

Operation of the interim Prior Informed Consent procedure
banned or severely restricted chemicals in international trade

Decision Guidance Document

Ethylene oxide



Interim Secretariat for the Rotterdam Convention
on the Prior Informed Consent Procedure of
Certain Hazardous Chemicals and Pesticides
International Trade

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Decision Guidance Documents

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Interim Secretariat for the Rotterdam Convention on the Prior
Informed Consent Procedure for Certain Hazardous Chemicals and
Pesticides in International Trade

Rome - Geneva, February 2001

Mandate

The Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade was adopted at the Conference of Plenipotentiaries held in Rotterdam on 10 and 11 of September 1998. The same Conference also adopted a Resolution on interim arrangements in order to operate an interim PIC procedure between the time of the adoption of the Convention and its entry into force, and to prepare for its effective operation once it enters into force.

Paragraph 7 of this Resolution decided that all chemicals that have been identified for inclusion in the PIC procedure under the original PIC procedure but for which Decision Guidance Documents have not yet been circulated before the date on which the Convention is opened for signature will become subject to the interim PIC procedure as soon as the relevant decision guidance documents have been adopted by the Intergovernmental Negotiating Committee (INC).

At its 7th session, held in Geneva on 30 October to 3 November 2000, the INC thus adopted decision guidance documents for ethylene dichloride and ethylene oxide (Decision INC-7/2) with the effect that these chemicals became subject to the interim PIC procedure.

The present decision guidance documents for ethylene oxide was communicated to the Designated National Authorities on 1 February 2001 with the request that they submit a response concerning the future import of the chemical to the Secretariat in line with Article 10, paragraph 2 of the Rotterdam Convention.

Disclaimer

The use of trade names in this document is primarily intended to facilitate the correct identification of the chemical. It is not intended to imply any approval or disapproval of any particular company. As it is not possible to include all trade names presently in use, only a number of commonly used and published trade names have been included in this document.

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PIC - Decision guidance document

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ABBREVIATIONS WHICH MAY BE USED IN THIS DOCUMENT

(N.B. Chemical elements and pesticides are not included in this list)

<u><</u>	<u>less than</u>
<u><=</u>	<u>less than or equal to</u>
<u><<</u>	<u>much less than</u>
<u>></u>	<u>greater than</u>
<u>>=</u>	<u>greater than or equal to</u>
<u>µg</u>	<u>Microgram</u>
<u>a.i.</u>	<u>active ingredient</u>
<u>ACGIH</u>	<u>American Conference of Governmental Industrial Hygienists</u>
<u>ADI</u>	<u>acceptable daily intake</u>
<u>ADP</u>	<u>adenosine diphosphate</u>
<u>ATP</u>	<u>adenosine triphosphate</u>
<u>BBA</u>	<u>Biologische Bundesanstalt für Land- und Forstwirtschaft</u>
<u>b.p.</u>	<u>boiling point</u>
<u>Bw</u>	<u>body weight</u>
<u>°C</u>	<u>degree Celsius (centigrade)</u>
<u>CA</u>	<u>Chemicals Association</u>
<u>CCPR</u>	<u>Codex Committee on Pesticide Residues</u>
<u>CHO</u>	<u>Chinese hamster ovary</u>
<u>D</u>	<u>Dust</u>
<u>EC</u>	<u>Emulsifiable concentrates</u>
<u>EC50</u>	<u>Effect concentration, 50%</u>
<u>ED50</u>	<u>Effect dose, 50%</u>
<u>EHC</u>	<u>Environmental Health Criteria</u>
<u>ERL</u>	<u>Extraneous residue limit</u>
<u>EU</u>	<u>European Union</u>
<u>FAO</u>	<u>Food and Agriculture Organization of the United Nations</u>
<u>g</u>	<u>Gram</u>
<u>GAP</u>	<u>Good agricultural practice</u>
<u>GL</u>	<u>Guideline level</u>

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ABBREVIATIONS WHICH MAY BE USED IN THIS DOCUMENT

<u>GR</u>	<u>Granules</u>
<u>ha</u>	<u>Hectare</u>
<u>i.m.</u>	<u>Intramuscular</u>
<u>i.p.</u>	<u>Intraperitoneal</u>
<u>IARC</u>	<u>International Agency for Research on Cancer</u>
<u>IC50</u>	<u>Inhibition concentration, 50%;</u>
<u>IPCS</u>	<u>International Programme on Chemical Safety</u>
<u>IRPTC</u>	<u>International Register of Potentially Toxic Chemicals</u>
<u>IUPAC</u>	<u>International Union of Pure and Applied Chemistry</u>
<u>JMPR</u>	<u>Joint FAO/WHO Meeting on Pesticide Residues (Joint Meeting of the FAO Panel Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues)</u>
<u>k</u>	<u>Kilo- (x 1000)</u>
<u>kg</u>	<u>Kilogram</u>
<u>Koc</u>	<u>Organic carbon-water partition coefficient</u>
<u>l</u>	<u>Litre</u>
<u>LC₅₀</u>	<u>Lethal concentration, 50%</u>
<u>LD₅₀</u>	<u>Lethal dose, 50%</u>
<u>LOAEL</u>	<u>Lowest observed adverse effect level</u>
<u>LD_{L0}</u>	<u>Lowest lethal dose</u>
<u>LOEL</u>	<u>lowest observed effect level</u>
<u>m</u>	<u>Metre</u>
<u>m.p.</u>	<u>melting point</u>
<u>mg</u>	<u>Milligram</u>
<u>ml</u>	<u>Millilitre</u>
<u>mPa</u>	<u>MilliPascal</u>
<u>MRL</u>	<u>maximum residue limit</u>
<u>MTD</u>	<u>maximum tolerated dose</u>
<u>NCI</u>	<u>National Cancer Institute</u>
<u>ng</u>	<u>Nanogram</u>
<u>NIOSH</u>	<u>National Institute of Occupational Safety and Health</u>
<u>NOAEL</u>	<u>no-observed-adverse-effect level</u>
<u>NOEL</u>	<u>no-observed-effect level</u>

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ABBREVIATIONS WHICH MAY BE USED IN THIS DOCUMENT

<u>OP</u>	<u>organophosphorus pesticide</u>
<u>PHI</u>	<u>pre-harvest interval</u>
<u>PIC</u>	<u>prior informed consent</u>
<u>Pow</u>	<u>octanol-water partition coefficient</u>
<u>POP</u>	<u>persistent organic pollutant</u>
<u>ppm</u>	<u>parts per million (used only with reference to the concentration of a pesticide in an experimental diet. In all other contexts the terms mg/kg or mg/l are used).</u>
<u>RfD</u>	<u>reference dose for chronic oral exposure</u>
<u>SBC</u>	<u>secretariat for the Basel Convention</u>
<u>SC</u>	<u>Soluble concentrate</u>
<u>SG</u>	<u>water soluble granules</u>
<u>SL</u>	<u>soluble concentrate</u>
<u>SMR</u>	<u>standardized mortality ratio</u>
<u>STEL</u>	<u>short term exposure limit</u>
<u>TADI</u>	<u>temporary acceptable daily intake</u>
<u>TLV</u>	<u>threshold limit value</u>
<u>TMDI</u>	<u>theoretical maximum daily intake</u>
<u>TMRL</u>	<u>temporary maximum residue limit</u>
<u>TWA</u>	<u>time weighted average</u>
<u>UNEP</u>	<u>United Nations Environment Programme</u>
<u>USEPA</u>	<u>United States Environmental Protection Agency</u>
<u>UV</u>	<u>Ultraviolet</u>
<u>VOC</u>	<u>volatile organic compound</u>
<u>WHO</u>	<u>World Health Organization</u>
<u>WP</u>	<u>wettable powder</u>
<u>Wt</u>	<u>Weight</u>

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Ethylene oxide

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Deleted: Ethylene oxide is used both as a pesticide and as an industrial chemical.¶

Pesticide uses: 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*). In the USA, less than 0.02% (500000 kg) of the production was used for sterilization in hospitals (*Glaser, 1979*). In Belgium, an estimated 0.07% of the total consumption of ethylene oxide (120000 kg) in 1980 was used in the health care and medical products industries (*Wolfs et al., 1983*).¶

Industrial uses: Virtually all 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; ethanalamines; and choline (*Glaser, 1979*).

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Common name Ethylene oxide (ISO)

Other names/synonyms oxirane (CA, IUPAC); dihydrooxirene; dimethylene oxide; 1,2-epoxyethane; ETO; ethene oxide; oxane; α , β -oxidoethane.

CAS-No. 75-21-8

Use category Pesticide

Use [Ethylene oxide is a powerful alkylating agent. Its chemical reactivity makes it a widely used intermediate in the chemical industry and an effective pesticide.](#)

[Ethylene oxide is reported for the following uses:](#)

Industrial use: [Virtually all ethylene oxide produced is used as an intermediate in the production of various chemicals, including ethoxylates, ethylene glycol, ethylamines, glycol-ethers, di-, tri- and polyethylene glycols and polyethylene terephthalate polyester. Certain of these chemicals are used in the production of surfactants, antifreeze and plastics for fibres, films and packaging materials.](#)

Sterilant use: [A small fraction of the total production of ethylene oxide, along with carbon dioxide and nitrogen, is used to sterilize instruments from the health care, pharmaceutical and wood products industries. Ethylene oxide is used in other industries where heat sensitive goods are sterilized \(*BUA, 1993*\).](#)

Pesticide use: [A small fraction of the total production of ethylene oxide is also used to control insects and micro-organisms in fumigation of herbs and spices and control of wool and fur pests. Limited uses are also reported for treatment of food storage areas, food processing, preserving plants and shearing. Previous uses were largely limited to fumigation of stored products and facilities.](#)

[In Canada in 1996, 95 % of production was used in the manufacture of ethylene glycol. An estimated 4 % was used in the manufacture of surfactants. In the USA, about 1% was used as an antimicrobial sterilant or as an insecticidal fumigant with less than 0.02% \(500000 kg\) of the production used for sterilization in health care \(*Glaser, 1979; WHO, 1978*\). In Belgium, an estimated 0.07% of the total consumption of ethylene oxide \(120000 kg\) in 1980 was used in the health care and medical products industries \(*Wolfs et al., 1983*\).](#)

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Trade names Anprolene; Melgas; Meralp; SterigasP (pure products); Carboxide; Cartox; Etox; Oxyfume 20; 30; Sterigas 90/10; Steroxide 20; T-gas (formulations with carbon dioxide); Oxyfume 12; Sterigas 12/88; Steroxide 12/88 (formulations with fluorocarbons); Etoxiat; Anprolene; Anproline.

Formulation types [Liquefied](#) gas.

Basic manufacturers Belco Resources, Inc.

PIC - Decision guidance document

Reasons for inclusion in the PIC procedure

Ethylene oxide is included in the PIC procedure based on reported bans and severe restrictions on as an agricultural pesticide. No control actions have been reported relating to its sterilant or in uses. Inclusion was recommended at the eighth meeting of the FAO/UNEP Joint Group of Experts on Prior Informed Consent.

Summary of control actions (see Annex 2 for details)

Control actions have been reported by 7 countries and the European Union. In 6 countries (A Belize, Germany, Slovenia, Sweden, United Kingdom) ethylene oxide was reported as banned pesticide use. China reported that its use as a pesticide has been restricted to the fumigation of storehouses, containers and cabins. In the European Union, pesticidal use for the control of wool pests and industrial uses are still allowed. Concern about the effects of the substance on human health, especially addressing carcinogenicity, is reported as the reason for the control actions by most countries.

Hazard classification by organization

WHO	Gaseous or volatile fumigant not classified under the WHO recommended classification of pesticides by hazard (IPCS, 1998-1999)
EPA	Group B1 (probable human carcinogen) (USEPA, 1998)
EU	Toxic; carcinogen, cat. 2; mutagen, cat. 2 (classification in accordance with Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances, 12/1991)
IARC	Group 1 (carcinogenic to humans) (IARC, 1994)

Protective measures that have been applied concerning the chemical

Measures to reduce exposure

Workplace controls are considered preferable to personal protective equipment. For some work, however (such as outside work, confined space entry, work done only sporadically, or work done while workers are being installed), personal protective equipment may be appropriate.

The following recommendations are only guidelines and may not apply to every situation:

Avoid skin contact with ethylene oxide. Wear protective gloves and clothing. Safety equipment suppliers/manufacturers can provide recommendations on the most suitable protective glove/protective clothing material for your operation.

All protective clothing (suits, gloves, footwear, headgear) should be clean, available each day, and before work. [Hoechst Celanese et al., \(1995\)](#) recommend chlorinated polyethylene, a synthetic rubber protective material. Improper use of respirators is dangerous. Such equipment should only be used if the employer has a written programme that takes into account workplace conditions, requirements for training, respirator fit testing and medical exams. At any exposure level, use an approved supplied respirator with a full face-piece operated in the positive pressure mode or with a full face-piece, helmet in the continuous flow mode, or use an approved self-contained breathing apparatus with a full face-piece operated in pressure-demand or other positive pressure mode.

Proper personal protective equipment should be used whenever there is a potential for ethylene oxide exposure.

exposure. Protective clothing should be suitable for ethylene oxide service. Many glove and suit materials are permeated by ethylene oxide and do not provide adequate protection. Even dilute solutions of ethylene oxide can cause severe chemical burns.

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Exposure to 800 ppm is immediately dangerous to life and health. If the possibility of exposure above 800 ppm exists, use an approved self-contained breathing apparatus with a full face-piece operating in continuous flow or other positive pressure mode (New Jersey Department of Health and Senior Services (1994)).

Spilled ethylene oxide should either be allowed to evaporate or be diluted with water 22:1 in an open area and 100:1 in closed area to eliminate a fire hazard.

Ethylene oxide is heavier than air and can travel across the ground and reach a remote source of ignition causing a flashback fire danger. Dangerous polymerisation can occur on contact with highly conductive surfaces.

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Packaging and Labelling

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Follow the FAO Revised Guidelines on Good Labelling Practice for Pesticides (1995).

The United Nations Committee of Experts on the Transportation of Dangerous Goods classifies ethylene oxide as a Class 2.3 chemical in:

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Hazard class 2.3

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Packing: Prevent contamination of packing material. Ethylene oxide can react with metals such as copper, silver, magnesium and their alloys, acids, alkalis, ammonia and many other materials.

Protect containers against physical damage, check for leakage intermittently. Store in distant outdoor tank or container protected from direct sunlight with insulating material, equipped with an adequate refrigeration and ventilation system. Indoor storage should be restricted to small quantities. Place material in a combustible liquid cabinet which is fireproof in conformity with regulation 1988).

Alternatives

No alternatives were reported by notifying countries.

Alternatives for stored products include chemical fumigants (aluminium phosphide, sulphur dioxide, phosphine, cyanide, carbon dioxide, irradiation, heat and cold treatment).

It is essential that before a country considers substituting any reported alternatives, it ensures that the alternatives are relevant to its national needs.

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Waste disposal

Waste should be disposed of in accordance with the provisions of the Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and Their Disposal, any guidelines thereunder (1994) and any other relevant regional agreements.

See the FAO Guidelines on Prevention of Accumulation of Obsolete Pesticide Stocks (1995), and Pesticide Storage and Stock Control Manual (1996).

Wear protective clothing and respiratory equipment suitable for hazardous materials.

Ethylene oxide is highly flammable. Incineration is not an option. Ethylene oxide disposal should be handled by someone with appropriate knowledge of ethylene oxide properties.

It should be noted that the methods recommended in literature are often not suitable in a specific context. Consideration should be given to the use of alternative destruction technologies.

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- Deleted: There is no specific antidote for ethylene oxide and the treatment is symptomatic. Persons who have been poisoned (accidentally or otherwise) should be transported immediately to a hospital and put under surveillance of properly trained medical staff. ¶
- ¶ Eyes: Immediately flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids. Seek medical attention immediately. ¶
- ¶ ... [12]) skin with plenty of soap
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- ... [13]): rinse his or her mouth and
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Exposure limits		
	Type of limit	Value
Food	MRLs (Maximum Residue Limits in mg/kg) in specified products (FAO/WHO 1969).	No MRLs allocated.
	JMPR ADI (Acceptable Daily Intake) in mg/kg diet (FAO/WHO 1969).	No ADI allocated.
Workplace	USA (Occupational Safety and Health Agency) 8 hour TWA (permissible exposure limit) 15 minute short-term exposure limit	1 ppm PEL 5 ppm STEL
	USA TLV-TWA (Threshold Limit Value, Time-Weighted Average) (ACGIH, 1999).	1 ppm (1.8mg/m ³)

First aid

First aid: Move victim to fresh air. Call emergency medical care. Apply artificial respiration if victim breathing. Do not use mouth-to-mouth method if victim ingested or inhaled the substance; induce artificial respiration with the aid of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Administer oxygen if breathing is difficult. Remove and isolate contaminated clothing and shoes. In case of contact with substance, immediately flush skin or eyes with running water for at least 15 minutes. In case of contact with liquefied gas, thaw frosted parts with lukewarm water. Keep victim calm and quiet. Keep victim under observation. Effects of contact or inhalation may be delayed. Ensure medical personnel are aware of the material(s) involved, and take precautions to protect them. (U.S. Department of Transportation, 1996).

- Annexes**
- Annex 1 Further information on the substance
 - Annex 2 Details on reported control actions
 - Annex 3 List of designated national authorities
 - Annex 4 References

Annex 1 – Further information on the substance

1 Chemical and physical properties

1.1 Identity Ethylene oxide is a colourless, flammable gas.

1.2 Formula C₂H₄O

Chemical name Oxirane (CA)

Chemical type Epoxide

1.3 Solubility Miscible with water and most organic solvents.

logPow -0.30 (*Hansch and Leo, 1995*)

1.4 Vapour pressure 146 kPa at 20°C (*WHO, 1985*)

1.5 Melting point -111 °C (*Budavari, 1989*)

1.6 Boiling point 11 °C

1.7 Flammability Flammability in air is from >3% volume. The flash point is -20°C.

1.8 Reactivity It is a highly reactive chemical.

2 Toxicity

2.1 General

2.1.1 Mode of action Ethylene oxide forms macromolecular adducts with proteins and nucleic Targets in proteins are the amino acids cysteine, histidine and valine terminal, as in haemoglobin). The major DNA adduct is 7-(2-hydroxy guanine (*Bolt et al., 1988*). Ethylene oxide is electrophilic and has alkylating effect on proteins and nucleic acids. It disperses rapidly relatively uniformly in the organism. Consequently, all tissue can be reached in theory and thus be exposed to the alkylating properties of ethylene oxide. The fact that gamete-producing cells are also exposed has been demonstrated (*BUA, 1993*).

2.1.2 Uptake In mice inhalation studies ethylene oxide has been demonstrated to be soluble in blood. Pulmonary uptake is expected to be fast and to depend on the alveolar ventilation rate and the concentration of ethylene oxide inspired air (*Ehrenberg et al., 1974*). Ethylene oxide is readily absorbed orally, dermally and inhaled and distributes itself in all tissues and blood stream (*BUA, 1993*).

2.1.3 Metabolism Available animal data indicate two possible pathways for the metabolism of ethylene oxide, i.e., hydrolysis and glutathione conjugation. Within 24

7-24% of the dose applied to dogs was excreted in the urine as 1,2-ethane (Martis et al., 1982 in WHO, 1985).

In the serum of 18 workers occupationally exposed to ethylene oxide blood concentration of 1,2-ethanediol was found to be elevated compared that in unexposed controls (Wolfs et al., 1983).

The results of studies on rats, rabbits and monkeys have shown that 1,2-ethanediol is metabolized but that most is excreted unchanged in the (Gessner et al., 1961; McChessney et al., 1971 in WHO, 1985).

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2.2 Known effects on human health

2.2.1 Acute toxicity

Symptoms of poisoning Respiratory tract irritation was reported as hoarseness (Thiess, 1963; coughing in 5 cases after acute accidental exposure to ethylene oxide (Metz, 1939 in WHO, 1985).

Acute effects on the nervous system in nearly all inhalation cases 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 and Erskine, 1938; Metz, 1939; Capellini and G 1965 in WHO, 1985; Thiess, 1963). Accidental skin exposure results effects on the nervous system, such as nausea and repeated vomiting (Sexton and Henson, 1949). Accidental exposure of the eyes to the vapour ethylene oxide can lead to conjunctivitis (Thiess, 1963; Joyner, Exposure of 12 men via a leaking sterilizer resulted in neurological disorders (Gross et al., 1979; Jay et al., 1982 in WHO, 1985).

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2.2.2 Short and long-term exposure

In 4 young men exposed intermittently for 2 - 8 weeks to ethylene oxide (because of a leaking sterilizer) at levels of approximately 1000 reversible peripheral neuropathy showing abnormal nerve conduction, headache, weakness and decreased reflexes in the extremities, lack of coordination, and a wide-based gait and a reversible acute encephalopathy headache, nausea, vomiting, lethargy, recurrent motor seizures, agitated a diffusely slow electroencephalogram were observed (Gross et al., 1983 in WHO, 1985).

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Polyneuropathy was also reported in 3 sterilizer operators (Kuzuhara 1983 in WHO, 1985).

In a study from the USSR it was reported that pregnancy toxemia in the latter half of pregnancy and other complications were higher in operators (14.7%) exposed to a maximum concentration level of 1 mg/m³ and laboratory workers (9.9%) than in administrative staff (4.6%) and outside controls. However, the primiparae among the operators lost less blood perinatally than those in the other groups. Spontaneous abortion occurred in 10% of operators, 7.9% of laboratory workers and in 7.7% of administrative staff. Findings in this study do not indicate any unequivocal adverse effects of ethylene oxide exposure at these concentrations on the outcome of pregnancy (Yakubova et al., 1976).

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An increase in chromosomal aberrations was found in the lymphocytes of workers sterilizing medical equipment in hospitals or factories (Abraham 1980; Pero et al., 1981; Högstedt et al., 1983). A 50% increase in aberration rate was found in workers exposed to ethylene oxide for 0.5-8 years.

mean number of micronuclei in the bone marrow cells of 64% of workers was 3 times higher than in the controls (Högstedt *et al.*, 1983).

A statistically significant correlation was found between sister chromatid exchange frequency and the level of ethylene oxide, as well as a correlation between sister chromatid exchange frequency and ethylene oxide exposure, smoking and age (Sarto *et al.*, 1984). In the USA, the chromatid exchange frequencies in the lymphocytes of 61 sterilization workers involved in sterilizing health-care products, were monitored over a period of years and compared with those of 82 unexposed controls. During the period, 8-hour Time-Weighted-Average (TWA) exposure, was reported less than 1.8 mg/m³. Prior to the start of the study, 8-hour TWA exposure between 0.9 and 36 mg/m³. In the USA, workers exposed to low level ethylene oxide, such as those at a worksite with 8-h time-weighted-average ethylene oxide levels below 1.8 mg/m³ prior to and during the study, consistently show increased frequencies of sister chromatid exchange. Workers who have been exposed to levels of 5-36 mg/m³ prior to the study showed an increased frequency of sister chromatid exchange; results were adjusted for smoking habits, sex and age (Stolley *et al.*, 1984).

Samples of blood were collected from a group of plant workers engaged in the manufacture of ethylene oxide for periods of up to 14 years, and also from a group of control personnel matched by age and smoking habits. Peripheral blood lymphocytes were cultured for cytogenetic analysis. Selected immunological and haematological parameters were also investigated. The results of the studies showed no statistically significant difference between the group of plant workers and the control group in respect to any of the biological parameters investigated in this study. Nevertheless, duration of employment in ethylene oxide manufacturing was positively correlated ($p < 0.05$) with frequency of chromosome breaks and with the percentage of neutrophil differential white blood cell count, and negatively correlated ($p < 0.05$) with the percentage of lymphocytes. As the values of these parameters remain within the normal limits of control populations, the correlations are considered to have no significance for health. (Van Sittert *et al.*, 1985).

A study was made of the effects of ethylene oxide on the health of sterilization workers and other personnel exposed while using ethylene oxide for the sterilization of disposable medical devices. The only significant findings were obtained by chromosomal analysis of cultured lymphocytes harvested from the workers. There were significant differences in the numbers and types of chromosomal aberrations between the exposed workers and the non-exposed controls (Richmond *et al.*, 1985).

The sister chromatid exchange rate in lymphocytes was not increased in groups of 28 and 14 sterilization workers exposed to 8-hour time-weighted averages below 1.8 mg/m³ for 2.5 years before the study (Högstedt 1983) and below 8 mg/m³ (Hansen *et al.*, 1984), respectively. Increased sister chromatid exchange rates were found in 4 other studies on sterilization workers (Garry *et al.*, 1979, Abrahams, 1980, Yager and Benz, 1983, Lichtenfeld *et al.*, 1984 in WHO, 1985). In a study on 41 sterilization workers in hospitals in Italy, increases in both sister chromatid exchanges and chromosomal aberrations were detected in lymphocytes of workers exposed to 8-hour time-weighted averages of either 0.63 mg/m³ or 19.3 mg/m³ (Garratt *et al.*, 1984).

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DNA repair inhibition was positively correlated with duration of exposure *et al.*, 1981). In 7.1% male workers, an increase in chromosomal aberration rate was found that was significant for the workers exposed for more than 10 years, but not for those accidentally exposed or exposed for an average period of 12 to 17 years (*Thiess et al.*, 1981).

2.2.3 Epidemiological studies

In a Swedish study on ethylene oxide exposure (*Högstedt et al.*, 1979) 11 cases of leukaemia appeared among 68 females working in a small factory sterilizing hospital equipment with a mixture of ethylene oxide and formaldehyde. A third case of 1 male was attributed to the possible exposure to other carcinogens (e.g. benzene). The concentration of ethylene oxide was in the range of 3.6-128 mg/m³, and the 8-hour time-weighted average breathing zone was calculated to be between 36 ± 18 mg/m³.

A second Swedish study to investigate the carcinogenic effects of ethylene oxide was conducted on 241 male workers in an ethylene oxide production plant. Twenty-three deaths occurred during the 16-year observation period dating from 1961-1977 (13.5 expected). The excess mortality was due to cancer and cardiovascular disease. Three cases of stomach cancer (1.5 expected) and 2 cases of leukaemia (0.14 expected) accounted for the excess mortality from cancer. No increase in mortality was observed among 66 unexposed controls. Average exposure levels were estimated to be 25 mg/m³ (*Högstedt et al.*, 1979b).

The ethylene oxide was manufactured by the chlorohydrin process. Significant exposure to other chemicals such as 1,2-dichloroethane, 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. During the 20-year period of observation, a total of 17 cases of cancer were notified to the Cancer Registry against 7.9 expected (*Högstedt et al.*, 1984 *in WHO*, 1985).

In a similar study in the USA, 767 male workers were exposed to ethylene oxide in a producing plant. Concentrations of ethylene oxide were reported to be below 18 mg/m³. There were 46 deaths against 80 expected (*IARC*, 1994).

Workers who had been employed for more than one year by a company producing ethylene oxide had been studied from 1960-1961. No significant differences had been found between workers permanently working in the ethylene oxide manufacturing area, those who had previously worked in another area, those working there intermittently and a further group who had worked in ethylene oxide production. However, a subgroup of individuals with high exposure had decreased haemoglobin concentrations and significant lymphocytosis. When workers were followed up from 1961-1977, those who had been exposed full-time to ethylene oxide production showed a considerable excess mortality, this being mainly due to an increased incidence of leukaemia, stomach cancer and diseases of the circulatory system. Although malignancies could not be linked to any particular chemical associated with ethylene oxide production it was considered that ethylene oxide and ethylene dichloride, possibly together with ethylene chlorohydrin and ethylene, were the causative agents (*Reynolds and Prasad*, 1982).

A multi-centre cohort study was carried out to study the possible association between exposure to ethylene oxide and cancer mortality. The study consisted of 2658 men from eight chemical plants of six chemical companies.

in the Federal Republic of Germany who had been exposed to ethylene for at least one year between 1928 and 1981. The number of subjects separate plants varied from 98 to 604. By the closing date of the study (December 1982) 268 had died, 68 from malignant neoplasms. For employees who had left the plant (2.4%) the vital status remained unknown. The standardized mortality ratio for all causes of death was 0.87 and for malignancies 0.97 compared with national rates. When local state rates were used the standardized mortality ratio were slightly lower. Two deaths from **leukaemia** were observed compared with 2.35 expected standardized mortality ratios for carcinoma of the **oesophagus** (2.0), carcinoma of the stomach (1.38) were raised but not significantly. In one case an internal "control group" was selected matched for age, sex, and date of entry into the factory and compared with the exposed group. In both groups a "healthy worker effect" was observed. The total mortality and mortality from malignant neoplasms was higher in the exposed than in the control group but differences were not statistically significant. There were no deaths from **leukaemia** in the exposed group and one in the control group (*Kiesselbach et al., 1990*).

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In the Federal Republic of Germany, 602 workers were investigated for mortality experience during the period 1928-1980. A subcohort of 351 workers was observed for more than 10 years. Control data came from a styrene plant and from national statistics. Exposure to ethylene oxide normally remained below 9 mg/m³. No information concerning the use of personal protective equipment was given. The workers were also exposed to many other chemicals. Exposure episodes to ethylene oxide concentrations above the background level were also observed. There were 56 deaths compared with 76.6 expected. Fourteen deaths from cancer against 14.6 expected. In the subcohort of 351 workers, there was a significant increase in mortality rate due to kidney disease (3 against 0.4 expected) (*Thiess et al., 1981*).

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A retrospective cohort study was conducted to examine the mortality experience of 2174 men employed between 1940 and 1978 by a chemical company and who had been assigned to a chemical production department that used or produced ethylene oxide. Comparisons were made with the general United States population, the regional population, and a group of 26965 unexposed men from the same plants. Comparison with general United States death rates showed fewer deaths than expected in the ethylene oxide group due to all causes and for total cancers. There was a statistically significant excess of deaths due to any cause. Seven deaths due to **leukaemia** and pancreatic cancer were observed with 3.0 and 0.9 deaths expected. Among the subcohort of men who worked where average and peak exposure levels were probably highest, however, one death due to pancreatic cancer (0.9 expected) and no deaths from **leukaemia** were observed. Four of the seven who died from **leukaemia** and six of the seven died from pancreatic cancer had been assigned to the chlorohydrin department where the potential for exposure to ethylene oxide was judged to have been low. The relative risk of death due to each disease was strongly related to duration of assignments to that department. When those who worked in the chlorohydrin department were excluded, there was no evidence for an association of exposure to ethylene oxide with pancreatic cancer or **leukaemia**. Together with the failure to show independent etiologic

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oxide associations, the chlorohydrin department results suggest **leukaemia** and pancreatic cancer may have been associated primarily production of ethylene chlorohydrin or propylene chlorohydrin, or both. results emphasize the importance of examining additional concurrent asynchronous exposure among human populations exposed to ethylene (Greenberg, 1990).

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A cohort study was carried out of mortality among 2876 men and women exposed to ethylene oxide during its manufacture and use in England and Wales. The study cohort included employees from three companies producing ethylene oxide and derivative compounds such as polyethylene glycol ethoxylates, from one company that manufactured alkoxides from ethylene oxide and from eight hospitals with ethylene oxide sterilizing units. industrial hygiene data were not available before 1977, since then the weighted average exposure has been less than 5 ppm in almost all jobs and less than 1 ppm in many. Past exposure was probably somewhat higher in contrast to other studies, no clear excess of **leukaemia** was noted (10 deaths occurred versus 2.09 expected), and no increase in the incidence of stomach cancer (five deaths occurred versus 5.95 expected) was observed. This lack of consistency with the results of earlier studies may be due to differences in exposure levels. Total cancer mortality was similar to that expected from national and local death rates from this disease. No excesses were noted in some specific cancers, but their relevance to ethylene oxide exposure was doubtful. No excess of cardiovascular diseases was found. While the results of this study did not exclude the possibility that ethylene oxide is a human carcinogen, they suggested that any risk of cancer from currently permitted occupational exposure is small (Gardner, 1989).

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Mortality from cancer among workers exposed to ethylene oxide has been studied in 10 distinct cohorts that include about 29800 workers and 1000 deaths. The study presents a review and meta-analysis of these studies primarily for **leukaemia**, non-Hodgkin's lymphoma, stomach cancer, pancreatic cancer, and cancer of the brain and nervous system. The magnitude and consistency of the standardized mortality ratios (SMRs) were evaluated for the individual and combined studies, as well as trends by intensity or frequency of exposure, by duration of exposure, and by latency (time since first exposure). Exposure to other workplace chemicals was examined as possible confounder variables. Three small studies initially suggested an association between ethylene oxide and **leukaemia**, seven subsequent studies the SMRs for **leukaemia** have been much lower. For the combined studies the SMR = 1.06 (95% confidence interval (95% CI) 0.73-1.48). There was a slight suggestion of a trend by duration of exposure ($p = 0.19$) and a suggested increase with longer latency ($p = 0.07$), but there was no overall trend in risk of **leukaemia** by intensity or frequency of exposure; nor did a cumulative exposure analysis in the largest study indicate a quantitative association. There was also an indication that in two studies with increased risks the workers had been exposed to other possible carcinogens. For non-Hodgkin's lymphoma there was a suggestive overall (SMR = 1.35, 95% CI 0.93-1.90). Breakdowns by exposure intensity or frequency, exposure duration, or latency did not indicate an association but a positive trend by cumulative exposure ($p = 0.05$) was seen in the largest study. There was a suggested increase in the overall SMR for stomach cancer (SMR = 1.28, 95% CI 0.98-1.65) (CI 0.73-2.26) when heterogeneity

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among the risk estimates was taken into account, but analyses by intention of duration of exposure or cumulative exposure did not support an association for stomach cancer. The overall SMRs and exposure-response analyses did not indicate a risk from ethylene oxide for pancreatic cancer (SMR = 0.98), brain and nervous system cancer (SMR = 0.89), or total cancer (SMR = 0.94). Although the current data do not provide convincing evidence that ethylene oxide causes leukemia or non-Hodgkin lymphoma, the issues are not resolved and await further studies of exposed populations (Shore, 1993).

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2.3 Toxicity studies with laboratory animals and *in vitro* systems

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2.3.1 Acute toxicity

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oral

The LD₅₀ for ethylene oxide, administered orally and dissolved in water was 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 and Woodard, 1971 in WHO, 1985).

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1,2-ethanediol, a metabolite, is less toxic: LD₅₀ for rat were above 1 mg/kg body weight, after oral administration, and 5210 mg/kg body weight after intravenous administration (Woodard and Woodard, 1971 in WHO, 1985).

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Dermal

After oral administration to rats, the difference between 0.1% mortality (975 mg/kg) and 99.9% mortality (975 mg/kg) was approximately 650 mg/kg body weight (Smyth *et al.*, 1941 in WHO, 1985).

Thirty 8-week old female icr/ha Swiss mice were painted thrice weekly on clipped dorsal skin with approximately 0.1 ml of 10% solution in acetone over life-time. Median survival time was 493 days; no skin tumors were observed (IARC, 1976).

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Inhalation

After inhalation, the 4-hour LC₅₀ were 1500 and 1730 mg/m³ for mouse and dog, respectively, and 2630 mg/m³ for rat (Jacobson *et al.*, 1956 in WHO, 1985).

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After inhalation for 4 hours, this difference was approximately 3000 mg/m³ for mice, and approximately 5000 mg/m³ in rats. No deaths occurred in dogs at 1280 mg/m³ (Jacobson *et al.*, 1956 in WHO, 1985). In another study guinea pigs died after inhalation of 450 mg ethylene oxide/m³ air for 8 hours but the majority died at 2400 mg/m³ (Waite *et al.*, 1930 in WHO, 1985).

In above mortality studies, the lungs and nervous system were the main target organs in rodents and dogs. In dynamic inhalation exposure studies on guinea pigs (Waite *et al.*, 1930 in WHO, 1985), rats, mice, and dogs (Jacobson 1956 in WHO, 1985), nasal irritation was the first clinical effect. Guinea pigs exhibited laboured breathing, vomited and suffered convulsions. Guinea pigs exposed to an ethylene oxide concentration of 13 000 mg/m³ for 2.5 hours were found lying on their sides, quiet and unable to stand. Gross pathological changes were observed in animals that did not survive, including moderate congestion in the lungs of dogs, minor patchy oedema in the lungs of dogs and congestion with oedema in the lungs of guinea pigs. In rats, moderate congestion with petechial 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/m³.

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Irritation

Skin irritation with hyperaemia, oedema and scar formation was observed from application of pads of cotton, moistened with solutions of ethylene oxide under a plastic cover on the shaved skin of rabbits (*Hollingsworth et al. in WHO, 1985*).

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If large amounts of material are involved, evaporation may cause sufficient cooling to cause a lesion similar to frostbite (*Hine and Rowe 1981 in WHO, 1985*).

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2.3.2 Short-term exposure

Inhalation exposure - Wistar rats, guinea pigs, rabbits and female rhesus monkeys were exposed to concentrations of ethylene oxide at different levels for 7 hours per day and 5 days per week. No adverse effects were observed in guinea pigs, rabbits and monkeys at 90 and 200 mg/m³, and in rats at 370 mg/m³. Rats showed elevated mortality rates from 370 mg/m³, rabbit mortality at 640 mg/m³, and all exposed animals died at 1510 mg/m³. At 370 mg/m³ adverse effects in lungs were observed. Even more severe lung injury was seen in rats at 640 mg/m³ and the higher exposure. Gross respiratory irritation was apparent in all species at 1510 mg/m³. Monkeys and rabbits exhibited paralysis of the hind legs at 370 mg/m³ and rats at 640 mg/m³ (*Hollingsworth et al., 1956 in WHO, 1985*).

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No effects were observed in relation to survival, body weight, clinical chemistry, white blood cell count, serum clinical chemistry, urine analysis, or histopathology in B6C3F1 mice of each sex exposed to concentrations of ethylene oxide at 0, 18, 86, 187, or 425 mg/m³ for 6 hours per day and 5 days per week. The exposure lasted for 10 weeks for males and 11 weeks for females. At the highest exposure level, changes at terminal sacrifice included an increased relative liver weight in female mice, and a decreased testis weight in males and a decreased relative spleen weight and haemoglobin concentration (*Snellings et al., 1984*).

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No effects were observed on mortality rate, body weight, electrocardiogram, blood-calcium and -urea, icteric index and rectal temperature in group 1 male beagle dogs each exposed to concentrations of ethylene oxide at 0, 18, 86, 187, or 530 mg/m³ for 1-3 days. Anaemia was noted at both exposure levels. Effects on the respiratory and nervous systems were shown at 530 mg/m³. Muscular atrophy was also observed (*Jacobson et al., 1956 in WHO, 1985*). No haematological changes were noted in groups of 3 male New Zealand rabbits exposed for 12 weeks to 0, 18, 90 or 450 mg/m³ (*Yager and 1982*). The white cell count was depressed in Fischer rats exposed in groups of 3 or 4, for 3 days, 6 hours per day, to 90, 270, or 810 mg/m³. (*Kligerman et al., 1983*).

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In 12 male cynomolgus monkeys exposed to 0, 90 or 180 mg ethylene oxide/m³ for 7 hours per day, 5 days per week, for 2 years the only treatment-related lesions found were in the *medulla oblongata* of the brain. Myofibrillar dystrophy was found in the *nucleus gracilis*, primarily in the exposed group. 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., 1985*). Paralysis of the hind limbs was observed in monkeys repeatedly exposed up to 32 weeks to 370 mg/m³ for 7 hours per day, 5 days per week (*Hollingsworth et al., 1956 in WHO, 1985*).

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2.3.3 Long-term exposure

In a combined toxicity-carcinogenicity study, groups of 120 male and female Fischer 344 rats were exposed to actual concentrations of ethylene oxide of 18 mg/m³ (10 ppm), 58 mg/m³ (32 ppm) and 173 mg/m³ (96 ppm) for 7 hours per day, 5 days per week, for 2 years.

6 hours per day, 5 days per week, over 25 months. Two control groups of 10 animals per sex were used. The mortality rates of male and female rats increased significantly from the 22nd or 23rd month, at the highest exposure level with a trend towards an increase at a level of 58 mg/m³. Body weights of both sexes were depressed at 173 mg/m³, from the end of the first week on until the end of the study. At 58 mg/m³, the body weights of female rats decreased between week 10 and 80. In females, the relative liver weights were increased in the 18th month at 173 mg/m³. Relative spleen weights were increased in rats that developed leukaemia. Haematological changes found in rats at all doses, but mainly at the end of the study in rats exposed to 173 mg/m³; these included an elevated leukocyte count in both sexes, and a depressed red blood cell count and haemoglobin values in females. Some of these rats had leukaemia. Non-neoplastic histopathological changes observed included an elevated frequency of focal hyperplasia of the adrenal cortices in both sexes and bone marrow hyperplasia in females at 173 mg/m³. Mild skeletal muscle atrophy was observed after 2 years of exposure to 173 mg/m³ (Snellings *et al.*, 1984).

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In another toxicity-carcinogenicity study (Lynch *et al.*, 1984 *in WHO*), groups of 80 male Fischer 344 rats were exposed to concentrations of ethylene oxide of 92 mg/m³ (51 ppm) and 182 mg/m³ (101 ppm) for 6 hours per day, 5 days per week, over 2 years. Eighty rats in the control group had a mortality rate increased at both exposure levels, the increase being significant at 182 mg/m³. Only 19% of the rats survived 2 years of exposure to 182 mg/m³ compared with 49% in the unexposed group. Body weights were reduced from the 3rd or 4th month onwards. The relative weights of adrenal and brain were increased at both exposure levels. The relative weights of lung and kidney were increased at 92 mg/m³. Serum aspartate aminotransferase activity was increased in rats exposed to 92 mg/m³. 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/m³. There were also increased incidences of inflammatory lesions in the lungs, nasal cavities, trachea and internal ear at both exposure levels. Cataracts developed in 9 out of 78 rats at 182 mg/m³, 3 out of 79 in the 92 mg/m³ group and 2 out of 77 in the controls.

2.3.4 Effects on reproduction

Ethylene oxide was injected intravenously on several days during embryonic organogenesis in the mouse. Skeletal malformations occurred in fetuses whose mother received 150 mg/kg which produced maternal toxicity. Doses of 75 mg/kg caused no defects. Rats were exposed on days 6-15 of gestation for 6 hours daily to 10-100 ppm. At the highest dose, fetal growth retardation occurred but there was no increase in congenital defects. (Shepard, 1986).

The offspring of DBA/2J male mice exposed to ethylene oxide by inhalation had an increased incidence of both dominant visible and electrophoretically detected mutations over that found in control populations. The progeny were obtained from matings during the exposure period and were products of germ cells that were exposed throughout the spermatogenic process. Apparently, male germ cells repeatedly exposed to ethylene oxide during spermatogenesis are susceptible to ethylene oxide induced transmissible damage (Lewis *et al.*, 1986).

The effects of systemic toxicity including reproductive toxicity of ethylene oxide

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oxide on female rats were studied. When Wistar female rats were exposed to 250 ppm of ethylene oxide for six hours per day, five days per week for 12 weeks, they showed inhibition of body weight gain and paralysis of the hind legs. **Haematological** examination revealed macrocytic normochromic **anaemia** with high reticulocyte counts. The oestrus cycle of the exposed group was prolonged and the percentage of the di-oestrus increased. There was no atrophy in the ovary or the uterus. However, the activity of glutathione reductase in the ovary decreased by 18% and the activity of glutathione-S-transferase increased by 30%. These results indicate that ethylene oxide has a similar effect on both female and male rats and that the female reproductive system is also affected (*Mori et al., 1989*).

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2.3.5 Mutagenicity

In a dose-response study, male mice were exposed to inhalation of ethylene oxide for 4 consecutive days. Mice were exposed for 6 hours per day to 100 ppm, 400 ppm, or 500 ppm ethylene oxide for a daily total of 1800, 2400, or 3000 ppm per hour, respectively. In the dose-rate study, mice were given a total exposure of 1800 ppm per hour per day delivered either at 300 ppm for 6 hours, 600 ppm in 3 hours, or 1200 ppm in 1.5 hours. Quantitative dominant-lethal responses were made on matings involving sperm exposed to late spermatids and early spermatozoa, the stages most sensitive to ethylene oxide. In the dose-response study, a dose-related increase in dominant-lethal mutations was observed, the dose-response curve proved to be **non-linear**. In the dose-rate study, increasing the exposure concentrations resulted in increased dominant-lethal responses. (*Gosslee, 1986*).

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Earlier studies revealed that ethylene oxide or ethyl methanesulfoxide induced high frequencies of midgestation and late foetal deaths and foetal malformations among some of the surviving foetuses when female mice were exposed at the time of fertilization of their eggs or during the early pronuclear stage of the zygote. Effects of the two mutagens are virtually identical. In order to investigate the mechanisms responsible for the dramatic effects in the pronuclear zygotes, the two compounds were used interchangeably in reciprocal experiments. First a reciprocal zygote-transfer study was conducted in order to determine whether the effect is directly on the zygotes or indirectly through maternal toxicity. And second cytogenetic analyses of pronuclear metaphase early cleavage embryos and midgestation foetuses were carried out. The zygote transplantation experiment rules out maternal toxicity as a factor in foetal maldevelopment. Together with the strict stage specificity observed in the earlier studies this result points to a genetic cause for the abnormality. However, the cytogenetic studies failed to show structural or numerical chromosome aberrations. Since intragenic base changes and deletion were also ruled out it appears that the lesions in question induced in zygotes by the two mutagens are different from conventional ones and therefore constitute a novel one in experimental mammalian mutagenesis. (*Kato et al., 1986*).

Ethylene oxide is a classical mutagen and a carcinogen based on evidence from studies in experimental animals. Chinese hamster V79 cells were treated for 2 hours with gaseous ethylene oxide, in a sealed treatment chamber, and assayed for survival and mutagenic response by analysis of resistance to 6-thioguanine or ouabain. Significant numbers of mutants were produced at both genetic markers by 1250 - 7500 ppm ethylene oxide. Similarly, primary Syrian hamster embryo cells were treated for 2 or 20 hours with gaseous ethylene oxide in sealed treatment chambers and subsequently assayed for survival and increased sensitivity to SA7 virus transform

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Treatment concentrations extended from toxic to several non-toxic concentrations. After 2 hours ethylene oxide treatment at 625-2500 ppm, a significant enhancement of virus transformation was observed. At 20 days after treatment, no enhancement was observed. Treatment of hamsters with ethylene oxide in both bioassay systems yielded concentration-related quantitative results, (Hatch *et al.*, 1986).

2.3.6 Carcinogenicity

Various animal studies indicate a clear evidence of the carcinogenicity of the substance (IARC, 1976; NTP, 1987).

Ethylene oxide was administered intragastrically by gavage at 2 and 7.5 mg/kg body weight to groups of 50 female Sprague-Dawley rats weekly for a period of nearly 3 years using salad oil as the solvent. In the forestomach, mainly squamous cell carcinomas were observed, dependent on the dosage. The first tumor occurred in the 79th week. Following tumor rates resulted 62 and 16%. In addition carcinomas, papillomas and reactive changes of the squamous epithelium of the forestomach were observed in other animals, but ethylene oxide did not induce tumors at sites away from the point of administration (Dunke, 1982).

Groups of F344 rats of each sex were exposed to either ethylene oxide (concentrations of 100, 33 or 10 ppm) or to room air 6 hours daily, 5 days a week, for up to 2 years. Three representative sections of the brain from each rat were evaluated. Of 23 primary brain tumors which were found, 2 were in control animals. Increased numbers of brain tumors were seen in 10 and 33 ppm ethylene oxide exposed male and female rats. Significant analyses were found for both males and females, indicating that ethylene oxide exposure > 10 ppm was related to the development of these brain tumors (Garman *et al.*, 1985).

3 Exposure

3.1 Food

Levels in food up to 2420 mg/kg wet weight have been reported for ethanediol and up to 65 mg/kg wet weight for 2,2'-oxybisethanol, 6-12 months after sterilization (Scudamore and Heuser, 1971). Food constituents can be alkylated. Hydroxyethylated derivatives of amino acids, vitamins, alcohols 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 foods (Oser and Hall, 1956; Gordon and Thornburg, 1959; Windmueller *et al.*, Pfeilsticker and Siddiqui, 1976).

3.2 Occupational

In a total of 8 production plants, the levels of worker exposure to ethylene oxide in recent years were reported to be generally below 18 mg/m³ (Högl *et al.*, 1979; Morgan *et al.*, 1981; Thiess *et al.*, 1981).

In the majority of samples, the concentration of ethylene oxide was less than 0.2 mg/m³ while in the remaining samples, concentrations were of up to 4.0 mg/m³ (Van Sittert *et al.*, 1985). In a plant in the USA, typical average exposure levels were reported to be 0.3 - 4.0 mg/m³ in 1979 (Flores, 1983 in Thiess *et al.*, 1985).

Thiess *et al.* (1981) reported an exposure of 3420 mg/m³ during a breakdown.

In four hospital sterilization units in France, in 1980, concentrations below 18 mg/m³ were reported.

0.9 and 410 mg/m³ were measured after sampling for several minutes (Mouilleseaux *et al.*, 1983).

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Exposure, after the opening of sterilizers, ranging from less than 0.2 to 1 mg/m³, 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/m³ measured by personal sampling (Lahaye *et al.*, 1984).

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In six hospital sterilization units in Italy, using pure ethylene oxide, the time-weighted average concentrations were 6.7 - 36 mg/m³ with an average of 19.3 mg/m³. Continuous sampling during the 5-min interval following opening of sterilizers revealed time-weighted average concentrations of 1.5 - 19.3 mg/m³. In two other hospitals in Italy, using 11% ethylene oxide in freon, the 8-hour time-weighted average level was 0.63 mg/m³, and the 5-min exposure average level was 15.5 mg/m³ (Sarto *et al.*, 1984).

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Time-weighted average exposure of Swedish personnel involved in sterilizing medical equipment in 1975 were 14 mg/m³, when the sterilizer door was open and 2.3 mg/m³ when the door was closed (Högstedt *et al.*, 1983).

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Pero *et al.* (1981) reported 1-hour time-weighted average personal exposure of up to 18 mg/m³ for a sterilization facility in Sweden.

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For workers in sterilization rooms of a hospital in the USA, 15-min exposures up to 86 mg/m³ were found with 8-hour time-weighted averages ranging from less than 0.13 to 7.7 mg/m³ and instantaneous peaks of up to 1430 mg/m³ (Hansen *et al.*, 1984).

Eight hour time-weighted averages of 0.9, 9 - 18, and 9 - 36 mg/m³ were measured before the 1980s at 3 work-sites in the sterilization facilities of a plant manufacturing health-care products (Stolley *et al.*, 1984).

3.3 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 as a gas.

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 12000 mg/m³ were measured 10 meters from an exhaust pipe on the outside wall (Dunkelberg and Harshbarger 1977).

3.4 Accidental poisoning

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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 3.1 for food. Aeration and storage conditions are very important, particularly with respect to possible human exposure.

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4 Effects on the environment

4.1 Fate

The main pathway of entry of ethylene oxide into the environment is through its escape into the atmosphere due to evaporation and with vented emissions 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 1000 tons per year.

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per tonne of ethylene oxide produced by catalytic oxidation. Sterilization 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 100 kilotonnes of ethylene oxide into the atmosphere in the USA, which is approximately 2% of the total production in the USA.

4.1.1 Persistence

At ambient levels, ethylene oxide will be removed from the atmosphere by oxidation by hydroxyl radicals. On the basis of a theoretical rate constant for this reaction, the atmospheric residence time of ethylene oxide is 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 (USEPA, 1983). Because of its high water solubility, ethylene oxide levels in air will 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 hour 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 WHO, 1985). In the presence of halide ions, chloroethanol will also be formed. In neutral water of 3% salinity, at least 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).

4.1.2 **Bioconcentration** Ethylene oxide is not expected to bioaccumulate.

4.2 Ecotoxicity

4.2.1 Fish

Fish are the most susceptible aquatic organisms. An LC₅₀ of 90 mg/l was observed for goldfish exposed for 24 hours (Bridie *et al.*, 1979).

4.2.2 Aquatic invertebrates

In *Daphnia magna* a 48h LC₅₀ of 212 mg/l was observed (Conway 1983).

4.2.3 Birds

There are no studies on the effects of ethylene oxide on birds.

4.2.4 Bees

There are no studies on the effects of ethylene oxide on bees.

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Annex 2 - Details on reported control actions

AUSTRIA

Effective: 1992
Control action: All uses banned [in agriculture](#).
Reasons: Carcinogenic and mutagenic properties.
Alternatives: Many alternatives for designated purposes.

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BELIZE

Effective: 1985
Control action: The substance is banned for use [in agriculture](#).
Uses still allowed: No remaining uses are allowed.
Reasons: Major fire and inhalation hazard.

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CHINA

Effective: 1985
Control action: Ethylene oxide has been banned for registration, production and use pesticide. It has never been produced and used as a pesticide.
Uses still allowed: Ethylene oxide has been restricted for use in fumigating of empty storeh container and cabin only.
Reasons: Ethylene oxide is highly toxic. Its use will produce severely harmful effe human health.

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EUROPEAN UNION

Effective: 1991
Control action: It is prohibited to use or place on the market all plant protection pro containing ethylene oxide as an active ingredient.
Uses still allowed: Pesticidal use for control of wool and fur pests and industrial uses ar allowed. Control of wool and fur pests is not covered by the plant prot legislation.
Reasons: The use of ethylene oxide for the fumigation of plants or plant produ storage leaves residues in foodstuffs which may give rise to harmful effe human and animal health. Ethylene oxide has been classified by the [Eurc Community](#) as a category 2 carcinogen (probably carcinogenic to hum Ethylene oxide has also been classified by the [European Community](#) category 2 mutagen (probably mutagenic to humans).

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(Member States of the European Union are: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ir Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom.)

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GERMANY

Effective: 1981
Control action: Totally banned for use as plant protection product.
Reasons: Highly toxic to warm blooded animals and man; suspected of h
 teratogenic effects; toxicologically critical residues in stored products (re
 with ingredients).

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SLOVENIA

Effective: 1997
Control action: Banned for use in agriculture.
Reasons: This chemical was banned from the use in agriculture due to the effect
 toxic properties to human health and the environment according to the o
 given by the Commission on Poisons.

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SWEDEN

Effective: 1991
Control action: Banned for use as a pesticide
Uses still allowed: No remaining uses allowed.
Reasons: This substance was suspended due to its carcinogenic properties.

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UNITED KINGDOM

Effective: 1990
Control action: All uses [revoked for agriculture](#) under the Control of Pesticides Regulation
Uses still allowed: No remaining uses allowed.
Reasons: Action taken due to evidence of carcinogenicity.

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Annex 3 – List of designated national authorities**AUSTRIA****CP**

Department II/3

Ministry of the Environment, [Youth and Family](#)

Vienna, A - 1010

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BELIZE**P**

The Secretary

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Pesticides Control Board, Central Farm

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C[Sanitation Engineer](#)[Public Health Bureau](#)[Ministry of Health](#)[Belize City](#)**CHINA****CP**[Chief Programme Officer](#)[Division of Solid Waste and Chemical Management, Department of Pollution Control](#)[State Environmental Protection Agency \(SEPA\)](#)No. 115, Xizhimennei [Nanxiaojie](#)

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Institute for the Control of Agrochemicals (ICAMA)

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EUROPEAN UNION**CP**

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GERMANY**CP**

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 Bundesanstalt für Arbeitsschutz und Arbeitsmedizin
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SWEDEN**CP**

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The National Chemicals Inspectorate (KemI)
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Telex 10460 AMS S

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UNITED KINGDOM

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Chemicals and Biotechnology Division
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Phone +44 171 8905230

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p.corcoran@detrbiotech.demon.co.uk¶

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Annex 4 – References

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There is no specific antidote for ethylene oxide and the treatment is symptomatic. Persons who have been poisoned (accidentally or otherwise) should be transported immediately to a hospital and put under surveillance of properly trained medical staff.

Eyes: Immediately flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids. Seek medical attention immediately.

Skin: Flush skin with plenty of soap and water for at least 15 minutes before removing contaminated clothing and shoes. If contact with liquified ethylene oxide occurs, immerse affected part in warm water. Seek medical attention.

Ingestion: Do not induce vomiting.

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rinse his or her mouth and then

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drink 2-4 cupfuls of water, and seek medical advice.

Inhalation: Remove from exposure into fresh air immediately.

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