Table 3. Acute aquatic toxicity[a]

Organism	Description	T (°C)	pH	Dissolved oxygen	Parameter	Test substance	C (r
Micro-organisms	activated sludge	22			50% growth inhibition	ethylene oxide 1,2-ethanediol	1 >
Crustacea	water flea *(Daphnia magna)*	17	7.0	minimal aeration	48-h LC_{50}	ethylene oxide 1,2-ethanediol 2-chloroethanol	21 1
Fish	fathead minnow *(Pimephales promelas)*	22	7.0	no aeration	96-h LC_{50}	ethylene oxide 1,2-ethanediol 2-chloroethanol	84
Fish	goldfish *(Carassius auratus)*	20	6-8	no aeration (> 4 mg/litre)	24-h LC_{50}	ethylene oxide 1,2-ethanediol	90
Fish	brine shrimp *(Artemia salina)*	24	7.0	minimal aeration	48-h LC_{50}	ethylene oxide 1,2-ethanediol 2-chloroethanol	74

[a] All tests were static. Water analysis for the substance under test was reporte
[b] Incubation on a shaker for 16 h.
[c] Medium was fresh water, reconstituted using dechlorinated, carbon-treated tap w concentration.
[d] Medium was local tap water; 6 fish per concentration.
[e] Medium was sea water, reconstituted using dechlorinated, carbon-treated tap wat concentration.

7. EFFECTS ON ANIMALS

7.1. Acute Exposures

7.1.1. Oral, intravenous, and inhalation studies

The LD_{50}s for ethylene oxide, administered orally and dissolved in water, were 330 mg/kg body weight for male rats and 280 and 365 mg/kg body weight for female and male mice, respectively (Smyth et al., 1941; Woodard & Woodard, 1971). After inhalation, the 4-h LC_{50}s were 1500 and 1730 mg/m^3 for mouse and dog, respectively, and 2630 mg/m^3 for rat (Jacobson et al., 1956). 1,2-Ethanediol, a metabolite, is less toxic: LD_{50}s for rat were above 10 000 mg/kg body weight, after oral administration, and 5210 mg/kg body weight, after intravenous administration (Woodard & Woodard, 1971).

The slope of the dose-response curve in relation to the mortality rate for ethylene oxide was steep. After oral administration to rats, the difference between 0.1% mortality (325 mg/kg) and 99.9% mortality (975 mg/kg) was approximately 650 mg/kg body weight (Smyth et al., 1941). After inhalation for 4 h, this difference was approximately 3000 mg/m^3, in mice, and approximately 5000 mg/m^3 in rats. No deaths occurred in dogs at 1280 mg/m^3 (Jacobson et al., 1956). While no guinea-pigs died after inhalation of 450 mg ethylene oxide/m^3 air for 8 h, the majority did so at 2400 mg/m^3 (Waite et al., 1930). In the above mortality studies, the lungs and nervous system were the main targets in rodents and dogs. In dynamic inhalation exposure studies on guinea-pigs (Waite et al., 1930), rats, mice, and dogs (Jacobson et al., 1956), nasal irritation was the first clinical effect, as evidenced by scratching the nose, nasal discharge, lachrymation, and salivation. Respiratory problems occurred ranging from gasping to laboured breathing. Dogs exhibited laboured breathing, vomited, and suffered convulsions. Guinea-pigs, exposed to a concentration of 13 000 mg ethylene oxide/m^3, for 2.5 h, were found lying on their sides, unable to stand, and quiet. Gross pathological changes in animals that did not survive included moderate congestion in the lungs of dogs, minor patchy oedema in the lungs of rats, and congestion with oedema in the lungs of guinea-pigs. In rats, moderate congestion with petecchial haemorrhage of the trachea was also observed. Lobular pneumonia and hyperaemia of the liver and kidneys were observed in guinea-pigs. Parenchymatous changes in the kidney of guinea-pigs were seen at 2300 mg/m^3.

Ataxia, prostration, laboured breathing, and occasional tonic convulsions were effects shown by rats and mice at lethal oral or intravenous doses of ethylene oxide (Woodard & Woodard, 1971). Vomiting was the only effect shown by dogs that had received 25 or 75 mg ethylene oxide/kg body weight intravenously (Martis et al., 1982).

In order to investigate the effects of residues of ethylene oxide or reaction products in sterilized medical equipment, rabbits were exposed for 2 h via polyvinyl chloride endotracheal tubes

containing 0, 80, or 600 mg ethylene oxide/kg material. There were no deaths, but rabbits receiving the tubes with the highest residues showed increased incidences of hyperaemia, oedema, leukocyte infiltration, and epithelial erosion of the larynx and trachea (Star et al., 1980). Two groups of nine dogs each were exposed through extracorporeal perfusion for 40 min via a polyvinyl chloride oxygenator containing 12 g ethylene oxide/kg material. Nine dogs with an interrupted pulmonary circulation died from shock and pulmonary oedema. Six out of 9 dogs with a preserved pulmonary circulation died from pulmonary distress. A group of 9 control dogs was treated in the same manner using a steam-sterilized oxygenator. Only 1 control dog died (Stanley et al., 1971).

7.1.2. Acute effects on eyes and skin

As noted above, ethylene oxide is an irritating agent for several different species. A maximum non-damaging concentration of 0.1% ethylene oxide in balanced physiological salt solution (prepared daily and kept at 0 °C) was established after instillation of 0.05 ml solution, every 10 min for 6 h, into the conjunctival sac of rabbits. The concentrations above 1% caused reversible changes in conjunctiva such as hyperaemia and swelling, and irreversible opacity, both in the cornea and in the lens. Possible reaction products, 2-chloroethanol and 1,2-ethanediol, were less irritating to the eye (McDonald et al., 1973). The results of *in vitro* tests with isolated rabbit cornea were in agreement with the results of these studies. In the *in vitro* tests, the endothelia were perfused for 1 - 3 h with a balanced salt solution containing 250 mg ethylene oxide, 2250 mg 2-chloroethanol, or 5000 mg 1,2-ethanediol/litre. No effects were observed on corneal thickness and cellular ultrastructure (Edelhauser et al., 1983).

Skin irritation with hyperaemia, oedema, and scar formation was observed from 6 min after application of pads of cotton, moistened with solutions of 100 or 500 g ethylene oxide/litre water, on the shaved skin of rabbits, under a plastic cover. The intensity of the response was reported to be roughly proportional to the length of exposure time (1 - 60 min) and the concentration (Hollingsworth et al., 1956).

According to Hine & Rowe (1981), liquid ethylene oxide is apparently without adverse effects on rabbit and human skin, on single mild exposures, if the material evaporates rapidly. If large amounts of material are involved, evaporation may cause sufficient cooling to cause a lesion similar to frost-bite.

7.2. Short-Term Studies

7.2.1. Inhalation exposure

Groups of 10 - 20 Wistar rats per sex, 8 guinea-pigs per sex, 1 - 2 rabbits per sex, and 1 - 2 female rhesus monkeys were each exposed to concentrations of ethylene oxide at levels of 0, 90, 200, 370, 640, or 1510 mg/m^3, for 7 h per day, and 5 days per week. The female monkeys were not tested at 90 mg/m^3, and an additional 3 male monkeys were tested at 640 mg/m^3. The test period varied with the species tested, and the severity of exposure, i.e., approximately 26 weeks at 90 mg/m^3, 25 - 32 weeks at 200 and 370 mg/m^3, 7 - 25 weeks at 640 mg/m^3, and 10 days at 1510 mg/m^3. Guinea-pigs, rabbits, and monkeys tolerated 90 and 200 mg/m^3, and rats tolerated exposure to 90 mg/m^3 without adverse effects on

general appearance, behaviour, mortality rate, growth, body and organ weight, gross- and histopathology. Rats showed elevated mortality rates from 370 mg/m^3, rabbits from 640 mg/m^3, and all exposed animals died at 1510 mg/m^3. Secondary respiratory infection caused the deaths of an appreciable number of rats and mice in these studies.

Surviving rats showed increased relative lung weights after 26 - 27 weeks at 200 and 370 mg/m^3. At 370 mg/m^3, haemorrhages, hyperaemia, emphysema, and local alveolar collapse were observed in these lungs. Lungs of male rabbits also showed hyperaemia and slight oedema at 370 mg/m^3. Even more severe lung injury was seen in rats at 640 mg/m^3 and the higher exposure. Gross respiratory tract irritation was apparent in all species at 1510 mg/m^3.

Delayed reversible effects were observed on the peripheral nervous system. Monkeys and rabbits exhibited paralysis of the hind legs at 370 mg/m^3 and, together with rats, at 640 mg/m^3. This was accompanied by atrophy of the muscles of the hind legs, except in rabbits at 370 mg/m^3. The effects on the peripheral nervous system were investigated further in monkeys, and loss of both sensory and motor function was noted at levels of 370 and 640 mg/m^3.

Significant increases in body weight were also observed in rats, at levels of 200 mg/m^3 or more. Rats showed slight but significant increases in the relative weights of kidney and liver at 370 mg/m^3 (Hollingsworth et al. 1956).

The findings of Jacobson et al. (1956) are in agreement with these results. Groups, comprising 20 male rats and 30 female mice each, were exposed to concentrations of ethylene oxide at levels of 0, 180, or 730 mg/m^3, for 6 h/day, and 5 days per week. The exposures lasted 26 weeks at 180 mg/m^3 and 6 weeks at 730 mg/m^3. Additional groups of 15 rats and mice at the higher, and 60 rats and mice at the lower, exposure level were used for interim gross pathology. No clear toxic effects were reported at 180 mg/m^3. No pathological changes were observed except for marked haemosiderosis in the spleen of a few rats at 730 mg/m^3. The highest exposure (730 mg/m^3) resulted in death for both species without clinical signs in mice. Effects on the respiratory and nervous system were shown by rats as laboured breathing, reddish nasal discharge, diarrhoea, tendency towards a side position, and dragging of the hind-quarters. Rats also lost weight, which was regained by survivors.

More recently, groups of 30 B6C3F1 mice of each sex were exposed to concentrations of ethylene oxide (purity 99.9%) at 0, 18, 86, 187, or 425 mg/m^3, for 6 h/day, and 5 days per week. The exposures lasted for 10 weeks for males and 11 weeks for females. No effects were observed in relation to survival, body weight, clinical signs, white blood cell count, serum clinical chemistry, urinalysis, and histopathology. At the highest exposure level, changes at terminal sacrifice included an increased relative liver weight in female mice, and a decreased testicular weight in males. A decreased relative spleen weight was observed at 187 and 425 mg/m^3 in both sexes. In addition, the red blood cell count, the packed cell volume, and the haemoglobin concentrations were decreased at 425 mg/m^3. Screening of neuromuscular function in groups of 5 female mice, in week 6, and 5 mice of both sexes, in

week 10 or 11, revealed altered reflex responses at 425 mg/m^3 and a dose-related trend in alterations of locomotor function from 86 mg/m^3 upwards (Snellings et al., 1984a).

Groups of 3 male beagle dogs each were exposed to concentrations of ethylene oxide (purity 99.7%) of 180 and 530 mg/m^3, for 1 - 3 days. No effects were observed on mortality rate, body weight, electrocardiogram, blood-calcium and -urea, icteric index, and rectal temperature. Anaemia was noted at both exposure levels. Effects on the respiratory and nervous systems were shown at 530 mg/m^3, such as hyperaemia and local alveolar collapse in lungs, vomiting, and occasional slight tremors and transient weakness in the hind legs. Muscular atrophy was also observed (Jacobson et al., 1956). No haematological changes were noted when groups each comprising 3 male New Zealand rabbits were exposed repeatedly for 12 weeks to 0, 18, 90, or 450 mg/m^3 (Yager & Benz, 1982). The white cell count was depressed in Fischer rats exposed in groups of 3 or 4, for 3 days, 6 h per day, to 90, 270, or 810 mg/m^3. There was a poor correlation with exposure level (Kligerman et al., 1983).

The possible neurotoxic effects of ethylene oxide noted in the above studies were investigated further in groups each comprising 12 male cynomolgus monkeys. These animals were exposed to 0, 90, or 180 mg ethylene oxide/m^3 (purity 99.7%), for 7 h per day, 5 days per week, for 2 years. In 2 monkeys per group, brain, ulnar and sciatic nerves, and spinal cord were examined histologically after exposure. No clinical signs were reported. The only treatment-related lesions found were in the medulla oblongata of the brain. Axonal dystrophy was found in the nucleus gracilis, primarily in the exposed groups. Demyelination of the terminal axons of the fasciculus gracilis occurred in one monkey at each exposure level, but not in the controls (Sprinz et al., 1982). Paralysis of the hind limbs was observed in monkeys repeatedly exposed for up to 32 weeks to 370 mg/m^3, for 7 h per day, 5 days per week (Hollingsworth et al., 1956).

7.2.2. Oral exposure

Groups of 5 Wistar rats each received, by gavage, 22 doses of 3, 10, or 30 mg ethylene oxide/kg body weight in 30 days and 15 doses of 100 mg/kg in 21 days. The vehicle was olive oil. There were 10 vehicle controls.

No effects on mortality rate, growth, haematology, blood urea-nitrogen, organ weights, gross- and histopathology were reported at the 3 lower dose levels. At 100 mg/kg, there was marked loss in body weight, gastric irritation, and slight (not further specified) liver damage (Hollingsworth et al., 1956).

7.3. Long-Term Inhalation Studies

In a combined toxicity-carcinogenicity study, groups of 120 male and 120 female Fischer 344 rats were exposed to actual concentrations of ethylene oxide of 18 mg/m^3 (10 ppm), 58 mg/m^3 (32 ppm), and 173 mg/m^3 (96 ppm), for 6 h per day, 5 days per week, over 25 months. Two control groups each comprising 120 male and 120 female rats were used. There was an exposure-free period of 2 weeks in month 15, because of infection with sialoacryoadenitis virus. Interim sacrfices occurred at 6, 12, and 18 months.

The mortality rates of male and female rats increased significantly from the 22nd or 23rd month, at the highest exposure,

with a trend towards an increase at a level of 58 mg/m^3. Body weights in both sexes were depressed at 173 mg/m^3, from the end of the first week onwards, until the end of the study. At 58 mg/m^3, the body weights of female rats were decreased between week 10 and 80. In females, the relative liver weights were increased in the 18th month at 173 mg/m^3. This effect on the liver could not be related to increases in the activities of serum alkaline phosphatase (EC 3.1.3.1), aspartate aminotransferase (EC 2.6.1.1), or alanine aminotransferase (EC 2.6.1.2), found mainly at the 2 highest exposures during interim sacrifices. Relative spleen weights were increased in rats that developed leukaemia (section 7.4.1). Haematological changes were found in rats at all doses, but mainly at the end of the study in animals exposed to 173 mg/m^3; these included an elevated leukocyte count in both sexes, and a depressed red blood cell count and haemoglobin value in females. Some of these rats had leukaemia.

Non-neoplastic histopathological changes observed included an elevated frequency of focal fatty metamorphosis of the adrenal cortices in both sexes and bone marrow hyperplasia in females at 173 mg/m^3. Although no effect was observed on the hind-quarter lift reflex, examined monthly, mild skeletal muscular atrophy was observed, after 2 years of exposure to 173 mg/m^3. Observations on general health and ophthalmology did not reveal anything abnormal. Neoplastic changes are reported in section 7.4.1 (Snellings et al., 1981, 1984b).

In another toxicity-carcinogenicity study (Lynch et al., 1984a), groups of 80 male Fischer 344 rats were exposed to actual concentrations of ethylene oxide of 92 mg/m^3 (51 ppm) and 182 mg/m^3 (101 ppm), for 7 h per day, 5 days per week, over 2 years. The control group also comprised 80 rats. There was an exposure-free period of 2 weeks in month 16 because of a pulmonary infection, which contributed to the mortality rate.

The mortality rate increased at both exposure levels, the increase being significant at 182 mg/m^3. Only 19% of the rats survived 2 years of exposure at 182 mg/m^3 compared with 49% in the unexposed group. Body weights were reduced from the 3rd or 4th month onwards. The relative weights of adrenals and brain were increased at both exposure levels. The relative weights of lung and kidney were increased at 92 mg/m^3. Serum aspartate aminotransferase activity was increased in rats exposed to 92 and 182 mg/m^3 (section 7.4.1). No other changes were found in haematology or clinical chemistry.

Non-neoplastic histopathological changes included an elevated incidence of vacuolization and hyperplasia or hypertrophy in the adrenals at both exposure levels, and of atrophy and degeneration of skeletal muscle fibres at 182 mg/m^3. There were also increased incidences of inflammatory lesions of the lungs, nasal cavities, trachea, and internal ear at both exposure levels. Eye cataracts developed in 9 out of 78 rats at 182 mg/m^3, 3 out of 79 in the 92 mg/m^3 group, and 2 out of 77 in the controls.

7.4. Carcinogenicity

7.4.1. Inhalation exposure

In the studies by Snellings et al. (1981, 1984b) (section 7.3) (Table 4), several neoplasms were induced by ethylene oxide. A dose-related increased incidence of mononuclear cell leukaemia was

found in both sexes, significant at the 2 highest exposures in females, from the 18th or 19th month onwards. Trend test revealed a treatment-related response in both sexes. In males, an increased incidence of peritoneal mesotheliomas originating from the testicular mesothelium, occurred at 58 and 173 mg/m^3 from the 23rd month onwards, and an increased incidence of subcutaneous fibroma was seen in male rats exposed to 173 mg/m^3 that had survived for 24 months. Trend analysis showed that there was a treatment-related increase in peritoneal mesothelioma. There was no increased incidence of pituitary tumours, but they appeared earlier in the 173 mg/m^3 group.

Following the report by Lynch et al. (1984a) of an increased incidence of brain tumours in Fischer 344 rats exposed to ethylene oxide (see below), the brain tissue from this study was re-examined both macro- and microscopically, and a dose-related incidence of primary brain tumours was observed at 58 and 173 mg/m^3 that appeared to be treatment related in the trend test, but was not statistically significant. The tumours were mainly diagnosed as gliomas and malignant reticular tumours. The percentage of rats with multiple neoplasms was greater than in controls at all exposure levels in females and at 173 mg/m^3 in males. At 58 and 173 mg/m^3, the percentage of female rats with at least one malignancy was increased. The authors considered that a contribution of the viral outbreak to the toxicity of ethylene oxide was unlikely (Snellings et al., 1981, 1984b).

Lynch et al. (1984a) (section 7.3, Table 4) also found an increased incidence of mononuclear cell leukaemia, which was significant at the lower exposure level. The absence of a dose-relationship was attributed to the increased mortality rate at 182 mg/m^3. Dose-related increased incidences of peritoneal mesotheliomas, originating from the testicular mesothelium, and of mixed-cell gliomas in the brain, were found. The increases in both tumours were significant at 182 mg/m^3 (Lynch et al., 1984a).

Table 4. Tumours induced by ethylene oxide in Fischer 344 rats

Concentration (mg/m^3)	Leukaemia (mononuclear)		Mesothelioma	Pituitary adenoma	Subcutaneous fibroma[a]	Brain[a]	
	M	F	M	M	F	M	M	F
Snellings et al. (1981, 1984b)								
173	26(119)[b]	28(113)	22(119)	27(117)	32(117)	11(30)	3(30)	2(26)
58	25(81)	24(79)	7(91)	16(79)	38(90)	1(39)	1(39)	2(48)
18	21(79)	14(77)	3(89)	27(80)	39(90)	3(51)	0(51)	0
0	20(116)	9(118)	2(114)	28(117)	38(119)	1(48)	1(48)	0
0	18(118)	13(117)	2(116)	22(117)	38(116)	2(49)	0(49)	0
Lynch et al. (1984a)[c]								
182	30(76)	NA	21(79)	21(67)	NA	NR	5(79)	NA
92	38(79)	NA	9(79)	20(66)	NA	NR	2(77)	NA
0	24(77)	NA	3(78)	48(73)	NA	NR	0(76)	NA

[a] Only animals that survived for 24 months were included, because these tumours appeared after the 18-month interim sacrifice.

[b] Numbers in brackets refer to the number of rats examined. They include interim and final kills.

[c] Only male rats were used.

NA = Not applicable.
NR = Not reported.

7.4.2. Oral exposure

Groups of 50 female Sprague Dawley rats received, in salad oil, 7.5 or 30.0 mg ethylene oxide/kg body weight, by gavage, in the empty stomach, twice a week, for 110 weeks. There were 50 vehicle controls, 50 untreated controls, and 50 positive controls. The rats were observed for their life span. No statistical analysis was reported. The mean survival period was over 100 weeks for all groups. The mortality rate increased at 30.0 mg/kg body weight, from week 100 onward. Elevated incidences of tumours were only observed in the forestomach, the first tumour appearing in week 79. The incidences of squamous cell carcinomas were 0/50, 8/50, and 29/50 at 0, 7.5, and 30 mg/kg body weight, respectively. At 30 mg/kg body weight, invasive growth and metastases were observed in 10 rats. At 30 mg/kg body weight, 2 fibrosarcomas were also noted. At both doses, the incidences of hyperplasia, hyperkeratosis, papillomas, and/or carcinomas were increased in the forestomach (Dunkelberg, 1982).

7.4.3. Subcutaneous exposure

Groups of 100 female NMRI mice were injected once a week with a tricaprylin solution containing 0.1, 0.3, or 1.0 mg ethylene oxide per animal, for 106 weeks. There were 200 vehicle controls and 200 untreated controls. From week 35 to week 85, the mortality rate increased by a maximum of 10% at a dose of 1.0 mg per mouse. The mean length of survival in this group was 75 weeks. An elevated incidence of tumours was only observed at the injection site, the first tumour appearing in week 79. There was a dose-related increased incidence of sarcomas, mainly fibrosarcomas, which was significant at 0.3 and 1.0 mg per mouse. The tumour incidence was 11% at the highest dose compared with 2% in vehicle controls (Dunkelberg, 1981).

7.4.4. Dermal exposure

Each of a group of 30 female Swiss Millerton mice received, for their lifetime, approximately 100 mg of a 10% solution of ethylene oxide (purity 99.7%) in acetone, brushed on the clipped dorsal uncovered skin, 3 times a week. A group of 60 mice did not receive any treatment, and a group of 60 mice received the vehicle only. No skin tumours were found, nor was there any sign of skin irritation. The median length of survival was 493 days for treated mice and 445 days for controls (Van Duuren et al., 1965). It is assumed that ethylene oxide, applied in this manner, evaporated rapidly from the skin.

7.5. Mutagenicity and Related End-Points

Almost all the reports available demonstrate the mutagenic action of ethylene oxide. A summary of mutagenicity tests with positive results is presented in Table 5.

Ethylene oxide is an alkylating agent (section 5.2). It has induced gene mutations in all plants, bacteria, fungi, insects, and mammalian cells investigated *in vitro,* with and without metabolic activation. Chromosome damage and sister chromatid exchanges were observed in plants, insects, and mammalian somatic cells exposed *in vivo* and *in vitro.* Fomenko & Strekalova (1973) and Strekalova et al. (1975) reported an increased incidence of chromosomal

aberrations in the bone-marrow cells of rats exposed by inhalation to concentrations of ethylene oxide vapour at 3.6 and 112 mg/m^3. Unscheduled DNA synthesis, induced by the *N*-acetoxy-2-acetylamino-fluorene, was inhibited by ethylene oxide in human lymphocytes *in vitro* (Pero et al., 1981). The positive results in the micronucleus tests are in agreement with those from a distribution study showing that ethylene oxide, or its metabolites, was retained in the bone marrow of mice (Appelgren et al., 1977). An increased incidence of micronuclei was observed after one intraperitoneal dose of 100 mg/kg body weight in mice (Lyarskii et al., 1983) and after 4 h of vapour exposure of rats to a concentration of 90 mg/m^3 (Embree & Hine, 1975).

Table 5. Mutagenic tests for ethylene oxide with positive results[a]

Test description	System description		Reference
	Organism	Strain/cell type	
Gene mutations			
Forward mutations	plant	barley	Ehrenberg et al. (1 1959)
Forward mutations		barley	Shulovsk et al. (19
Forward mutations		rice	Jana & Roy (1975)
Forward mutations		pea	Blixt et al. (1963)
Reverse mutations	bacterium	*Escherichia coli* SD-4	Hussain & Osterman (1984)
Reverse mutations (base-pair substitutions)		*Salmonella typhimurium* TA1535, TA100	Rannug et al. (197 Kauhanen (1978)[b]; Pfeiffer & Dunkelbe (1980)
Reverse mutations		*Bacillus subtilis* (spores) HA101, TKJ5211, TKJ8201	Tanooka (1979)
Reverse mutations	fungus	*Neurospora crassa* (macroconidia)	Kolmark & Westerga (1953); Kolmark & K (1968)
Forward mutations		*Aspergillus nidulans*	Morpurgo (1963)
Forward mutations		*Schizosaccharomyces pombe* Pl	Migliore et al. (1
Sex-linked recessive lethals	insect	*Drosophila melanogaster*	Bird (1952); Nakao Auerbach (1961)
Forward mutations on specific locus	mammal (*in vitro*)	Chinese hamster ovary cells	Tan et al. (1981)[b]; Zamora et al. (198
Chromosome damage			
breaks, erosions, contractions	plant	*Tradescantia paludosa* (pollen)	Smith & Lofty (195
translocations		barley	Ehrenberg et al. (1 1959)
breaks		barley	Moutschen-Dahmen et (1968)
breaks		wheat (hexaploid)	MacKey (1968)
translocations	insect	*Drosophila melanogaster*	Nakao & Auerbach (
small deletions (min)	insect	*Drosophila melanogaster*	Fahmy & Fahmy (197

Table 5. (contd.)

Test description	System description		Reference
	Organism	Strain/cell type	
Chromosome damage (contd.)			
breaks, gaps, exchanges, complexes	human (*in vitro*)	anion cells	Poirier & Papadopou (1982)
sister chromatide exchanges	human (*in vitro*)	lymphocytes fibroblasts	Star (1980a); Garry et al. (1982
	rat (inhalation)	lymphocytes	Kligerman et al. (1
	rabbit (inhalation)	lymphocytes	Yager & Benz (1982)
sister chromatide exchanges, breaks, acentric fragments, dicentrics, triradials, quadriradials, complex rearrangements	monkey (inhalation)	lymphocytes	Lynch et al. (1984b
chromosomal aberrations	rat (inhalation)	bone marrow cells	Strekalova et al. (
breaks, gaps, rearrangement, exchanges, ring formations	rat (inhalation)	bone marrow cells	Embree & Hine (1975
micronuclei	mouse (ip)	polychromatic erythrocytes	Conan et al. (1979) Jenssen & Ramel (19 Lyarskii et al. (19
micronuclei	mouse (iv)	polychromatic erythrocytes	Appelgren et al. (1
heritable translocations	mouse (ip)	germ cells	Generoso et al. (19
dominant lethals	mouse (inhalation)	germ cells	Cumming & Michaud (
	mouse (ip)		Generoso et al. (19 Lyarskii et al. (19
	mouse (inhalation)		Generoso et al. (19

Table 5. (contd.)

Test description	System description		Reference
	Organism	Strain/cell type	
dominant lethals (contd.)	rat (inhalation)		Embree et al. (1977

DNA repair

unscheduled DNA synthesis	mouse (inhalation)	germ cells	Cumming & Michaud (
unscheduled DNA synthesis	human (*in vitro*)	lymphocytes	Pero et al. (1981)

[a] For details of these studies, see text and data profile (IRPTC, 1984).
[b] A similar effect after metabolic activation by rat liver microsomal fraction.
[c] A slight reduction in mutagenicity after metabolic activation by mouse liver microsomal fraction.
[d] 2-year exposure groups of 12 male monkeys to 0, 90, and 180 mg/m^3 for 7 h per da 5 days per week.

Dose-related damage to germ cells was established in the mid and late spermatid stages in the dominant lethal assay. One oral dose of 100 mg/kg body weight in mice generated inconsistent results (Appelgren et al., 1977), but 150 mg/kg proved positive (Generoso et al., 1980). After short-term repeated exposures, dominant lethals were induced in mice at intraperitoneal doses from 40 mg/kg body weight, given over a period of 3 months, 5 times per week (Lyarskii et al., 1983) and at vapour exposures from 460 mg/m^3, for 6 h/day, 5 days per week, over 11 weeks (Generoso et al., 1983). Heritable translocations were induced in the germ cells of mice after repeated intraperitoneal exposure, at doses of 30 mg/kg body weight or more, for 5 days/week, over a 5-week period (Generoso et al., 1980). Recent studies have investigated the dose-response of inhaled ethylene oxide and have compared effects of different dose rates (contributions of different concentrations and durations of exposure, maintaining total exposure (C x t) constant) on the dominant-lethal response in male mice. In the dose-reponse study, male mice were exposed by inhalation to ethylene oxide at concentrations of 540, 720, or 900 mg/m^3 (300, 400, or 500 ppm), respectively. Exposures were for 6 h/day, for 4 consecutive days. A dose-related increase in dominant-lethal mutations was observed; however, the dose-response curve was nonlinear, i.e., increasing embryonic mortality occurred with increasing mg/m^3 x h. In the dose-rate study, mice had a total exposure of 3240 mg/m^3 (1800 ppm) x h/day for 4 consecutive days, delivered either at 540 mg/m^3 (300 ppm) in 6 h, 1080 mg/m^3 in 3 h, or 2160 mg/m^3 (1200 ppm) in 1.5 h. The highest airborne concentration resulted in the greatest embryonic mortality, 64%, versus 32 and 11% for the intermediate and lowest airborne concentrations, respectively (Generoso et al., 1985). According to an abstract, DNA repair was induced in the germ cells of mice exposed to 540 mg/m^3, for 8 h. The repair seemed inhibited at higher exposures (Cumming & Michaud, 1979). No details were available.

Negative results were observed on a few occasions only. In one study, with vapour-exposed rats, chromosome aberrations or slowing of mitotic activity and cell cycle kinetics were not observed in lymphocytes at levels at which sister chromatid exchanges occurred (Kligerman et al., 1983). In a dominant-lethal assay with mice, relatively high intravenous doses of ethylene oxide (up to 100 mg/kg body weight) did not cause any treatment-related effects (Appelgren et al., 1977). An intraperitoneal dose of 10 mg/kg body weight to mice was reported to give a slight increase in the number of polychromatic erythrocytes with micronuclei, but the statistical analysis was not adequate (Conan et al., 1979).

7.6. Effects on Reproduction

Rats and guinea-pigs were exposed to vapour concentrations of 370 and 640 mg ethylene oxide/m^3, for 7 h per day, 5 days per week, for up to 32 weeks. Among other effects (section 7.2.1), degeneration of testes tubules was observed at the higher exposure level in guinea-pigs, while at 370 mg/m^3, there was a decrease in the relative weights of testes in rats and guinea-pigs, which was not statistically significant (Hollingsworth et al., 1956). Significantly-decreased absolute testicular weights were observed in mice exposed to ethylene oxide at a concentration of 425 mg/m^3, for 6 h/day, 5 days per week, over 10 - 11 weeks (Snellings et al., 1984a). However, the testicular effects may have been secondary to toxic effects (e.g., growth inhibition). Male and female Fischer 344 rats exposed repeatedly to concentrations of ethylene oxide of up to 182 mg/m^3, for 6 h/day, 5 days per week, over 25 months, did not show any histopathological effects on the reproductive tissues (Snellings et al., 1981).

When groups of 12 male Cynomolgus monkeys were exposed to concentrations of ethylene oxide at 90 or 180 mg/m^3, for 7 h/day, 5 days per week, over 2 years, spermatogenic functions were found to differ from those of controls. At both exposure levels, sperm motility and sperm count were decreased and the sperm drive range was increased, but there was no increase in effect with increase in dose. The incidence of abnormal sperm heads did not change (Lynch et al., 1984c).

Groups, each comprising 30 male and 30 female Fischer 344 rats, were exposed to concentrations of ethylene oxide (purity 99.9%) of 18, 58, or 173 mg/m^3, for 6 h/day, 5 days per week, over 12 weeks. Two control groups of 30 rats per sex each were exposed to air only. After mating, females were further exposed for 7 days/week, up to 3 weeks after delivery, with the exception of the first 5 days of lactation. Effects on the reproductive performance were detected. The number of pups per litter was decreased at 173 mg/m^3, as well as the number of implantation sites per female, and the number of fetuses born per implantation site. The number of females with a gestation period longer than 22 days was also

increased at this concentration, but no effects were noted on the average length of the gestation period. Neither parents nor pups showed signs of toxicity from ethylene oxide. The percentages of pregnant females and fertile males were not affected (Snellings et al., 1982a).

7.7. Teratogenicity

Groups of 22 female Fischer 344 rats were exposed to concentrations of ethylene oxide of 18, 58, or 173 mg/m^3, for 6 h/day, on days 6 - 15 of gestation. Two control groups comprising 22 rats each were exposed to air only. The numbers of pregnant dams ranged from 17 to 22. Maternal behaviour was normal, and there were no deaths. The only effect on the fetuses was a 5 - 8% decrease in weight at 180 mg/m^3 (Snellings et al., 1982b).

Groups of 32 - 45 female Sprague Dawley rats were exposed to concentrations of ethylene oxide (purity 99.7%) of 0 or 270 mg/m^3, for 7 h/day, on days 7 - 16 of gestation (Group 1) or on days 1 - 16 of gestation (Group 2) or during 3 weeks before mating (5 days per week), and on days 1 - 16 of gestation (Group 3). No dams died, but body weights were decreased in Group 3. In all exposed groups, the relative and absolute weights of kidney and spleen were

increased. The results of histopathological examination did not show any abnormalities. There was a significant increase in resorptions per litter and per implantation site in Group 3, with no significant effects on the number of implants, live fetuses, and pregnancies. In all exposed groups, weights and lengths of the fetuses were decreased. Reduced ossification of sternebrae and primary skull was observed (Hackett et al., 1982).

New Zealand rabbits were similarly exposed to a concentration of ethylene oxide of 270 mg/m^3 from days 1 - 19 or from days 7 - 19 of gestation. There was no evidence of toxicity in the mothers, embryos, or fetuses, or of developmental defects (Hackett et al., 1982).

Groups of 24 - 37 female CD-1 mice each received, intraveneously, doses of 0, 75, or 150 mg ethylene oxide (purity not stated)/kg body weight in an aqueous dextrose solution on days 4 - 6, 6 - 8, 8 - 10, or 10 - 12 of pregnancy. Dams exposed on days 6 - 8 of pregnancy did not show toxic signs. In the other groups, at the highest dose, toxic signs such as weakness, laboured respiration, and tremor were observed with a mortality rate of 19 - 48%. In the group without signs of maternal toxicity, fetotoxicity was observed at 150 mg/kg, as shown by a 20% decrease in mean fetal weight. Fetal malformations were shown in 19.3% of fetuses in exposed litters compared with 2% in control groups. These malformations were mainly fused cervical arches. In addition, fused thoracic arches, scrambled and fused sternebrae, and fused, branched, or missing thoracic ribs were observed (Laborde & Kimmel, 1980).

8. EFFECTS ON MAN

8.1. Exposure of the Skin and Eyes

Undiluted ethylene oxide, applied to the skin of volunteers, evaporated rapidly without leaving any mark or irritation. A 15-min exposure to cotton wool soaked in undiluted ethylene oxide also did not produce any effects (Greaves Walker & Greeson, 1932). However, with exposure to larger quantities, there may be sufficient cooling to produce a lesion similar to frost-bite (Hine & Rowe, 1981). Skin injury following exposure to aqueous solutions of ethylene oxide is characterized by the appearance of oedema and erythema, 1 - 5 h after exposure, followed by the formation of vesicles. On healing, incrustation, often with itching and desquamation, is observed. The magnitude of the skin injury seems to depend on the length of contact and the concentration, a 50% aqueous solution (500 g/litre) being most hazardous. More concentrated solutions were less harmful. The lowest concentration tested, a 1% solution, produced a mild reaction after a 50-min exposure. Such effects have been observed in a number of accidents (Sexton & Henson, 1949, 1950; Joyner, 1964; Ippen & Mathies, 1970). Vapour exposure was found to produce the above dermal effects, mainly on the humid parts of the skin (Ippen & Mathies, 1970). The effects were also found, to different extents, after exposure via ethylene oxide-sterilized materials such as face masks, gloves, and surgical gowns (Royce & Moor, 1955; Marx et al., 1969; Hanifin, 1971; Biro et al., 1974; Lamy et al., 1974). Patch tests on volunteers with various sterilized materials containing residues of ethylene oxide and its reaction products, showed erythema, without oedema, after 4 - 8 h of contact, from a residue level of 890 mg ethylene oxide/kg up to 2890 mg/kg of a polyvinyl chloride block. Most skin types tolerated residues of ethylene oxide of up to 2270 mg/kg polyvinyl chloride film, 2800 mg/kg brown-milled rubber, and 5100 mg/kg non-woven fabric (Shupack et al., 1981).

Accidental skin exposure to a 1% aqueous solution, from the waist down, was also reported to result in effects on the nervous system, such as nausea and repeated vomiting (Sexton & Henson, 1949).

Accidental exposure of the eyes to the vapour of ethylene oxide can lead to conjunctivitis (Thiess, 1963; Joyner, 1964). Exposure of 12 men via a leaking sterilizer resulted in neurological disorders (section 8.3) in 4 of the men, 3 of whom had eye cataracts; one of the latter also showed an increase in corneal thickness. Two additional men showed only an increase in corneal thickness (Gross et al., 1979; Jay et al., 1982). In one case of accidental exposure of the eyes to pure ethylene oxide, only slight irritation of the conjunctiva was seen (Thiess, 1963).

The implantation of artificial lenses, sterilized with ethylene oxide, in 103 eyes was compared with the implantation of lenses, sterilized with sodium hydroxide (200 control eyes), in a retrospective study. The follow-up period was 10 months for the exposed patients. Post-operative inflammatory complications occurred in 30% of the eyes exposed to residues of ethylene oxide or its reaction products compared with 9% of the control eyes. Cystoid macular oedema with reduction in visual acuity developed in 16% of the exposed eyes and in 7% of the control eyes (Stark et al., 1980).

8.2. Sensitization

No dermal sensitization was observed in a total of 47 workers frequently exposed to ethylene oxide (Royce & Moor, 1955; Thiess, 1963). In another study using patch tests, one of 12 volunteers showed a recurrent reaction, 3 weeks after the trial. When challenged afterwards with a 2 mm-thick patch of polyvinyl chloride containing 100 mg ethylene oxide/kg, a mild reaction was observed, which reappeared after 3 weeks (Shupack et al., 1981) (section 8.1). When the skin of 8 workers was exposed repeatedly to aqueous solutions of ethylene oxide, all sites of previous contact, with and without a primary reaction, flared up in 3 of them showing pruritus, erythema, and slight oedema, 5 - 9 days after the last exposure (Sexton & Henson, 1950). Another case of an apparently allergic reaction was reported. The patient concerned was exposed to ethylene oxide via a sterilized face mask (Alomar et al., 1981).

A case of anaphylaxis has been reported in a patient receiving haemodialysis treatment with equipment that had been sterilized with ethylene oxide (Poothullil et al., 1975). A cause-effect relationship with ethylene oxide exposure was demonstrated by haptan specificity (Dolovich & Bell, 1978).

8.3. Accidental Inhalation Exposure

Respiratory tract irritation was reported as hoarseness (Thiess, 1963) and cough (Metz, 1939) in 5 cases of acute accidental exposure to ethylene oxide vapour.

Acute effects on the nervous system in nearly all inhalation cases were marked by nausea, recurrent vomiting, and headache. Less frequently reported effects included decreased consciousness (one case of coma), excitement, sleeplessness, muscular weakness, diarrhoea, and abdominal discomfort (Blackwood & Erskine, 1938; Metz, 1939; Thiess, 1963; Capellini & Ghezzi, 1965).

Because of a leaking sterilizer, 4 young men were exposed intermittently, for 2 - 8 weeks, to ethylene oxide at levels of approximately 1000 mg/m^3. Three of the men developed a reversible peripheral neuropathy showing abnormal nerve conduction and, in 2 cases, headache, weakness and decreased reflexes in the extremities, incoordination, and a wide-based gait. The fourth man developed a reversible acute encephalopathy with headache, nausea, vomiting, lethargy, recurrent motor seizures, agitation, and a diffusely slow electroencephalogram (Gross et al., 1979). Following this, 6 more cases were reported concerning sterilizer operators, suffering from reversible peripheral neuropathy following ethylene oxide exposure for 0.5 - 1.5 years. Finelli et al. (1983) described 3 persons showing subacute polyneuropathy with bilateral foot-drop, slowing of nerve conduction velocity, and denervation potential on electromyography as the main findings. All 3 persons had noticed the smell of ethylene oxide regularly at work, while 2 persons experienced eye irritation. Polyneuropathy was also reported in 3 sterilizer operators by Kuzuhara et al. (1983). Two of these cases were described in detail. Sural nerve biopsies revealed axonal degeneration with mild changes in the myeline sheath. Unmyelinated fibres were also involved. Muscle biopsies showed typical denervation atrophy.

8.4. Other Accidental Exposures

Severe respiratory problems due to inflammatory reactions in the trachea and larynx were reported in 17 hospital patients who had received endotracheal intubation. The tubes had been sterilized with ethylene oxide (Marx et al., 1969; Holley & Gildea, 1971; Lipton et al., 1971; Mantz et al., 1972).

Reversible vocal paralysis was reported to be associated with ethylene oxide exposure in 5 cases: one woman had been exposed to vapour (Troisi, 1965), and the other 4 patients were exposed via sterilized endotracheal tubes (Holley & Gildea, 1971). The vocal cords showed no or only slight damage. In one of these patients, who died from a cause unrelated to the intubation, myelin degeneration of parts of the nervus vagus was noted at autopsy. It was suggested, therefore, that the paralysis was of neural origin.

Four cases of shock, 1 - 10 h after endovascular examination, were associated with the catheters used, which contained residues of ethylene oxide. The presence of bacterial toxins was considered unlikely. One patient died as a result of renal insufficiency (Lebrec et al., 1977). Cases of cardiovascular collapse in children, 3 of which were fatal, were considered by the authors to be the result of residues of ethylene oxide in a heart-lung machine on the basis of subsequent studies on dogs (Stanley et al., 1971) (section 7.1.1). Among others, Hirose et al. (1963) and Clarke et al. (1966) measured haemolysis due to residues in ethylene oxide-sterilized plastic tubes *in vitro*.

8.5. Occupational Inhalation Exposure

The health status of 37 male operators from an ethylene oxide-producing plant in the USA during the period 1953 - 62 was compared with that of age-matched operators from other production units. The average employment period was 11 years for exposed workers and 12 years for controls. The usual average exposure level was between 9 and 18 mg/m^3, with occasional peaks up to 230 mg/m^3 for one particular job (collecting a sample of the product). According to the medical records, the health of the exposed workers was somewhat better than that of the controls. A physical examination

and extensive clinical tests did not reveal any exposure-related effects with the exception of a slightly increased white blood cell count (Joyner, 1964).

Chromosomal damage was found in a group of 12 workers from a hospital sterilization facility in the USA (section 8.6). The maximum exposure concentration measured during sterilization was 65 mg/m^3. Another group of 12 persons, who worked in the adjacent operating room area, volunteered as representatives of an unexposed or accidentally exposed group. To insure adequate control throughout the study, unexposed laboratory staff members served as a third group. Frequently-reported subjective complaints indicated irritation of the mouth, throat, and eyes, and effects on the nervous system, such as headache, nausea, speech difficulty, memory loss, dizziness, and incoordination (Garry et al., 1979).

In Belgium, a group of 18 workers, using or distributing the sterilant ethylene oxide, was compared with a well-matched control group by means of a questionnaire, and by analyses for urinary retinol-binding protein and albumin, beta-microglobulin, and chromosomal damage in lymphocytes. The overall mean exposure level was 7.6 mg/m^3, and the time-weighted average exposure, over a working day, ranged between 0.2 and 95 mg/m^3. A significant increase in the incidence of sleeplessness and leg cramps was recorded, but not irritation or allergy. These studies did not reveal any abnormalities with the exception of an increase in sister chromatid exchanges in lymphocytes (Wolfs et al., 1983; Laurent et al., 1984; section 8.7).

In a plant in Bulgaria, 196 workers engaged in the production of ethene and ethylene oxide were examined. About 73% of all concentrations of ethylene oxide measured were 1 mg/m^3 or less, while 27% were between 1 mg/m^3 and 3.5 mg/m^3. Significant increases were found in deviations of the autonomous nervous system and in neurosis-like manifestations, especially in female workers (Spasovski et al., 1980). Because of a mixed exposure, it is difficult to evaluate the findings.

Haematological changes were reported in a group of 27 workers in an ethylene oxide manufacturing and processing plant, in Sweden, in 1967. The exposure period varied from 2 to 20 years, the average length being 15 years. Controls worked with ethylene oxide in other departments, where no leakages were possible. No exposure data were reported. When 2 cases of anaemia were excluded, there was still a significantly-decreased haemoglobin value in exposed workers. There was a 30% increase in the number of lymphocytes, and one case of chronic lymphatic leukaemia was noted (Ehrenberg & Hällström, 1967).

In the Federal Republic of Germany, 279 employees from 8 plants in which alkene oxides were produced or processed, were examined for morbidity during 1978. They were employed for an average of 10.8 years. Of these workers, 21 had been involved in accidents with ethylene oxide. Taking into account age and length of exposure, they were compared with groups of industrial and clerical workers within the same company. The exposure concentrations were not reported. The workers were also exposed to many other chemicals, some of which may be carcinogenic for man.

No abnormalities were found that could be related to exposure to ethylene oxide or propylene oxide. The investigators related increases in haemoglobin and mean erythrocyte volume to smoking habits. Slight lymphocytosis was found to be unrelated to exposure time, though there was a distinct age influence (Stocker & Thiess,

1979).

8.6. Mortality Studies

Two studies were conducted in Sweden to investigate the possible neoplastic effects from occupational exposure to ethylene oxide (Hogstedt et al., 1979a,b, 1984). The first study originally included 58 male and 172 female workers in a small factory, sterilizing hospital equipment with a 1:1 mixture of ethylene oxide and methyl formate, over a period from 1968 to 1977 (Hogstedt et al., 1979a).

Two cases of leukaemia (one was diagnosed as chronic myeloid leukaemia and the other as acute myelogenous leukaemia) occurred among 68 women who were exposed to vapours from sterilized boxes stored for weekly periods in a factory storage hall where about 30 persons were exposed at any one time. A third case was the local male manager who developed primary macroglobulinaemia (Morbus Waldenström; this case was later diagnosed as a non-Hodgkin lymphoma), 9 years after the installation of the sterilization equipment; his exposure was estimated to be about 3 h per week in the storage hall. He is also reported to have had some exposure to benzene in the past. The concentration of ethylene oxide in the hall was in the range of 3.6 - 128 mg/m^3, and the 8-h time-weighted average in the breathing zone was calculated to be between 36 ± 18 mg/m^3. The other workers had occasional exposure to ethylene oxide, and 7 operators had relatively high exposure (amount unspecified) during the sterilization process.

In a follow-up study (Hogstedt et al., 1984), a further case of leukaemia was found in a woman who had been exposed to ethylene oxide in the storage hall between 1969 - 72. In this study, the cohort consisted of 203 workers who had been employed for more than one year at the plant.

Altogether, 4 deaths from malignancies of the lymphoreticular system were reported from this factory. The expected number was 0.3.

A second study to investigate the carcinogenic effects of ethylene oxide was conducted on 241 Swedish male workers in an ethylene oxide-producing plant (Hogstedt et al., 1979b). These men were examined medically in 1960. Twenty-three deaths occurred during the 16-year observation period dating from 1961 - 77 (13.5 expected). The excess mortality was due to cancer and cardiovascular disease. Three cases of stomach cancer (0.4 expected) and 2 cases of leukaemia (one chronic myeloid and once acute myeloid leukaemia) (0.14 expected) accounted for the excess mortality from cancer. No increase in mortality was observed among 86 maintenance workers exposed intermittently to ethylene oxide

among 66 unexposed controls. Average exposure levels during 1941 - 47 were estimated to be below 25 mg/m^3 and, during the 1950s up to 1963, these levels were 10 - 50 mg/m^3, but peak exposures above the odour threshold (about 1000 mg/m^3) were known to occur.

The ethylene oxide was manufactured by the chlorohydrin process so that significant exposure to other chemicals such as 1,2-dichloroethane, ethylene, ethylene-chlorohydrin, and bis(2-chloroethyl)ether might have occurred.

This investigation was followed up by a study that extended the period of observation up to 1982. Seven more deaths had occurred among the workers exposed to ethylene oxide for the whole of the

working day against 6.6 expected. Three of these were due to cancer (1.6 expected). Two of these 3 cases were cancer of the stomach (0.2 expected) and one an oesophageal cancer (0.04 expected). In the period from 1961 - 82, 6 deaths due to stomach or oesophageal cancer had occurred in workers exposed to ethylene oxide for the whole of the working day (0.7 expected). Alimentary tract cancer was observed in 2 maintenance workers (0.8 expected) and in 1 unexposed worker (0.8 expected). One new case of chronic myeloid leukaemia was reported during this follow-up period. During the 20-year period of observation, a total of 17 cases of cancer were notified to the Cancer Registry against 7.9 expected (Hogstedt et al., 1984).

The Task Group evaluated these data and concluded that the evidence was adequate to consider the mixtures of compounds to which these workers were exposed as carcinogenic for human beings, but inadequate to label ethylene oxide as a proved human carcinogen. This conclusion was in agreement with that arrived at by an International Agency for Research on Cancer Working Group (IARC, 1985).

A similar study in the USA concerned 767 male workers at an ethylene oxide producing plant. They were employed for at least 5 years between January 1955 and December 1977 and "potentially exposed". Concentrations of ethylene oxide were reported to be below 18 mg/m^3, but no further details concerning exposure levels were reported. Exposure to other chemicals was not reported. Control data came from national statistics and was adjusted for sex, age, and calendar time. There were 46 deaths against an expected 80; there were 11 malignant neoplasms against 15.2 expected. No statistically-significant excess deaths could be found due to any cause. There were no deaths due to leukaemia, 3 deaths from pancreatic cancer (0.8 expected), 1 death from bladder cancer (0.3 expected), 2 deaths from brain cancer (0.7 expected), and 2 deaths from Hodgkin's disease (0.4 expected) (Morgan et al., 1981).

In the Federal Republic of Germany, 602 workers were investigated for mortality experience during the period 1928 - 80. The workers had been employed for at least 6 months in 8 plants producing or processing ethylene oxide and propylene oxide. A subcohort of 351 workers was observed for more than 10 years.

Control data came from a styrene plant and from national statistics. Since 1978, exposure to ethylene oxide had normally remained below 9 mg/m^3. In the past, occasional excursions above 90 mg/m^3 (50 ppm) had been reported. On one occasion during plant breakdown, 3420 mg/m^3 (1900 ppm) was measured. No statements were offered concerning human exposure or the use of personal protective equipment. The workers were also exposed to many other chemicals, some of which might be carcinogenic for human beings. There were 56 deaths compared with 76.6 expected. There were 14 deaths from cancer compared with 16.6 expected. No statistically-significant excess deaths could be found due to any cause in the cohort. In the subcohort of 351 workers, there was a significant increase in mortality rate due to kidney disease (3 against 0.4 expected). There was 1 death from gall bladder cancer, 1 death from urinary bladder cancer, 1 death from brain cancer, and 1 death from myeloid leukaemia. Two stomach tumours were observed compared with 1.8 expected (Thiess et al., 1981a,b).

8.7. Mutagenicity and Related End-Points

An increase in chromosomal aberrations was found in the

lymphocytes of 3 groups of workers sterilizing medical equipment in hospitals or factories (Abrahams, 1980; Pero et al., 1981; Högstedt et al., 1983). A 50% increase in aberration rate was found in 28 workers exposed to 8-h time-weighted average concentrations of ethylene oxide below 1.8 mg/m^3 in the 2.5 years before the study. Before this period, higher exposures were reported to have occurred. The workers had been exposed for 0.5 - 8 years. The mean number of micronuclei in the bone marrow cells of 18 of these workers was 3 times higher than in the controls (Högstedt et al., 1983). Pero et al. (1981) found that, while workers exposed to concentrations of ethylene oxide between 0.9 and 1.8 mg/m^3, for 40 h per week, did not show an increased aberration rate; others, exposed to bursts of ethylene oxide at concentrations between 9 and 18 mg/m^3, for 8 h per week, did. The Task Group noted that the sterilization procedure involved the use of a 50:50 mixture of ethylene oxide and methyl formate. At the same time, DNA repair, induced *in vitro* by the mutagen *N*-acetoxy-2-acetylamino-fluorene, was reversibly inhibited in the low exposure group compared with an unexposed control group, but not affected in the other group. DNA repair inhibition was positively correlated with duration of exposure (Pero et al., 1981). In 43 male workers from the cohort of 602 workers (section 8.5) (Thiess et al., 1981b), an increase in chromosomal aberration rate was found that was significant for the workers exposed for more than 20 years, but not for those accidentally exposed or exposed for average periods of 12 and 17 years (Thiess et al., 1981a).

In another ethylene oxide manufacturing plant, no chromosomal aberrations were detected in the lymphocytes of 36 male workers. These men had been exposed for 1 - 14 years to average concentrations of up to 0.28 mg/m^3 (van Sittert et al., 1985).

The sister chromatid exchange rate in lymphocytes was not increased in groups of 28 and 14 sterilization workers exposed to 8-h time-weighted averages, below 1.8 mg/m^3 for 2.5 years before the study (Högstedt et al., 1983) and below 8 mg/m^3 (Hansen et al., 1984), respectively. In the second study, peaks up to 1430 mg/m^3 were also measured. Increases in sister chromatid exchange rate were found in 4 other studies on sterilization workers (Garry et al., 1979; Abrahams, 1980; Yager et al., 1983; Laurent et al., 1984). In one of these studies, in which 75 workers were exposed to levels generally below an 8-h time-weighted average of 90 mg/m^3, this increase was found in cells together with quadriradial aberrations (Abrahams, 1980). In the other studies, groups were small, exposure conditions often unclear, and the number of metaphases scored, in some cases, limited. Yager et al. (1983) only found an increased sister chromatid exchange rate at relatively high calculated integrated doses of more than 100 mg per person. The length of exposure to ethylene oxide averaged 3.6 min per day; these tasks were performed between 6 and 120 times during the 6-month study period. Laurent et al. (1984), studied sister chromatid exchange rates in 2 groups of ethylene oxide-exposed workers (estimated ethylene oxide dose in past 2 years, 530 - 715 mg and 1185 - 5800 mg, respectively) as well as unexposed controls. Although the sister chromatid exchange rates in the high-exposure group did not differ significantly from the rates in the low-exposure groups (not adjusted for smoking), the difference among non-smokers between the exposed (n = 20) and the controls (n = 15) was significant.

In a study on 41 sterilization workers in 8 hospitals in Italy, increases in both sister chromatid exchanges and in chromosomal aberrations were detected in lymphocytes; these effects persisted

for months after exposure was reduced or interrupted. The workers were exposed to average 8-h time-weighted averages of either 0.63 mg/m^3 or 19.3 mg/m^3 (section 4.3). A statistically-significant correlation was found between sister chromatid exchange frequency and the level of ethylene oxide, as well as a multiple correlation between sister chromatid exchange frequency and ethylene oxide exposure, smoking, and age (Sarto et al., 1984). Similarly, in the USA, the sister chromatid exchange frequencies in the lymphocytes of 61 sterilization workers involved in sterilizing health-care products, were monitored over a period of 2 years and compared with those of 82 unexposed controls. During the study period, 8-h time-weighted-average exposures were reported to be less than 1.8 mg/m^3. Prior to the start of the study, 8-h time-weighted averages between 0.9 and 36 mg/m^3 were measured. Results were adjusted for smoking habits, sex, and age. Workers exposed to low levels of ethylene oxide such as those at a worksite with 8-h time-weighted-average ethylene oxide levels below 1.8 mg/m^3 prior to and during the study, did not show increased frequencies of sister chromatid exchange. Workers who had been exposed to levels of 5 - 36 mg/m^3, prior to the study, showed an increased frequency of sister chromatid exchange that persisted for at least 24 months after cessation of exposure (Stolley et al., 1984).

8.8. Effects on Reproduction

In a study from the USSR (Yakubova et al., 1976), the course of pregnancy and birth was followed in 57 operators, 38 laboratory workers, and 65 adminstrative staff in an ethylene oxide-producing plant, the majority of the women being between 20 and 29 years of age. A group of 50 pregnant women working outside the plant served as additional controls. It was estimated that the operators were exposed to ethylene oxide concentrations of 0.2 - 0.3 mg/m^3 for 80% of the working time and 1.0 mg/m^3 for the remaining 20%, while the laboratory workers were exposed only to the lower concentrations.

Pregnancy toxaemia in the latter half of pregnancy and other complications were higher in the operators (14.7%) and laboratory workers (9.9%) than in the administrative staff (4.6%) and outside controls (8%). On the other hand, the primiparae among the operators lost less blood perinatally than those among the other groups. Spontaneous abortion occurred in 6 out of 57 (10.5%) operators, 3 out of 38 (7.9%) laboratory workers, and in 5 out of 65 (7.7%) administrative staff. The operators were subjected to the additional stress of high levels of noise and vibration and wide variations in atmospheric temperatures.

Findings in this study do not indicate any unequivocal adverse effect of ethylene oxide exposure at these concentrations on the outcome of pregnancy.

An increase in spontaneous abortions was also found in a study on Finnish hospital sterilizing staff in 1980, using questionnaires and hospital discharge records. The sterilizing agents were ethylene oxide, glutaraldehyde, and formaldehyde. Controls were nursing auxiliaries, from various hospitals, who did not work in sterilization, anaesthetization, or X-ray recording departments. Results were adjusted for age, parity, decade of the reported pregnancy, coffee and alcohol consumption, and smoking habits.

The rate of spontaneous abortions in the sterilization staff members as a whole (9.7% in 1443 pregnancies) was similar to the rate in the controls (10.5% in 1179 pregnancies). A significant increase, however, was observed when the adjusted spontaneous

abortion rate in the sterilization staff who were exposed during pregnancy (15.1% in 545 pregnancies) was compared with the rate in the staff members who were not exposed during pregnancy (4.6% in 605 pregnancies). On the basis of a separate study, the time-weighted average exposure concentration was estimated to be in the range of 0.18 - 0.90 mg/m^3 (0.1 - 0.5 ppm), with peak concentrations up to 450 mg/m^3 (250 ppm). It was considered by the authors that exposure to ethylene oxide accounted for most of the excess spontaneous abortions (Hemminki et al., 1982).

In a new analysis of the data, controls were chosen from the same hospitals, and only pregnancies that started during hospital employment were analysed in all groups. The spontaneous abortion rate was still highest for the pregnancies during which exposure to ethylene oxide took place (20.4%), and the difference compared with controls (11.3%) was significant. The abortion rate of the group exposed to glutaraldehyde alone (16.6%) was also significantly elevated (Hemminki et al., 1983).

Despite any methodological shortcomings of this reproductive study, such as (a) the statement by Hemminki in 1983 that there was limited exposure data, which prevented a comparison between abortion rates and defined exposure levels; and (b) the fact that the ethylene oxide-exposed and unexposed cohorts were not balanced with regard to the incidence of prior abortions, there is a suggestion of an association between ethylene oxide exposure and adverse pregnancy outcome.

9. EVALUATION OF THE HEALTH RISKS FOR MAN AND EFFECTS ON THE ENVIRONMENT

Human exposure is mainly through inhalation of the vapour. Residues in medical equipment that has been sterilized with ethylene oxide and not sufficiently aerated can migrate into tissues and blood, producing primarily local effects (section 8.4). Oral ingestion of ethylene oxide residues in most fumigated or sterilized foodstuffs is unlikely, as they disappear rapidly through evaporation or reaction with food constituents. A major conversion product in foodstuffs is 2-chloroethanol, which is more persistent than ethylene oxide (section 4.2.1).

Most ethylene oxide is used in the chemical plant in which it is produced. Because of the explosion hazard, ethylene oxide is stored and handled in chemical process plants in closed, automated systems. This equipment is often located outdoors, and, except during maintenance, workers have a minimal chance of exposure. Air samples collected in processing areas of chemical production plants have shown that ethylene oxide vapour concentrations are generally less than 4 mg/m^3 with occasional high peak exposures (section 4.3). Occupational exposure to ethylene oxide tends to be much higher in health instrument manufacture and in hospitals than in the chemical processing industries. Ethylene oxide concentrations near malfunctioning or improperly designed equipment may reach hundreds of mg/m^3 of air for brief periods. However, 8-h time-weighted average breathing-zone air concentrations in hospitals are generally less than 36 mg/m^3. It should be emphasized that the exposure of hospital workers to ethylene oxide tends to be of a short-term and intermittent nature with the likelihood of exposure to short-term (5 - 120 min) concentrations of about 100 mg/m^3 and to peak concentrations of up to 1800 mg/m^3 following the opening of sterilization chambers (section 4.3).

Ethylene oxide has a high solubility in water but will evaporate to a great extent. Degradation of ethylene oxide in neutral water is slow, even in the presence of aerobic microorganisms. Because of the low log *n*-octanol water-partition coefficient, it is unlikely that ethylene oxide and its conversion products (such as 1,2-ethanediol) will bioaccumulate. The toxicity of ethylene oxide for aquatic organisms is low (all available LC_{50}s are above approximately 90 mg/litre) (Table 3). The probable effects of ethylene oxide on the aquatic environment are, therefore, considered negligible (sections 3.2, 6). There are no data concerning the toxicity of ethylene oxide for terrestrial organisms.

No ambient air monitoring data are available from which the effects of ethylene oxide on the health of man and the environment can be assessed. However, the risk for health from exposure to ethylene oxide in the ambient air, apart from point source emissions and accidental spillage, is likely to be negligible.

Inhaled ethylene oxide is readily absorbed into the blood, distributed throughout the body, and rapidly metabolized. The half-life in the tissues of man and rodents is approximately 10 min; clearance from the blood of dogs occurred with a half-life of 33 min (section 5.2). Marked nausea and profuse vomiting following dermal exposure of man to aqueous solutions of ethylene oxide suggest that absorption can occur through the skin (section 5.1).

Case reports indicate that headache, nausea, vomiting, dyspnoea, and respiratory tract irritation are common effects of acute inhalation exposure to ethylene oxide (section 8.3). Case reports and the results of animal studies indicate that sensorimotor neuropathies may follow repeated exposure to concentrations of ethylene oxide recognizable by its odour (approximately 900 mg/m^3 or more) (sections 2.2, 7.2.1, 8.3).

Dermatological effects in man following skin contact with ethylene oxide include erythema, oedema, and vesiculation, in that order. The severity of the skin injury is related to concentration (a 50% (500 g/litre) solution being most hazardous) and duration of contact. Liquid ethylene oxide, as it vaporizes, can result in a freeze burn. On repeated exposure, ethylene oxide may cause delayed allergic contact dermatitis (sections 8.1, 8.2). Ethylene oxide and its conversion products are irritating to the eyes and can produce corneal injury. Cataracts have occurred following repeated exposure to concentrations of the vapour recognizable by its odour (approximately 900 mg/m^3 or more) (Table 1, sections 8.1, 8.3).

Ethylene oxide directly alkylates proteins and DNA and is mutagenic in microorganisms, plants, insects, mammalian cells *in vitro,* and mammals *in vivo*, including both gene mutations and chromosomal abnormalities (section 7.5). In man, ethylene oxide induces chromosomal aberrations and sister chromatid exchanges in lymphocytes at air concentrations found at the workplace (section 8.7). Tissue distribution studies provide evidence that ethylene oxide reaches the gonads, supporting the findings of heritable mutations in insects and rodents (sections 5.2, 7.5). Ethylene oxide may, therefore, be considered a potential human mutagen for both somatic and germ cells.

The potential of ethylene oxide to cause teratogenic or adverse reproductive effects has been examined in 4 animal species (mouse, rat, rabbit, and monkey) by 2 routes of administration. Results

from these studies showed that ethylene oxide is toxic to reproductive function in both males (reduced sperm number and sperm motility, and an increased time to traverse a linear path) and females (depression of fetal weight gain, fetal death, and fetal malformation). The levels needed to produce these fetal effects approach or equal the dose needed to produce maternal toxicity (section 7.6). The results of animal studies suggest possible reproductive impairment in human males but are inadequate for assessing the fetal risk. Data on reproductive effects in human beings are insufficient; one study, however, suggests an increase

in spontaneous abortion rate in women occupationally exposed to ethylene oxide (section 8.8). However, the reported time-weighted average air concentrations may not reflect the exposure levels that induced the effect.

It has been clearly demonstrated in experimental animal studies that ethylene oxide is carcinogenic via different routes of exposure (intragastric, subcutaneous injection, and inhalation). In 2 inhalation studies, confirmatory data demonstrated dose-related increases in the incidences of leukaemia, peritoneal mesothelioma, and cerebral glioma (section 7.4). Although the evidence for the carcinogenicity of ethylene oxide in man is inadequate, epidemiological studies indicate that exposure to ethylene oxide (in mixtures with other chemicals) increases the risk of malignancies (section 8.6).

Taking into account available data concerning the alkylating nature of ethylene oxide, the demonstration of DNA adducts, the overwhelming positive *in vivo* responses in mutagenic and clastogenic assays, the reproducible positive carcinogenic findings in animals, and the epidemiological findings suggesting an increase in the incidence of human cancer, ethylene oxide should be considered as a probable human carcinogen, and its levels in the environment should be kept as low as feasible.

10. RECOMMENDATIONS FOR FURTHER RESEARCH

1. The study indicating that exposure to ethylene oxide may be associated with spontaneous abortion needs to be corroborated and the implication explored further.

2. The possible effects of ethylene oxide on the reproductive function of man should be studied.

3. The epidemiological studies indicating an increased risk of cancer in workers exposed to ethylene oxide in combination with other chemicals strongly suggest that additional epidemiological studies should be carried out on populations whose exposure has been primarily to ethylene oxide, including adequate quantification of past exposure.

4. The temporal relationships of air concentrations of ethylene oxide and duration of exposure must be examined to determine which of these two factors has the greater impact on health.

5. Development of methods and research should be conducted to assess the endogenous occurrence of hydroxyethylation and the exogenous (environmental) contribution of ethylene oxide and its precursors to the formation of macromolecular adducts as markers of internal dose.

11. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

An International Agency for Research on Cancer Working Group (IARC, 1985) evaluated the carcinogenicity of ethylene oxide and concluded that:

"There is sufficient evidence for the carcinogenicity of ethylene oxide to experimental animals; there is limited evidence for the carcinogenicity to humans of exposures to ethylene oxide in combination with other chemicals; there is inadequate evidence for the carcinogenicity to humans of exposures to ethylene oxide alone. Taken together, the data indicate that ethylene oxide is probably carcinogenic to humans."

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See Also:
Toxicological Abbreviations
Ethylene oxide (HSG 16, 1988)
Ethylene oxide (ICSC)
ETHYLENE OXIDE (JECFA Evaluation)
Ethylene oxide (FAO Meeting Report PL/1965/10/2)
Ethylene oxide (FAO/PL:1968/M/9/1)
Ethylene oxide (WHO Pesticide Residues Series 1)
Ethylene oxide (CICADS 54, 2003)
Ethylene Oxide (IARC Summary & Evaluation, Volume 60, 1994)