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CONSIDERATION OF DRAFT DECISION GUIDANCE DOCUMENTS REFERRED TO THE INTERIM CHEMICAL REVIEW COMMITTEE BY THE INTERGOVERNMENTAL NEGOTIATING COMMITTEE FOR THE FOLLOWING FOUR CHEMICALS: ETHYLENE DICHLORIDE, ETHYLENE OXIDE, MALEIC HYDRAZIDE AND BROMACIL

Note by the secretariat

Addendum

Annexed to the present addendum is the draft decision guidance document for the following chemical:

Chemical	CAS number	Category
Ethylene oxide	75-21-8	Pesticide

* UNEP/FAO/PIC/ICRC.1/1.

Annex

PIC - Decision guidance document for a banned or severely restricted chemical

Ethylene oxide

Published:

Common name	Ethylene oxide (ISO)
Other names/ synonyms	oxirane (CA, IUPAC); dihydrooxirene; dimethylene oxide; 1,2-epoxyethane; ethene oxide; oxane; alpha, beta-oxidoethane.
CAS-No.	75-21-8
Use category	Pesticide
Use	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; ethanolamines; and choline *(Glaser, 1979)*.
Trade names	Anprolene; Melgas; Merpal; 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; Amprolene; Anproline.
Formulation types	Liquified gas.
basic manufacturers	Belco Resources, Inc.

Reasons for inclusion in the PIC procedure

Ethylene oxide is included in the PIC procedure as a pesticide. Inclusion was recommended at the eighth meeting of the FAO/UNEP Joint Group of Experts on Prior Informed Consent following detailed discussions during the sixth and seventh meetings. It is included in the procedure on the basis of the control actions reported by a number of Governments.

Summary of control actions (see Annex 2 for details)

Control actions have been reported by 7 countries and the European Union. In 6 countries (Austria, Belize, Germany, Slovenia, Sweden, United Kingdom) ethylene oxide was reported as banned. China reported that its use has been restricted to the fumigation of empty storehouses, containers and cabins. In

the European Union, pesticidal use for the control of wool and for pests and industrial uses are still allowed. Concern about the effects of the substance on human health is reported as the reason for the control actions by most countries.

Hazard classification by organization

WHO	Not classified under the WHO Recommended Classification of Pesticides by Hazard.
EPA	Toxicity class I (pure), (known human carcinogen).
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).
IARC	Group 2A (probable human carcinogen).

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 workplace controls 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/clothing material for your operation.

All protective clothing (suits, gloves, footwear, headgear) should be clean, available each day, and put on before work. ACGIH recommends chlorinated polyethylene as a 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 worker training, respirator fit testing and medical exams. At any exposure level, use an approved supplied-air respirator with a full facepiece operated in the positive pressure mode or with a full facepiece, hood or helmet in the continuous flow mode, or use an approved self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode.

Exposure to 8000 ppm is immediately dangerous to life and health. If the possibility of exposure above 8000 ppm exists, use an approved self-contained breathing apparatus with a full facepiece operated in continuous flow or other positive pressure mode *(USEPA, 1986).*

Packaging and labelling

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

The United Nations Committee of Experts on the Transportation of Dangerous Goods classifies the chemical in:

Hazard class 2.3

Packing: Protect containers against physical damage, check for leakage intermittently. Store in distant outdoor tank or container protected from direct sunlight, lined with insulating material, equipped with an adequate refrigeration and water

system. Indoor storage should be restricted to small quantities. Place material in a combustible liquid cabinet which is fireproof in conformity with regulations *(ITII, 1988).*

Alternatives

No alternatives were reported by notifying countries.

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

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 and any guidelines thereunder *(SBC, 1994)*.

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

Wear protective clothing and respiratory equipment suitable for toxic materials.

Evaporation and open burning: (a) Place on ground in an open area. Evaporate or burn by igniting from a safe distance. (b) Dissolve in benzene, petroleum ether or higher alcohol such as butanol. Dispose by burning the solvents. Recommendable method: Incineration. Peer review: Ethylene oxide boils at 11 °C, therefore burning in an incinerator can cause difficulties unless a gas feed can be arranged. It is soluble in water or alcohol and these solvents can be burned (*IRPTC, 1985*).

It should be noted that the methods recommended in literature are often not suitable in a specific country. High temperature incinerators may not be available. Consideration should be given to the use of alternative destruction technologies.

Exposure limits

	Type of limit	Value
Food	MRLs (Maximum Residue Limits in mg/kg) in specified products (FAO/WHO 1969).	No MRLs.
	JMPR ADI (Acceptable Daily Intake) in mg/kg diet (FAO/WHO 1969).	No ADI.
Workplace	USA (ACGIH) TLV-TWA (Threshold Limit Value, Time-Weighted Average in mg/m^3).	0.5 mg/m^3.

First aid

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. Have the victim rinse his or her mouth and then drink 2-4 cupfuls of water, and seek medical advice.

Inhalation: Remove from exposure into fresh air immediately.

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**	C_2H_4O
	Chemical name	Oxirane (CA)
	Chemical type	Epoxide
1.3	**Solubility**	Miscible with water and most organic solvents.
	logP_{ow}	-0.30 *(Hansch and Leo, 1995)*
1.4	**Vapour pressure**	146 kPa at 20°C *(EHC)*
1.5	**Melting point**	-111 °C *(Budavari, 1989)*
1.6	**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 acids. Targets in proteins are the amino acids cysteine, histidine and valine (if N-terminal, as in hemoglobin). The major DNA adduct is 7-(2-hydroxyethyl)-guanine *(Bolt, 1988)*. Ethylene oxide is electrophilic and has direct alkylating effect on proteins and nucleic acids. It disperses rapidly and 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 demostrated *(BUA, 1993).*

2.1.2 **Uptake**

In mice inhalation studies ethylene oxide has been demonstrated to be very soluble in blood. 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)*. Ethylene oxide is readily absorbed by oral, dermal and inhalatory routes and distibutes itself in all tissues via the 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 hours, 7-24% of the dose applied to dogs was excreted in the urine as 1,2-ethanediol (*Martis et al., 1982 in EHC)*.

In the serum of 18 workers occupationally exposed to ethylene oxide, 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 is excreted unchanged in the urine *(Gessner et al., 1961; McChessney et al., 1971 in EHC)*.

2.2 Known effects on human health

2.2.1 Acute toxicity

Symptoms of poisoning

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

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), over-excitement, sleeplessness, muscular weakness, diarrhoea, and abdominal discomfort *(Blackwood and Erskine, 1938; Metz, 1939; Thiess, 1963; Capellini and Ghezzi, 1965 in EHC)*. Accidental skin exposure resulted in effects on the nervous system, such as nausea and repeated vomiting *(Sexton and 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 *(Gross et al., 1979; Jay et al., 1982 in EHC).*

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 mg/m^3, 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 with headache, nausea, vomiting, lethargy, recurrent motor seizures, agitation and a diffusely slow electroencephalogram were *observed (Gross et al., 1979 in EHC)*.

Polyneuropathy was also reported in 3 sterilizer operators *(Kuzuhara et al., 1983 in EHC)*.

In a study from the USSR it was reported that pregnancy toxaemia in the latter half of pregnancy and other complications were higher in operators (14.7%) exposed to a maximum concentration level of 1 mg/m^3 and laboratory workers (9.9%) than in administrative staff (4.6%) and outside controls (8%). However, the primiparae among the operators lost less blood perinatally than those in the other groups. Spontaneous abortion occurred in 10.5% of operators, 7.9% of laboratory workers and in 7.7% of administrative staff. Findings in this study do not indicate any unequivocal adverse effect of ethylene oxide exposure at these concentrations on the outcome of pregnancy *(Yakubova et al., 1976).*

An increase in chromosomal aberrations was found in the lymphocytes 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 workers exposed to ethylene oxide for 0.5-8 years. The mean number of micronuclei in the bone marrow cells of 64% of these 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 multiple correlation between sister chromatid exchange frequency and ethylene oxide exposure, smoking and age *(Sarto et al., 1984).* 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-hour Time-Weighted-Average (TWA) exposure wwas reported to be less than 1.8 mg/m^3. Prior to the start of the study, 8-hours (TWA) between 0.9 and 36 mg/m^3 were measured. In the USA 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; 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 immune and hematological parameters were also investigated. The results of these 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 the frequency of chromosome breaks and with the percentage of neutrophils in a differential white blood cell count, and negatively correlated ($p< 0.05$) with the percentage of lymphocytes. As the values of these parameters remained within the normal limits of control populations, the correlations were 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 sterilizer workers and other personnel exposed while using ethylene oxide for 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 nonexposed 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/m^3 for 2.5 years before the *study (Högstedt et al., 1983)* and below 8 mg/m^3 *(Hansen et al., 1984),* respectively. 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 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 of workers exposed to 8-hour time-weighted averages of either 0.63 mg/m^3 or 19.3 mg/m^3.

DNA repair inhibition was positively correlated with duration of exposure *(Pero 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 20 years, but not for those accidentally exposed or exposed for average periods of 12 to 17 years *(Thiess et al., 1981).*

2.2.3 **Epidemio-**

In a Swedish study on ethylene oxide exposure *(Hogstedt et al., 1979a)* two cases of leukaemia appeared among 68 females working in a small factory

logical studies

sterilizing hospital equipment with a mixture of ethylene oxide and methyl formate. A third case of 1 male was attributed to the possible exposure to other carcinogens (e.g. benzene). The concentration of ethylene was in the range of 3.6-128 mg/m^3, and the 8-hour time-weighted average in the breathing zone was calculated to be between 36 ± 18 mg/m^3.

A second Swedish study to investigate the carcinogenic effects of ethylene oxide was conducted on 241 male workers in an ethylene oxide-producing 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 (0.4 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 below 25 mg/m^3 *(Högstedt et al., 1979b).*

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. 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 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/m^3. 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 this area, those working there intermittently and a further group who had never worked in ethylene oxide production. However, a subgroup of individuals with high exposure had decreased hemoglobin concentrations and signficant lymphocytosis. When workers were followed up from 1961-1977, those who had been exposed full-time to ethylene oxide production showed a considerably excess mortality, this being mainly due to an increased incidence of leukemia, 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 or ethylene, were the causative agents *(Reynolds, 1982).*

A multi-centre cohort study was carried out to study the possible association between exposure to ethylene oxide and cancer mortality. The cohort consisted of 2658 men from eight chemical plants of six chemical companies in the Federal Republic of Germany who had been exposed to ethylene oxide for at least one year between 1928 and 1981. The number of subjects in the separate plants varied from 98 to 604. By the closing date of the study (31 December 1982) 268 had died, 68 from malignant neoplasms. For 63 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 all

malignancies 0.97 compared with national rates. When local state rates were used the standardized mortality ratio were slightly lower. Two deaths from leukemia were observed compared with 2.35 expected standardized = 0.85. Standardized mortality ratios for carcinoma of the esophagus (2.0) and carcinoma of the stomach (1.38) were raised but not significantly. In one plant 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; the differences were not statistically significant. There were no deaths from leukemia in the exposed group and one in the control group *(Kiesselbach, 1990)*.

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 had 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 concentration above the background level were also observed. There were 56 deaths compared with 76.6 expected. Fourteen deaths from cancer against 16.6 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).*

A retrospective cohort study was conducted to examine the mortality experience of 2174 men employed between 1940 and 1978 by a large 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 with a group of 26965 unexposed men from the same plants. Comparisons 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 no statistically significant excess of deaths due to any cause. Seven deaths each due to leukemia and pancreatic cancer were observed with 3.0 and 4.1 deaths expected. Among the subcohort of men who worked where both average and peak exposure levels were probably highest, however, one death due to pancreatic cancer (0.9 expected) and no deaths due to leukemia were observed. Four of the seven who died from leukemia and six of the seven died from pancreatic cancer had been assigned to the chlorohydrin department where the potential for exposure to ethylene oxide is 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 men who worked in the chlorohydrin department were excluded, there was no evidence for an association of exposure to ethylene oxide with pancreatic cancer or leukemia. Together with the failure to show independent ethylene oxide associations, the chlorohydrin department results suggest that leukemia and pancreatic cancer may have been associated primarily with production of ethylene chlorohydrin or propylene chlorohydrin, or both. These results emphasize the importance of examing additional concurrent asynchronous

exposure among human populations exposed to ethylene *oxide (Greenberg, 1990).*

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 glycols and ethoxylates, from one company that manufactured alkoxides from ethylene oxide and from eight hospitals with ethylene oxide sterilizing units. While industrial hygiene data were not available before 1977, since then the time 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 leukemia was noted (three 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. Small excesses were noted in some specific cancers, but their relevance to ethylene oxide exposure was doubtful. No excess of cardiovascular disease 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).*

Mortality from cancer among workers exposed to ethylene oxide has been studied in 10 distinct cohorts that include about 29800 workers and 2540 deaths. The study presents a review and meta-analysis of these studies, primarily for leukemia, 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 were examined as possible confounder variables. Three small studies initially suggested an association between ethylene oxide and leukemia, but in seven subsequent studies the SMRs for leukemia 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 leukemia 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 potential carcinogens. For non-Hodgkin's lymphoma there was a suggestive risk 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 among the risk estimates was taken into account, but analyses by intensity or duration of exposure or cumulative exposure did not support a causal 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 consistent and convincing evidence that ethylene oxide causes leukemia or non-Hodgkin's lymphoma, the issues are not resolved and await further studies of exposed populations *(Shore,1993).*

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

2.3.1 Acute toxicity

oral

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 and Woodard, 1971 in EHC).*

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 and Woodard, 1971 in EHC*).

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 in EHC).*

Dermal

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 for life-time. Median survival time was 493 days; no skin tumors were observed. *(IARC, 1976)*.

Inhalation

After inhalation, the 4-hour 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 in EHC).*

After inhalation for 4 hours, 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).* In another study no guinea pigs died after inhalation of 450 mg ethylene oxide/m^3 air for 8 hours, but the majority died at 2400 mg/m^3 *(Waite et al., 1930 in EHC).* 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 in EHC),* rats, mice, and dogs *(Jacobson et al., 1956),* nasal irritation was the first clinical effect. Dogs exhibited laboured breathing, vomited and suffered convulsions. Guinea pigs, exposed to an ethylene oxide concentration of 13 000 mg /m^3 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 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.

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., 1956*

in EHC).

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

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 of exposure for 7 hours per day and 5 days per week. No adverse effects in guinea pigs, rabbits and monkeys at 90 and 200 mg/m^3, and in rats at 90 mg/m^3. 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. At 370 mg/m^3, adverse effects in lungs were observed. 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. Monkeys and rabbits exhibited paralysis of the hind legs at 370 mg/m^3 and rats at 640 mg/m^3. *(Hollingsworth et al., 1956 in EHC).*

No effects were observed in relation to survival, body weight, clinical signs, white blood cell count, serum clinical chemistry, urinalysis and histopathology in B6C3F1 mice of each sex exposed to concentrations of ethylene oxide at 0, 18, 86, 187, or 425 mg/m^3 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 testicular weight in males and a decreased relative spleen weight and haemoglobin concentration *(Snellings et al., 1984).*

No effects were observed on mortality rate, body weight, electrocardiogram, blood-calcium and -urea, icteric index and rectal temperature in groups of 3 male beagle dogs each exposed to concentrations of ethylene oxide of 180 and 530 mg/m^3 for 1 - 3 days. Anaemia was noted at both exposure levels. Effects on the respiratory and nervous systems were shown at 530 mg/m^3. Muscular atrophy was also observed *(Jacobson et al., 1956).* No haematological changes were noted in groups of 3 male New Zealand rabbits exposed for 12 weeks to 0, 18, 90 or 450 mg/m^3 *(Yager and Benz, 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/m^3. *(Kligerman et al., 1983).*

In 12 male cynomolgus monkeys exposed to 0, 90 or 180 mg ethylene oxide/m^3 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. 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 hours per day, 5 days per *week (Hollingsworth et al., 1956).*

2.3.3 **Long-term exposure**

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 hours per day, 5 days per week, over 25 months. Two control groups of animal per sex were used. 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. Relative spleen weights were increased in rats that developed leukaemia. 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. Mild skeletal muscular atrophy was observed after 2 years of exposure to 173 mg/*m^3 (Snellings et al., 1981, 1984)*.

In another toxicity-carcinogenicity study *(Lynch et al., 1984),* groups of 80 male Fischer 344 rats were exposed to concentrations of ethylene oxide of 92 mg/m^3 (51 ppm) and 182 mg/m^3 (101 ppm) for 7 hours per day, 5 days per week, over 2 years. Eighty rats in the control group. 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. 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.

2.3.4 Effects on reproduction

Ethylene oxide was injected intravenously on several days during organogenesis in the mouse. Skeletal malformations occurred in foetuses 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, foetal 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 at risk were obtained from matings during the exposure period and were the products of germ cells that were exposed throughout the entire spermatogenic process. Apparently, male germ cells repeatedly exposed to ethylene oxide during spermatogenesis are susceptible to ethylene oxide induced transmissible damage *(Lewis, 1986).*

The effects of systemic toxicity including reproductive toxicity of ethylene 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 ten weeks, they showed inhibition of body weight gain and paralysis of the hindlegs. Hematogological examination revealed macrocytic and normochromic anemia with high reticulocyte counts. The oestrus cycle of the exposed group was prolonged and the percentage of the di-oestrus stage increased. There was no atrophy in the ovary or the uterus. However, the activity of glutathione reductase in the ovary decreased by 18% and that 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, 1989).*

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 300 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 in 6 hours, 600 ppm in 3 hours, or 1200 ppm in 1.5 hours. Quantitation of dominant-lethal responses was made on matings involving sperm exposed as 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 were observed, the dose-response curve proved to be nonlinear. In the dose-rate study, increasing the exposure concentrations resulted in increased dominant-lethal responses. *(Gosslee, 1986)*.

Earlier studies revealed that ethylene oxide or ethyl methanesulfonate induced high frequencies of midgestation and late foetal deaths and of 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. Thus in investigating the mechanisms responsible for the dramatic effects in the early pronuclear zygotes, the two compounds were used interchangeably in the 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 metaphases early cleavage embryos and midgestation foetuses were carried out. The zygote transplantation experiment rules out maternal toxicity as a factor in the foetal maldevelopment. Together with the strict stage specifically observed in the earlier studies this result points to a genetic cause for the abnormalities. However the cytogenetic studies failed to show structural or numerical chromosome aberrations. Since intragenic base changes and deletions may also be ruled out it appears that the lesions in question induced in zygotes by the two mutagens are different from conventional ones and therefore could be a novel one in experimental mammalian mutagenesis. *(Katoh, 1989)*.

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 sealed treatment chambers, and assayed for survival and mutagenic response by analysis of induced 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 transformation. 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 hours after treatment no enhancement was observed. Treatment of hamster cells with ethylene oxide in both bioassay systems yielded concentration-related, quantitative results. *(Hatch, 1986).*

2.3.6 **Carcinogenicity**

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

Ethylene oxide was administered intragastrically by gavage at 2 dosages, 30 and 7.5 mg/kg body weight to groups of 50 female Sprague-Dawley rats twice weekly for a period of nearly 3 years using salad oil as the solvent. It induced local tumors, mainly squamous cell carcinomas of the forestomach, dependent on the dosage. The first tumor occurred in the 79th week. The following tumor rates resulted 62 and 16%. In addition carcinomata in situ, 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 (*Dunkelberg, 1982).*

Groups of F344 rats of each sex were exposed to either ethylene oxide vapor (concentrations of 100, 33 or 10 ppm) or to room air 6 hours daily, 5 days per 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 100 ppm and 33 ppm ethylene oxide exposed male and female rats. Significant trend analyses were found for both males and females, indicating that ethylene exposure > 10 ppm was related to the development of these brain tumors*. (Garman R.H. 1985).*

3 Exposure

3.1 **Food**

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 and 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 and Hall, 1956; Gordon and Thornburg, 1959; Windmueller et al., 1959; Kröller, 1966; 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/m^3 *(Högstedt et al., 1979b; Morgan et al., 1981; Thiess et al., 1981).*

In the majority of samples, the concentration of ethylene oxide was less than 0.2 mg/m^3 while in the remaining samples concentrations were of up to 11.6 mg/m^3 *(van Sittert et al., 1985).* In a plant in the USA, typical average daily

exposure were reported to be 0.3 - 4.0 mg/m^3 in 1979 *(Flores, 1983).*

Thiess *et al.* (1981) reported an exposure of 3420 mg/m^3 during a plant breakdown.

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 *(Mouilleseaux et al., 1983).*

Exposure 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 *(Lahaye et al., 1984).*

In 6 hospital sterilization units in Italy, using pure ethylene oxide, the 8-hour 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 112.5 mg/m^3. In 2 other hospitals in Italy, using 11% ethylene oxide in freon, the 8-hour time-weighted average level was 0.63 mg/m^3, and the 5-min exposure average level was 15.5 mg/m^3 *(Sarto et al., 1984).*

Time-weighted average exposure 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 *(Högstedt et al., 1983).*

Pero *et al*. (1981) reported 1-hour time-weighted average personal exposure of up to 18 mg/m^3 for a sterilization facility in Sweden.

For workers in sterilization rooms of a hospital in the USA, 15-min exposure of up to 86 mg/m^3 were found with 8-hour 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).*

Eight hour time-weighted averages of 0.9, 9 - 18, and 9 - 36 mg/m^3 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 in 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 12000 mg/m^3 were measured 2 – 3 meters from an exhaust pipe on the outside wall *(Dunkelberg and Hartmetz, 1977).*

3.4 **Accidental poisoning**

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 worker exposure.

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 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.

4.1.1 Persistence

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 (*USEPA, 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 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 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).*

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 LC_{50} 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 LC_{50} of 212 mg/l was observed *(Conway et al., 1983).*

4.2.3 Birds

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

4.2.4 Bees

Ethylene oxide is not toxic to bees *(Conway et al., 1983).*

Annex 2 - Details on reported control actions

AUSTRIA

Effective: 1992

Control action: All uses banned.

Reasons: Carcinogenic and mutagenic properties.

Alternatives: Many alternatives for designated purposes.

BELIZE

Effective: 1985

Control action: The substance is banned for use.

Uses still allowed: No remaining uses are allowed.

Reasons: Major fire and inhalation hazard.

CHINA

Effective: 1985

Control action: Ethylene oxide has been banned for registration, production and use as a 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 storehouse, container and cabin only.

Reasons: Ethylene oxide is highly toxic. Its use will produce severely harmful effects to human health.

EUROPEAN UNION

Effective: 1991

Control action: It is prohibited to use or place on the market all plant protection products containing ethylene oxide as an active ingredient.

Uses still allowed: Pesticidal use for control of wool and fur pests and industrial uses are still allowed. Control of wool and fur pests is not covered by the plant protection legislation.

Reasons: The use of ethylene oxide for the fumigation of plants or plant products in storage leaves residues in foodstuffs which may give rise to harmful effects on human and animal health. Ethylene oxide has been classified by the European Community as a category 2 carcinogen (probably carcinogenic to humans). Ethylene oxide has also been classified by the European Community as a category 2 mutagen (probably mutagenic to humans).

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

GERMANY

Effective: 1981

Control action: Totally banned for use as plant protection product.

Reasons: Highly toxic to warm blooded animals and man; suspected of having teratogenic effects; toxicologically critical residues in stored products (reaction with ingredients).

SLOVENIA

Effective: 1997

Control action: Banned for use in agriculture.

Reasons: This chemical was banned from the use in agriculture due to the effect of its toxic properties to human health and the environment according to the opinion given by the Commission on Poisons.

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.

UNITED KINGDOM

Effective: 1990

Control action: All uses revoked under the Control of Pesticides Regulations.

Uses still allowed: No remaining uses allowed.

Reasons: Action taken due to evidence of carcinogenicity.

Annex 3 – List of designated national authorities

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CP **DNA** Industrial Chemicals and Pesticides

P **DNA** Pesticides

C **DNA** Industrial Chemicals

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