**Environmental Health Criteria 33**

# EPICHLOROHYDRIN

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The **International Programme on Chemical Safety (IPCS)** is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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The WHO Task Group for the Environmental Health Criteria for Epichlorohydrin met in Brussels from 19 to 22 September, 1983. Professor A. Lafontaine opened the meeting and welcomed the participants on behalf of the host government, and Dr M. Mercier, Manager, IPCS, on behalf of the heads of the three IPCS co-sponsoring organizations (ILO/WHO/UNEP). The Group reviewed and revised the second draft criteria document and made an evaluation of the health risks of exposure to epichlorohydrin.

The efforts of Dr G.J. Van Esch and Dr T. Vermeire, who were responsible for the preparation of the draft, and of all who helped in the preparation and the finalization of the document are gratefully acknowledged.

* * *

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PREFACE

A partly new approach to develop more concise Environmental Health Criteria documents has been adopted with this issue. While the document is based on a comprehensive search of the available, original, scientific literature, only key references have been cited. A detailed data profile and a legal file on epichlorohydrin can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone No. 988400 or 985850).

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

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

# 1. SUMMARY

Epichlorohydrin is a highly reactive and flammable chemical. It is used as an intermediate in the production of numerous substances, notably glycerol and epoxy resins. It can be detected using gas chromatography at concentrations as low as 0.25 mg/m³ in air and 40 µg/litre in water.

Human exposure mainly occurs at the place of work through inhalation and skin contact.

Limited data are available concerning the occurrence of epichlorohydrin in occupational and ambient air, and in water and food. Occupational air levels generally seem to remain below 18.9 mg/m³. Epichlorohydrin is released to the environment as a result of its manufacture, use, and disposal. Migration into food and drinking-water of epichlorohydrin used as a cross-linking agent in packaging materials and epoxy resins is possible, but is expected to be low.

In the troposphere, epichlorohydrin is probably photodegraded. The rate of disappearance from water or aqueous media is expected to be rapid through hydrolysis or evaporation. The compound has been shown to be biodegradable. Bioaccumulation seems unlikely and the acute toxicity for aquatic organisms is moderate to low.

Epichlorohydrin is absorbed rapidly via the skin, gastrointestinal tract, and, in vapour form, via the lungs. It is distributed widely throughout the body. In rodents, retention in tissues mainly occurs at the portal of entry, i.e., the nasal epithelium during inhalation and the stomach after oral exposure. The extent of alkylation of macromolecules by the epoxide is unknown. In rats, most absorbed epichlorohydrin is metabolized rapidly, partly to carbon dioxide, which is excreted via the lungs, and partly to urinary metabolites, mainly conjugates. Hydrolysis is the most probable first reaction in the metabolic pathway of epichlorohydrin, resulting in the formation of 3-chloro-1,2-propanediol, which is much less toxic.

The few human studies available and also animal studies show effects on the central nervous system, respiratory tract, liver, blood, eyes, and skin. The degenerative effects on the kidney tubuli with cortex necrosis, which are very conspicuous in studies on rodents, have not been found in human beings, so far. Epichlorohydrin vapour is strongly irritating to the eyes and respiratory tract and local contact will result in protracted skin burns, though the effects may not appear until some time after exposure. Epichlorohydrin can sensitize the skin. In rats, the toxic effects of epichlorohydrin occur first in the epithelia of the nose and stomach where

inflammation and degenerative changes develop, with hyperplasia and squamous cell metaplasia. Ultimately, after a long latent period, papillomas and squamous cell carcinomas are induced. In mice, epichlorohydrin induces local skin carcinomas following subcutaneous injection and can act as a weak initiator, when applied to the skin. Epidemiological studies to date have not provided evidence of malignant neoplasms in human beings due to exposure to epichlorohydrin. However, the epidemiological data do not have a sufficient number of recorded deaths to detect a weak carcinogenic response. Therefore, a longer observation time will be needed before a final assessment can be made.

Epichlorohydrin is mutagenic in most short-term assays. Conflicting results were obtained when the lymphocytes of workers, occupationally exposed to concentrations below 18.9 $mg/m^3$, were examined for chromosomal aberrations.

The compound has caused sterility in male rats and mice. However, a fertility study in male workers did not reveal any effects on the reproductive system. No evidence has been obtained of any embryotoxic, fetotoxic, or teratogenic effects.

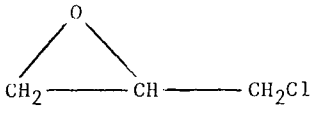
On the basis of the above data, it can be assumed that epichlorohydrin is mutagenic and carcinogenic for animals. Therefore, exposure of human beings should be avoided due to its possible carcinogenicity to human beings as was also assessed by IARC (1982). In dealing with this chemical, impervious protective clothing and breathing protection should be worn. Rubber and leather are unsuitable materials, in this respect. Contaminated clothing should be removed and the skin should be washed carefully.

# 2. PROPERTIES AND ANALYTICAL METHODS

## 2.1 Chemical and Physical Properties

Epichlorohydrin ($C_3H_5ClO$) is a colourless liquid the vapour of which forms explosive mixtures with air. Phosgene, hydrogen chloride, and carbon monoxide are liberated during burning. Acids, caustic solutions, and halide salts initiate polymerization reactions. The compound is very reactive with metals such as zinc and aluminium, anhydrous metal halides, strong acids and bases, and alcohol-containing materials. In the presence of moisture, epichlorohydrin attacks steel.

Chemical structure:



CAS registry number: 106-89-8

RTECS registry number: TX4900000

Common synonyms: alpha-epichlorohydrin, CEP, 1-chloro-2,3-epoxypropane, 3-chloro-1,2-epoxypropane (IUPAC), (chloromethyl) ethylene oxide, chlormethyl oxirane, 2-(chloro-methyl) oxirane, 1-chloropropene oxide, 3-chloropropene oxide, 3-chloro-1,2-propylene oxide, (DL)-alpha-epichlorohydrin, ECH, ECHH, EPI, 1-epichlorohydrin, 1,2-epoxy-3-chloropropane, 2,3-epoxypropyl chloride, gamma-chloropropylene oxide, glycerol epichlorohydrin, glycidyl chloride

Trade names: SKEKHC

Some physical and chemical data on epichlorohydrin

| | |
|---|---|
| physical state | liquid |
| colour | colourless |
| odour | chloroform-like, threshold 38-95 mg/m³ air |
| relative molecular mass | 92.53 |
| melting point | -26 °C |
| boiling point | 115 °C |

| | |
|---|---|
| water solubility | 66 g/litre, 20 °C |
| log n-octanol-water partition coefficient | 0.30 |
| density | 1.18 g/ml, 20 °C |
| relative vapour density | 3.21 |
| vapour pressure | 1.7 kPa (12.5 mm Hg), 20 °C |
| flash point (open-cup) | 34 °C |
| flammable limits | 0.15-0.82 g/litre |

Conversion factor for epichlorohydrin:

| | |
|---|---|
| epichlorohydrin | 1 ppm ≈ 3.78 mg/m³ |

## 2.2 Analytical Methods

A summary of methods for the sampling and determination of epichlorohydrin in air, water, and food is presented in Table 1.

Table 1. Sampling, preparation, analysis

| Medium | Sampling method | Analytical method | Detection limit | Comments | Reference |
|---|---|---|---|---|---|
| air (occupational) | sampling on charcoal | desorption with carbon disulfide, gas chromatography with flame ionization detection | 1 µg (2 - 30 litre sample) | recommended for the range 2 - 60 mg/m³ (20 litre sample) | NIOSH (1984) |
| air (occupational) | sampling in 40% sulfuric acid with oxidation to formaldehyde | colorimetry | 0.5 mg/m³ | interference from formaldehyde and compounds with vicinal terminal hydroxyl groups | Jaraczewska & Kaszper (1967) or Daniel & Gage (1956) |
| air | sampling on Tenax porous polymer | desorption by heating gas chromatography with flame ionization detection | | | Brown & Purnell (1979) |
| water | | extraction with carbon tetrachloride infra-red spectroscopy | 3 mg/litre | no interference from glycerine, glycidol, and monochlorohydrin | Adamek & Peterka (1971) |
| water | | potentiometric titration | | reaction with sodium sulfite and titration of the liberated sodium hydroxide; aldehydes interfere | Swan (1954) |
| water | | gas chromatography and mass spectrometry | 40 µg/litre | headspace analysis signal - noise ratio is 5:1 at detection limit | Piringer (1980) |
| food | extraction by closed-system vacuum distillation | gas chromatography | | determination of epichlorohydrin in corn starch down to 30 mg/kg | Daniels et al. (1981) |

# 3. SOURCES IN THE ENVIRONMENT, ENVIRONMENTAL TRANSPORT AND DISTRIBUTION

## 3.1 Industrial Production, Uses, Disposal of Wastes

### 3.1.1 Industrial production

Figures concerning the total world production are not available. In the USA, production increased from 156 kilotonnes in 1973 (Santodonato et al., 1980) to 250 kilotonnes in 1975 (NIOSH, 1976) and 213 kilotonnes in 1978 (Rose & Lane, 1979).

Epichlorohydrin is also produced in Czechoslovakia, France, the Federal Republic of Germany, the Netherlands, and the USSR (Fishbein, 1976).

The compound is usually prepared from propene, which is chlorinated to allyl chloride. The allyl chloride is chlorinated in water by hypochlorous acid to yield a mixture of isomeric glycerol chlorohydrins. After dehydrochlorination with alkali, epichlorohydrin can be separated by steam distillation. Possible impurities associated with this process are: chlorinated ethers, chlorinated, saturated, and unsaturated short-chain aliphatic hydrocarbons, 1,4-dichlorohexane, dichloropropanols, 1,2-dichloropropene, cis- and trans-1,3 dichloropropene, glycidol, alpha- and beta-monochlorohydrin, and 1,2,3-trichloropropene. The commercial product is more than 98% pure (WHO, 1978; Santodonato et al., 1980).

### 3.1.2 Uses

Epichlorohydrin is mainly used for the manufacture of glycerine and unmodified epoxy resins. It is also used in the manufacture of elastomers, glycidil ethers, cross-linked food starch, wet strength resins for the paper industry, water-treatment resins, surfactants, ion-exchange resins, plasticizers, dyestuffs, pharmaceutical products, oil emulsifiers, lubricants, and adhesives. It may also be used as a solvent for resins, gums, cellulose, esters, paints, and lacquers, and as a stabilizer in chlorine-containing substances such as rubber, pesticide formulations, and solvents (Santodonato et al., 1980).

### 3.1.3 Disposal of wastes

Aqueous, epichlorohydrin-containing wastes are saponified by caustic solutions and the resulting glycerol is biodegraded in sewage-treatment plants (Anon, 1971). Concentrated wastes

are destroyed in special incinerators with flue-gas washing to avoid the formation and emission of phosgene (Ottinger et al., 1973).

### 3.2 Environmental Transport and Distribution

Environmental contamination by epichlorohydrin mainly occurs via air ducts and waste disposal of heavy ends in industries that produce or use epichlorohydrin. Assuming an industrial production of 181 kilotonnes in the USA, it was estimated that these 2 pathways accounted for the transport of 273 and 193 tonnes, respectively, into the environment in 1977. Other contaminants associated with these industrial processes are allyl chloride, trichloropropanes, chloroethers, and dichlorohydrins. Epichlorohydrin can also be lost to the environment via industrial water, during transport and storage, by volatilization during use, and by inadvertant industrial production (Santodonato et al., 1980).

The half-life for the reaction of epichlorohydrin with water, at room temperature, to form 3-chloro-1,2-propanediol (alpha-chlorohydrin) was found to be 148, 79, and 62 h, respectively, in neutral, acidic, and alkaline solutions containing 9 mg of the compound per litre, initially. The rate of hydrolysis increased 7-fold, when the temperature was raised to 40 °C. The presence of nucleophilic ions also increased the rate of hydrolysis (Piringer, 1980). Once in the troposphere, photodegradation takes place (Dilling et al., 1976).

Epichlorohydrin was biodegraded slowly by aerobic bacteria from the effluent of a biological waste-treatment plant, after adaptation. Five days after seeding, the biological oxygen demand amounted to 14% of the theoretical oxygen demand (Bridie, 1979b). When a solution containing epichlorohydrin at 169 mg/litre was incubated with activated sludge micro-organisms, 89% of the compound had disappeared within 24 h (measured by the chemical oxygen demand removal efficiency). Controls revealed that 73% of this loss could be accounted for by evaporation (Matsui et al., 1975).

# 4. ENVIRONMENTAL LEVELS AND EXPOSURES

## 4.1 Occurrence

No data are available that indicate that epichlorohydrin occurs naturally in ambient air, water, soil, or biota.

On the basis of use patterns and the physical and chemical properties of epichlorohydrin, it can be derived that human exposure is mainly occupational, through vapour inhalation, sometimes accompanied by direct skin contact. Slight exposure may occur via food.

## 4.2 Occupational Exposure

Data from 7 plants in the USA, engaged in the production of epichlorohydrin, glycerol, or epoxy resins, from 1973 onwards, showed that 7-h or 8-h time-weighted-average exposures to epichlorohydrin ranged from less than 0.04 mg/m³ air to 57 mg/m³. The median was below 8 mg/m³ air (NIOSH, 1976; Oser, 1980). In 2 other epoxy resin plants, the time-weighted-average exposures for 1973-76 were generally below 3.8 mg/m³ air, except for those of laboratory personnel in one of the plants, which varied between 3.8 and 18.9 mg/m³ (Shellenberger et al., 1979). A survey of epichlorohydrin exposure in European manufacturing plants in 1977-78 indicated that personal exposures were at, or below, 3.8 mg/m³ air (TWA) (Tassignon et al., 1983). In glycerol-manufacturing plants in the USSR, the concentrations ranged from 12 to 21 mg/m³ air. It was not reported whether these values were time-weighted-averages over a working day (Petko et al., 1966).

## 4.3 General Population Exposure

At a distance of 100-200 m from a factory discharging epichlorohydrin into the atmosphere, in the USSR, the airborne epichlorohydrin concentration ranged from 0.5 to 1.2 mg/m³ air. At 400 m, 5 out of 29 samples revealed levels exceeding 0.2 mg/m³, while no epichlorohydrin was detected at 600 m (Fomin, 1966). Two reports were available concerning the migration of epichlorohydrin from various epoxy resin-coated materials into water or food. In one case, no epichlorohydrin could be detected in the water. The detection limit was reported to be 3 µg/litre water (Lierop, 1978). In the other case, foods, preserved in cans coated with epoxyphenolic lacquers, were found to contain epichlorohydrin, phenol, and formaldehyde (Pestova, 1979).

# 5. CHEMOBIOKINETICS AND METABOLISM

## 5.1 Absorption

When the tails of mice were immersed in undiluted epichlorohydrin for 15-60 min, most mice died, showing severe systemic poisoning (Kremneva & Tolgskaja, 1961; Pallade et al., 1967). Within 7 days, 50% of rabbits died after the application of epichlorohydrin at 0.75 g/kg body weight on an occluded patch of shaved skin for 24 h (Lawrence et al., 1972).

Eight hours after oral administration of epichlorohydrin to rats, less than 10% of the dose was recovered in the gastrointestinal tract; peak tissue levels occurred approximately 2 h after dosing in males and 4 h in females (Weigel et al., 1978). Almost all orally ingested epichlorohydrin was absorbed from the gastrointestinal tract of rats. The plasma concentration of epichlorohydrin or its metabolites in rats was 36.1 mg/litre, 3 h after oral administration of 100 mg/kg body weight and 18.3 mg/litre directly after inhalation at a level of 378 mg/m$^3$ (Smith et al., 1979). In mice, peak concentrations in blood of only 0.5 mg/litre were reached within the first 5 min following oral administration of 200 mg epichlorohydrin/kg body weight (Rossi et al., 1983b).

It can be concluded that epichlorohydrin is absorbed well by all routes in all species tested.

## 5.2 Distribution

After absorption by rats, epichlorohydrin was distributed widely throughout many tissues. Concentrations of epichlorohydrin found in blood, 2-4 h after oral ingestion, were subsequently exceeded by a factor of 2 or more in the stomach and intestines, the kidneys, the prostate and lacrimal glands, and the liver. Directly after inhalation, such levels occurred mainly in the epithelium of the nasal turbinates, the lacrimal glands, kidneys, liver, and large intestines (Weigel et al., 1978; Smith et al., 1979).

## 5.3 Metabolic Transformation and Excretion

After a single oral administration to rats of 1 or 100 mg of labelled epichlorohydrin per kg body weight or a 6-h exposure at levels of 3.78 or 378 mg/m$^3$ air, approximately 90% of absorbed epichlorohydrin was excreted within 72 h, regardless of the level or the route of exposure. It was excreted as carbon dioxide via the lungs (25 - 42% of the absorbed dose) or as other metabolites via the urine (46 - 54%

of the absorbed dose). No unchanged epichlorohydrin was excreted via these routes. The results were not affected by the position of the $^{13}C$-label, indicating that, if any carbon-to-carbon bond is broken, the entire molecule is metabolized to carbon dioxide. Urinary excretion was a biphasic process, the slow phase starting 24 h after exposure (Smith et al., 1979).

The following metabolites have so far been identified in the urine of rats: 2,3-dihydroxypropyl-S-cysteine and its mercapturic acid, beta-chlorolactic acid, oxalic acid, and 1,3-(bis-mercaptyl)propanol-2-ol. The first 2 compounds were also found in the urine of rats given 3-chloro-1,2-propanediol (alpha-chlorohydrin) (Jones et al., 1969; Fakhouri & Jones, 1979). In in vitro studies, it was shown that epichlorohydrin was hydrolysed into 3-chloro-1,2-propane-diol by the microsomal epoxide hydrolase(s) (EC 3.3.2.3) of mouse liver in the absence of NADPH, the roles of protein or glutathione in this detoxification being insignificant (Rossi et al., 1983a). Within 20 min of the oral or intraperitoneal administration of epichlorohydrin in mice, the compound was no longer detectable in the blood by gas chromatography with mass spectrometric detection, while the level of 3-chloro-1,2-propane-diol reached a peak. The latter was measurable up to 5 h after exposure (Rossi et al., 1983b). It was proposed that the biodegradation of the epichlorohydrin molecule was initiated by enzymatic or non-enzymatic hydrolysis, possibly also yielding 1-hydroxy-2, 3 epoxypropane (glycidol), after which conjugation with glutathione took place via glutathione transferases (EC 2.5.1.18). Direct conjugation of epichlorohydrin with glutathione was also proposed. A minor reaction could be oxidation via 3-chloro-1,2-propanediol and beta-chlorolactic acid to oxalic acid (Shram et al., 1981a; Fakhouri & Jones, 1979).

Epichlorohydrin is an alkylating agent and has been found to react with the nucleic-acid bases deoxyguanosine and deoxyadenosine in vitro (Hemminki et al., 1980).

## 6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

A summary of the acute toxicity of epichlorohydrin for aquatic organisms and plants is presented in Table 2. The subject of biodegradation has already been discussed in section 3.3.2.

Table 2. Acute aquatic toxicity

| Organism | Description | T (°C) | pH | Hardness ($mgCaCO_3$/ litre | Flow or stat[1] | Parameter | Concentration (mg/litre) | Reference |
|---|---|---|---|---|---|---|---|---|
| algae | blue algae (*Microcystis aeruginosa*) | 27 | 7.0 | | stat | 8-day MIC[2] | 6.0 | Bringmann (1975)[3] |
| algae | green algae (*Scenedesmus quadricauda*) | 27 | 7.0 | | stat | 8-day MIC | 5.4 | Bringmann & Kühn (1977a)[3] |
| bacteria | *Pseudomonas putida* | 25 | 7.0 | | stat | 16-h MIC | 55 | Bringmann & Kühn (1977a)[3] |
| protozoa | *Entosiphon sulcatum* | 25 | 6.9 | | stat | 72-h MIC | 35 | Bringmann (1978)[4,7] |
| protozoa | *Chilomonas paramecium* | 25 | 7 | | stat | 72-h MIC | 29 | Bringmann & Kühn (1981)[5,7] |
| protozoa | *Uronema parduczi* | 25 | 7 | | stat | 72-h MIC | 57 | Bringmann & Kühn (1981)[6,7] |
| crustacea | water flea (*Daphnia magna*) | 20-22 | 7.6-7.7 | | stat | 24-h $LC_{50}$ | 30 | Bringmann & Kühn (1977b)[8,14] |
| fish | goldfish (*Carassius auratus*) | 20 | 6-8 | | stat | 24-h $LC_{50}$ | 23 | Bridié et al. (1979a)[9] |
| fish | golden orfe (*Leuciscus idus*) | | 7.5 | | stat | 48-h $LC_{50}$ | 24 | Juhnke & Lüdemann (1978)[10,14] |
| fish | zebra fish (*Brachydanio rero*) | | 7.5 | | stat | 96-h $LC_{50}$ | 30.5 | Wellens (1982)[11,14] |

Table 2 (contd).

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| fish | bluegill sunfish (*Lepomis marcochirus*) | 23 | 7.6 | 55 | stat | 96-h $LC_{50}$ | 35 | Dawson et al. (1977)[12,14] |
| fish | harlequin fish (*Rasbora heteromorpha*) | 20 | 7.2 | 20 | flow | 48-h $LC_{50}$ | 36 | Alabaster (1969)[14] |
| fish | tidewater silversides (*Menidia beryllina*) | 20 | 7.9 | 55 | stat | 96-h $LC_{50}$ | 18 | Dawson et al. (1977)[13,14] |

Notes

1. Flow through or static method.
2. MIC = Minimum inhibitory concentration for cell multiplication.
3. Growth was measured turbidimetrically, no analysis for epichlorohydrin was reported.
4. Bactivorous, beta-mesosaprobic, flagellate.
5. Saprozoic, flagellate.
6. Bactivorous, holozoic, ciliate.
7. Growth was measured by an electronic cell counter, no analysis for epichlorohydrin was reported.
8. Test water was oxygen saturated, hardness was 16° (German), $LC_0$ was 20 mg/litre, $LC_{100}$ was 44 mg/litre.
9. 6 fish per concentration, no aeration, analysis for epichlorohydrin by gas chromatography or by total organic carbon analysis.
10. Aeration, $LC_0$ was 12 mg/litre, $LC_{100}$ was 35 mg/litre.
11. No aeration, $LC_0$ was 26 mg/litre, $LC_{100}$ was 31 mg/litre.
12. Discontinuous aeration.
13. Salt water species, continuous aeration, specific gravity of salt water was 1.018.
14. No analysis for epichlorohydrin was reported.

# 7. EFFECTS ON ANIMALS

## 7.1 Short-Term Exposures

After acute intoxication through oral, inhalation, or skin exposure, death was generally due to respiratory failure (Freuder & Leake, 1941). At lethal doses, histopathological changes were found in the lungs, liver, kidneys, adrenals, and thyroid of mice and rats (Grigorowa et al., 1974). Acute respiratory irritation with haemorrhages and severe oedema occurred in rats after inhalation or oral application (Kremneva & Tolgskaja, 1961; Laskin et al., 1980).

In general, rats were more sensitive to epichlorohydrin than mice, especially with regard to kidney toxicity (Quast et al., 1979a,b).

Relevant acute mortality data are shown in Table 3.

Table 3. Acute mortality after oral intake or inhalation of epichlorohydrin

| Species | Route | Vehicle | Parameter studied | Value | Reference |
|---|---|---|---|---|---|
| rat | oral | none | $LD_{50}$ | 260 (mg/kg body weight) | Lawrence et al. (1972) |
| rat | inhalation | - | 6-h $LC_{50}$ | 1360 ($mg/m^3$) | Laskin et al. (1980) |
| rat | inhalation | - | 4-h $LC_{50}$ | 2400 ($mg/m^3$) | Grigorowa et al. (1974) |
| mouse | oral | none | $LD_{50}$ | 236 (mg/kg body weight) | Lawrence et al. (1972) |
| mouse | inhalation | - | 2-h $LC_{50}$ | 3000 ($mg/m^3$) | Grigorowa et al. (1974) |
| rabbit | dermal | none | 24-h $LC_{50}$ | 754 (mg/kg body weight) | Lawrence et al. (1972) |

### 7.1.1 Oral exposure

Rats received 11 - 80 mg of epichlorohydrin per kg body weight, orally or intraperitoneally, 3 - 7 times a week for

2 - 12 weeks. Reduced body weight gain, an increase in the relative weight of the kidneys, heart, and liver, and haematological changes were observed. Degeneration of kidney tubuli was found at exposure levels of 40 and 80 mg/kg body weight. Two rats died (1 at 40 mg/kg and 1 at 80 mg/kg). The most frequently observed haematological changes were a decreased haemoglobin concentration and haematocrit and changes in (differential) white cell counts (Lawrence et al., 1972; Van Esch, 1981). A decreased cytochrome P-450 content was reported in the liver, kidneys, and testes of rats after an oral dose of 80 mg/kg body weight (Moody et al., 1982).

Kidney damage together with vacuolization and fatty degeneration of the liver were found in rats and mice after oral administration of epichlorohydrin at 325 or 500 mg/kg body weight. Foci of necrosis were also observed in the gastrointestinal tract (Kremneva & Tolgskaja, 1961).

### 7.1.2 Subcutaneous exposure

The kidneys were the main target organ, also at non-lethal doses. Rats injected once, subcutaneously, with approximate $LD_{50}$ doses of 150 or 180 mg epichlorohydrin per kg body weight showed nephrotoxic degeneration of the epithelium of the proximal tubules with ischemic cortex necrosis, in the first days after exposure (Pallade et al., 1967). This phase was accompanied by anuria or oliguria and death at a dose level of 100 - 125 mg/kg body weight (Pallade et al., 1967, 1968; Fakhouri & Jones, 1979). Renal insufficiency was illustrated further at a dose of 125 mg/kg body weight by functional disturbances such as proteinuria, an increased sodium-ion concentration in the urine, and an increased potassium-ion concentration in serum (Pallade et al., 1968). The activity of the enzymes cytochrome-c-oxidase (EC 1.9.3.1), catalase (EC 1.11.1.6), glutamic pyruvic transaminase (EC 2.6.1.2) and, to a lesser extent, alkaline phosphatase (EC 3.1.3.1) and glutamic oxaloacetic transaminase (EC 2.6.1.1) was inhibited in renal tissue, while catalase activity was increased in urine (Pallade et al., 1970). Regeneration of the kidneys in surviving rats started 5 days after exposure (Pallade et al., 1967).

Doses of 50 and 75 mg/kg body weight administered to rats resulted in polyuria and the excretion of large quantities of glucose. Many crystals of calcium oxalate were found in the diuretic urine (Fakhouri & Jones, 1979).

### 7.1.3 Inhalation exposure

The 14-day mortality response of rats, after a single inhalation exposure, increased over a narrow concentration

range. At 1280 mg/m³, the observed mortality rate was 5% compared with 75% at 1395 mg/m³ (Laskin et al., 1980).

Twenty-four hours after a single 4-h inhalation exposure of rats to epichlorohydrin levels of 7 - 350 mg/m³, polyuria was accompanied by increases in kidney weight and in the specific gravity, and the protein and chloride contents of the urine. In this study, bromosulphthalein retention decreased and the liver weight increased (Szumskaja, 1971).

Slight histopathological liver changes were also found in mice after a 2-h inhalation exposure to a concentration of 1680 mg/m³ (Grigorowa et al., 1974). Other signs of liver toxicity were an increased pentobarbital sleeping time in mice (Lawrence et al., 1972) and a dose-related decrease in histaminase (EC 1.4.3.6) activity in rats (Soloimskaja, 1967).

Daily 4-h inhalation exposures of rats during 4 weeks to an epichlorohydrin concentration of 30 mg/m³ also produced signs of kidney and liver toxicity (Grigorowa et al., 1977). When rats were exposed continuously to 0.2 mg/m³ for 98 days, no effects were observed. At 2 mg/m³, an increase in the number of altered leukocytes was reported, while at 20 mg/m³, slight histopathological changes were seen in the lungs, kidneys, heart, and neurons, together with a reduction in body weight gain (Fomin, 1966).

When rats were exposed to epichlorohydrin concentrations in air of up to 377 mg/m³, 9 - 18 times, for 4 - 7 h/day, during 1.5 - 4 weeks, there were no deaths. Mild nasal irritation occurred at a concentration of 102 mg/m³. The most pronounced effect was inflammation and degeneration of the epithelium in the nasal turbinates, with hyperplasia and squamous cell metaplasia at 377 mg/m³. At concentrations of 211 mg/m³ or more, body weight gain was reduced. At a concentration of 377 mg/m³, the kidney tubuli were dilated and the tubular epithelial cells were swollen, proteinuria was also found. Other changes at 377 mg/m³ were: leukocytosis, liver congestion, oedema, consolidation, congestion and inflammation of the lungs, and changes in the increased relative weight of the adrenals, slight epithelial desquamation and oedema of the thyroid, and atrophy of the thymus (Gage, 1959; Grigorowa et al., 1974; Quast et al., 1979b).

In a 90-day study, rats were exposed 6 h/day, for 5 days a week to epichlorohydrin concentrations in air of 19, 94, or 189 mg/m³. Of the rats that survived, some were killed after 30 days, and some at the end of the study. No effects were found on haematology, urinalysis, and biochemistry. At the two highest concentrations, the epithelium of the nasal turbinates showed dose-related changes, similar to those described above and the relative kidney weights were increased. At 189 mg/m³, body weight gain was reduced and

focal tubular nephrosis with dilated tubules was observed in the kidneys. Minimal changes were observed in the adrenals, the contents of the epididimydes, and in the liver (Quast et al., 1979a). In a similar study the changes in the nose and the kidneys appeared to be reversible (John et al., 1983b).

#### 7.1.4 Effects on the eyes and skin

Application of an 80% solution of epichlorohydrin in cottonseed oil caused corneal damage in the rabbit eye. A 20% solution induced definitive conjunctival and palpebral irritation with oedema.

Severe skin irritation was seen in a 24-h occluded patch test on the shaved back of rabbits using a 5% solution of epichlorohydrin in cottonseed oil (Lawrence et al., 1972).

When 15 guinea-pigs were treated dermally with a 5% solution of epichlorohydrin in ethanol, sensitization was observed in 9 animals after a challenge dose, 2 weeks later, with a 1% solution during 24 h (Thorgeirsson & Fregert, 1977). A negative result was obtained in a skin maximization test using a 0.01% solution of epichlorohydrin in cottonseed oil (Lawrence et al., 1972).

### 7.2 Carcinogenicity

#### 7.2.1 Short-term studies

##### 7.2.1.1 Oral exposure

Groups of 20 male Wistar rats received 0, 20, 40, or 80 mg of epichlorohydrin per kg body weight in distilled water, by stomach tube, 5 times per week for 12 weeks. The animals were killed after 1, 2, 4, or 12 weeks. At the highest dose, 2 rats died and a reduced body weight gain was noted. From the first week onwards, a time- and dose-related increase was observed in the changes in the basal cell layer of the forestomach such as thickening of the stomach wall, haemorrhaging, hyperplasia, and an increased number of mitotic figures and nuclei. After 12 weeks at 80 mg/kg body weight, 2 out of 5 rats had papillomas and squamous cell carcinomas (Van Esch & Wester, 1982b).

#### 7.2.2 Long-term studies

##### 7.2.2.1 Oral exposure

Groups of 18 male Wistar rats received epichlorohydrin in the drinking-water at concentrations of 0, 375, 750, and 1500 mg/litre over a period of 81 weeks. At intervals, the

exposure was stopped for some days because of the poor condition of the rats. The average total intakes were, respectively, 0, 8.8, 15.7, and 26.6 mg per rat, per day. All surviving rats were examined at 81 weeks. The survival rates were, respectively, 55, 50, 55, and 67%. Body weights were reduced in a dose-related manner.

The incidence of hyperplasia of the forestomach epithelium at 0, 375, 750, and 1500 mg/litre was 0, 78, 90, and 100%, respectively. The incidence of papillomas was 0, 0, 10, and 58%, respectively, and the incidence of carcinomas, 0, 0, 10, and 17%, respectively. The number of tumours of the forestomach per rat rose from 5.6 at the lowest dose level to 32.8 at the highest. Two out of the 12 surviving rats receiving 1500 mg/litre had squamous cell carcinomas in the oral cavity (Konishi et al., 1980).

Groups of 50 male and 50 female Wistar rats received 0, 2, and 10 mg of epichlorohydrin per kg body weight in distilled water, by stomach tube, 5 times per week for 104 weeks. Gross and histopathological studies were carried out on all animals; haematological studies were carried out at week 55 on 10 rats per sex and per dose.

In males, the body weight gain was significantly and dose-dependently reduced. An elevated mortality rate was noted, reaching a maximum of 60%. A high mortality rate, especially in females, between weeks 20 and 50 was due to obstruction by hair balls in the intestines, caused by the composition of the diet. A dose-related decrease was found in the number of leukocytes in the females. The incidence of hyperplasia of the forestomach epithelium at 0, 2, and 10 mg/kg body weight for female and male rats was 6 and 10%, 24 and 48%, and 14 and 12%, respectively. The incidence of papillomas at this site was 4 and 2%, 4 and 12%, and 0 and 4%, respectively, and the incidence of carcinomas, 0%, 4 and 12%, and 48 and 70%. Females were less affected than males. The first carcinomas appeared after 20 months of exposure (Van Esch & Wester, 1982a).

7.2.2.2 Inhalation exposure

Groups of 100 male Sprague-Dawley rats were exposed for their lifetime (16 - 136 weeks), for 6 h per day and 5 days per week, to epichlorohydrin vapour at concentrations of 38 and 113 mg/m$^3$ air. The controls comprised 100 air-treated and 50 untreated rats. Survival was poor in both exposed and unexposed rats. A mortality rate of 45% was reached in week 45 at 38 mg/m$^3$ air and in week 60 at 113 mg/m$^3$ air. After week 40, a reduced body weight gain was seen at 113 mg/m$^3$ air. In all cases, severe lung congestion, bronchiolectasis, and pneumonia were observed. At the highest concentration, 1

papilloma was detected in the nasal cavity after 57 weeks and 1 squamous cell carcinoma after 107 weeks. At 38 mg/m$^3$, 1 pituitary adenoma was found compared with two at 113 mg/m$^3$ air. No tumours were detected in the controls. The kidney tubules were dilated and degenerated in 24% of air-treated rats, in 37% of the rats exposed to epichlorohydrin at 38 mg/m$^3$, and in 65% of the rats exposed to 113 mg/m$^3$ (Laskin et al., 1980).

A group of 140 male Sprague-Dawley rats was exposed for 30 days, 6 h per day, to epichlorohydrin vapour at a concentration of 378 mg/m$^3$ and observed for the lifetime. The controls comprised 100 air-treated and 50 untreated rats. Almost all animals showed inflammation of the mucous membranes of the turbinates, larynx, and trachea. Dilatation of the renal cortical and medullary tubules, which were filled with hyaline casts, was seen more frequently in exposed rats than in controls. Between 330 and 933 days from the start of exposure, 17 exposed rats showed 15 squamous cell carcinomas and 2 papillomas of the nasal epithelium. One bronchial papilloma was observed at day 583 after the start of exposure. Four exposed rats had pituitary adenomas and one rat had a squamous cell carcinoma of the forestomach. None of these tumour types was found in the controls (Laskin et al., 1980).

#### 7.2.2.3 Subcutaneous exposure

Each of a group of 50 female ICR/HA Swiss mice received a dose of 1.0 mg of epichlorohydrin in tricaprylin, subcutaneously, once a week, for up to 580 days. A group of 100 mice did not receive any treatment and a group of 50 mice received the vehicle only. Local skin sarcomas were found in 6 treated mice and 1 vehicle-treated mice. A local adenocarcinoma was found in one treated rat. The median survival time was 486 days (Van Duuren et al., 1974).

#### 7.2.2.4 Intraperitoneal exposure

Each of a group of 30 female ICR/HA Swiss mice received an intraperitoneal dose of 1.0 mg of epichlorohydrin in tricaprylin, once a week, for up to 450 days. A group of 100 mice did not receive any treatment and a group of 50 mice received the vehicle only. Papillary tumours were observed in the lungs of 11 exposed and 10 vehicle control mice (Van Duuren et al., 1974).

#### 7.2.2.5 Dermal exposure

A group of 40 C3H mice was painted three times a week with "one brushful" of undiluted epichlorohydrin on the clipped

midline of the back for up to 25 months. At month 17, 30 mice were still alive and, at month 24, only 1. No tumours were found (Weil et al., 1963).

Each of a group of 50 female ICR/HA Swiss mice received 2.0 mg epichlorohydrin in acetone applied to the shaven skin, three times a week, for up to 580 days. A group of 100 mice did not receive any treatment and a group of 50 mice received the vehicle only. No tumours were found. The median survival time was 506 days (Van Duuren et al., 1974).

In an initiation-promotion study, each of 30 female ICR/HA Swiss mice received a single dose of 2.0 mg of epichlorohydrin in acetone applied to the skin, followed 2 weeks later by applications of 2.5 µg of phorbol myristate acetate in acetone three times a week for up to 385 days. Several control groups were used. After 106 weeks, 9 exposed mice had developed skin papillomas compared with none of the vehicle controls, and 3 out of a group of 30 that had received the promotor only. One exposed mouse developed a skin carcinoma compared with none of the controls. The median survival time was over 385 days (Van Duuren, 1974).

## 7.3 Mutagenicity

A summary of mutagenicity tests with positive results is given in Table 4. The direct alkylating agent epichlorohydrin (Hemminki et al., 1980) induced gene mutations in all cellular systems and chromosome damage, including sister chromatid exchanges, in eukaryotes. Negative results were obtained in dominant lethal assays with mice (Epstein et al., 1972; Shram et al., 1976) and in tests for chromosomal aberrations in rat bone marrow cells after *in vivo* exposure (Dabney et al., 1979; Shram et al., 1981a). In contrast with other tests, one test with mouse bone marrow cells did not show chromosome aberrations (Rossi et al., 1983b). One DNA-repair test with rat hepatocytes also failed to show a positive mutagenic effect (Probst et al., 1981).

## 7.4 Effects on Reproduction

Epichlorohydrin induced antifertility effects in male rats resembling those induced by alpha-chlorohydrin after a single oral or intraperitoneal dose of 50 mg/kg body weight (Jones et al., 1969). Male fertility was also reduced after daily oral doses of 10 mg/kg body weight, 5 days per week, for 3 months, while doses of 2 mg/kg body weight were without effect (van Esch, 1981). After 7 daily oral doses of 15 mg/kg body weight, this effect was reversible in rats within one week (Hahn, 1970). While 5 oral doses of 20 mg/kg body weight caused reversible sterility in male rats, 5 daily doses of

Table 4. Mutagenic tests with positive results[a]

| | Test description | System description: Species | System description: Strain | Reference |
|---|---|---|---|---|
| G | eceriferum mutants | plants | barley | Lundqvist et al. (1968) |
| E | reverse mutations | bacteria | Escherichia coli $WP_2$ uvrA | Kline et al. (1982) |
| N | reverse mutations (base-pair substitution, frame-shifts) | | Salmonella typhimurium TA1535, TA100, GA46 | Shram et al. (1976)<br>Laumbach et al. (1977)<br>Bridges (1978)<br>Andersen et al. (1978)[b]<br>Stolzenberg & Hine (1979)[b]<br>Voogd et al. (1981)[b] |
| E | | | | |
| M | | | | |
| U | reverse mutations in host-mediated assay | bacteria in mice (intraperitoneal, urine) and men (urine) | Salmonella typhimurium TA1535, TA100, G46, TA1950 | Shram et al. (1976)<br>Kilian et al. (1978) |
| T | forward mutations | bacteria | Klebsiella pneumoniae | Knaap et al. (1982) |
| A | reverse mutations | fungi | Neurospora crassa | Kølmark & Giles (1955) |
| T | Reverse mutations, gene conversion, mitotic crossing over | | Saccharomyces cerevisiae D7 | Vashihat et al. (1980) |
| I | forward mutations | | Schizosaccharomyces pombe P1 | Migliore et al. (1982)[b]<br>Rossi et al. (1983a,b) |
| O | sex-linked recessive lethals | insects | Drosophila melanogaster | Knaap et al. (1982) |
| N | forward mutations | mammalian cells | mouse lymphoma cells | Knaap et al. (1982) |
| | exposure in utero | mammalian cells | Syrian hamster | Shram et al. (1981b) |
| S | forward mutations | | embryonic cells | |

Table 4. (contd)

| | | | | |
|---|---|---|---|---|
| C H R O M O S O M E | chromosome aberrations | plants | Vicia faba root tip | Loveless (1951) |
| | chromosome breaks | mammalian cells | Chinese hamster cells | Sasaki et al. (1980) |
| | chromatid and chromosome breaks | | human lymphocytes | Kucherova et al. (1976) |
| | chromatid and chromosome breaks and sister chromatid exchanges | | human lymphocytes | Norppa et al. (1981) |
| | sister chromatid exchanges | | human lymphocytes | White (1980)[b] |
| | sister chromatid exchanges | | human lymphocytes | Carbone et al. (1981)[b] |
| D A M A G E | chromosome aberrations | mammalian cells, in vivo intraperitoneal or inhalation exposure | mouse bone marrow cells and rat lymphocytes | Shram et al. (1976) Shram et al. (1981a) |
| | aberrations and morphological anomalies | in vivo inhalation exposure | mouse spermatogonia and sperm | Shram et al. (1981a) |
| D N A R E P A I R | Rec-assay | bacteria | Bacillus subtilis | Kada (1981)** |
| | Pol-assay | | Escherichia coli | Rosenkranz (1981) |

[a] Epichlorohydrin was also tested in the International Collaborative Program on short-term test for carcinogenicity (De Serres & Ashby, 1980). The consensus data were, that epichlorohydrin: (a) was positive in all bacterial mutagenicity assays, in all microbial DNA damage repair assays, and in all yeast assays with only two exceptions, i.e., it was questionable in one Salmonella assay and negative in one Rec assay; (b) increased unscheduled DNA synthesis (two out of three assays) and sister chromatid exchange, and induced point mutations in mammalian cells in vitro; (c) was generally negative in vivo, except in the sister chromatid exchange test.

[b] Metabolic activation abolished or decreased the mutagenic activity and increased the rate of survival.

50 mg/kg body weight or one single dose of 100 mg/kg body weight caused permanent sterility. In permanently sterile male rats, large retention cysts were found in the ductuli efferentes and proximal caput of the reproductive organs (Cooper et al., 1974). When male rabbits and male and female rats were exposed for 6 h daily, 5 days per week, to epichlorohydrin vapour at concentrations of 0, 19.7, 93.4, and 189.0 mg/m³ air for 10 weeks, a dose-related transient infertility was induced at the 2 higher levels in male rats, but not in female rats or male rabbits. Microscopic examination did not reveal any abnormalities in the reproductive organs. The sperm of rabbits was investigated, but no adverse effects were found (John et al., 1983b). The sperm of rats that had received 25 or 50 mg epichlorohydrin/kg body weight orally, showed an increased percentage of abnormal sperm heads at the higher dose and a reduced number of sperm heads at the lower dose, while no changes were observed in the weight and microscopic picture of the testes (Cassidy et al., 1983).

## 7.5 Teratogenicity

Female rats received orally 0, 40, 80, or 160 mg and female mice 0, 80, 120, or 160 mg of epichlorohydrin per kg body weight per day in cottonseed oil, between the 6th and the 15th day of pregnancy. Although the higher dose levels were toxic to the dams, no embryotoxic, fetotoxic, or teratogenic effects were observed (Marks et al., 1982). Similar negative results were obtained, when female rats and rabbits inhaled vapours of epichlorohydrin at concentrations of 0, 9.4, or 94.5 mg/m³ air for 7 h/day, between the 6th and the 15th or 18th day of pregnancy (John et al., 1983a).

# 8. EFFECTS ON MAN

## 8.1 Controlled Studies

In the USSR, 5 human volunteers showed significant electroencephalogram changes in the voltage of spikes of the alpha rhythm, when they were exposed to epichlorohydrin vapour at a concentration of 0.3 mg/m³ air for up to 18 min (Fomin, 1966).

Burning of the eyes and nasal mucosa was reported to occur at an epichlorohydrin vapour concentration of 76 mg/m³ air, while throat irritation, which lasted for 48 h, was experienced at 151 mg/m³ (Wexler, 1971).

The sensitization capacity of epichlorohydrin was tested on 1 volunteer. After an occluded patch test of 2 days with 0.1 - 1.0% solutions of epichlorohydrin in ethanol, a late reaction developed after 8 - 11 days. After a challenge exposure of 2 days, erythema was seen immediately after using a 0.01% solution; a "positive reaction" was seen, using a 0.1% solution (Fregert & Gruvberger, 1970).

## 8.2 Accidental Exposures

Seven cases of epichlorohydrin spills on the hands, thighs, or feet have been extensively described. In 2 of the cases, epichlorohydrin had been mixed with methanol. All spills resulted in protracted chemical burns with a latent period of between 10 min and several hours before the first symptoms and redness appeared. Doctors were consulted after periods ranging from 2 h to 5 days. The most frequent signs were redness, swelling, oedema, erosion, and ulceration. Two of the exposed persons were re-exposed within 8 days and 20 months, respectively. No sensitization was noted. Epichlorohydrin was found to penetrate rubber gloves and leather shoes (von Ippen & Mathies, 1970).

One case was reported of a 39-year-old man who inhaled a few deep breaths of epichlorohydrin vapour. Initially, only slight irritation of the eyes and throat was experienced with headache, nausea, and vomiting; later, chronic asthmatic bronchitis developed. Several biopsies over a 2-year period showed fatty degeneration together with functional disturbances of the liver (Schultz, 1964).

## 8.3 Epidemiological Studies

### 8.3.1 Sensitization

In a group of 34 workers with hypersensitivity towards epoxy resins, 6 were found to be hypersensitive to 1%

epichlorohydrin (Jiràsek & Kalensky, 1962). One case of allergic contact dermatitis in relation to epichlorohydrin in a solvent cement was also reported (Beck & King, 1983).

### 8.3.2 Carcinogenic effects

A retrospective cohort study for mortality experience during the period 1966-77 was conducted in the USA on 864 male workers, exposed during the manufacture of epichlorohydrin for more than 3 months, before 1966. There were no exposure data. The reference population consisted of white males from Louisiana and Texas. A total of 52 deaths was recorded. The observed number of deaths in the entire cohort was less than the expected number for all causes, except for primary lung cancer (9 cases) and leukaemia (2 cases). When only the 31 deaths were considered from a fairly young cohort of 715 men with more than 15 years of exposure, the incidences of death due to all cancers (13), primary lung cancer (8), leukaemia (2), and suicide were higher than expected, but none of the increases was significant. Four of the lung cancer cases had also been exposed to isopropyl alcohol (Enterline, 1977; Enterline & Henderson, 1978). In a further update of the study through 1979, 13 more deaths were identified including 1 due to lung cancer. It was reported that one case, originally diagnosed as primary lung cancer, later appeared to be a reticulum cell sarcoma, and that a second case was found to be an adenocarcinoma with unknown primary site. The increased incidence of lung cancer was still not significant. All but 1 of 7 confirmed lung cancer cases were smokers. Four of the 6 lung cancer cases in one plant had also been previously engaged in an isopropyl alcohol manufacturing plant. Here, the excess in lung cancer was only among workers previously employed at the isopropyl alcohol manufacturing unit. However, a slight excess in lung cancer cases was also observed (4 against 3.09 expected) in the other plant (Enterline & Hartley, 1981).

Another retrospective cohort study for mortality experience during the period 1957-76 was carried out on 553 white employees with a potential for epichlorohydrin exposure in a plant manufacturing epoxy resins and glycerol. The time-weighted average exposures to epichlorohydrin ranged from below 3.8 mg/m$^3$ air to 18.9 mg/m$^3$. The exposure period was between 1 month and 15 years. Workers could also have been exposed to allyl chloride and solvents. The reference population comprised white males from Texas. A total of 12 deaths was recorded. The observed number of deaths was lower than, or equal to, the expected number for all causes except accidents (Shellenberger et al., 1979).

A study was also undertaken on the mortality rate up to 1978 in 606 male workers whose average age was 42 years and who had at least one year of exposure prior to 1968, at 4 European sites engaged in the production of epichlorohydrin, epoxy resins, glycerine, and other chemicals derived from epichlorohydrin. Personal exposures in 1977-78 were at, or below, a time-weighted-average of 3.78 mg/m³. Earlier exposures occasionally reached levels high enough to be irritating (38 - 95 mg/m³). The mean duration of the exposure to epichlorohydrin was 9.3 years. Of the cohort, 45% had more than 10 years of exposure. The death statistics of the countries in which the plants were situated served as a reference. A total of 10 deaths were recorded. No excess mortality for cancer (4 deaths) was observed in the entire cohort, in a subgroup with more than 10 years of exposure, or in a subgroup with 10 or fewer years of exposure (Tassignon et al., 1983).

### 8.3.3 Mutagenic effects

Cytogenetic analyses of peripheral lymphocytes were reported for 3 groups of workers. In a group of 35 workers in an epichlorohydrin-producing plant in Czechoslovakia, who were exposed for 2 years to concentrations between 0.5 and 5.0 mg/m³ air, an increase in chromatid and chromosome breaks and in aberrant cells was found, which was related to the length of exposure. Pre-exposure values were used as control data (Kucherova et al., 1977). When the same group was re-examined after another 2 years, using matched controls and with an average exposure level below 1 mg/m³ air, the number of breaks per cell was unchanged and only a slight increase was found in the number of aberrant cells (Shram, 1981). Four years later, when the average exposure level was down to 0.4 mg/m³ air, significant clastogenic effects were no longer found. The clastogenic effect of epichlorohydrin on human lymphocytes therefore seems to be related to the extent of the more recent exposures (Shram et al., 1983). Another group of 93 workers in the USA, probably exposed to average concentrations below 18.9 mg/m³ air, showed increases in aberration rates compared with 75 pre-employment individuals. Significant differences were found in the distribution of individuals with chromatid and chromosome breaks, aberrant cells, and severely damaged cells (Picciano, 1979). In the lymphocytes of 191 workers, probably exposed to average concentrations below 18.9 mg/m³ air, no significant increases in aberrations were found compared with a control group of 63 pre-employment individuals (Barna-Lloyd et al., 1979).

### 8.3.4 Effects on reproduction

The fertility status of 64 glycerol workers, in the USA, exposed to epichlorohydrin, allyl chloride, and 1.3-dichloropropene was compared with that of a control group of 63 workers who had not been engaged in handling chlorinated hydrocarbons for more than 5 years. No association was found between exposure levels, exposure duration, or exposure intensity and sperm characteristics or hormone levels. The volunteer rate was 64% (Venable et al., 1980). A similar negative result for the sperm count and hormone levels was obtained for a group of 128 workers from 2 plants compared with external chemical plant workers, who had not been exposed to any chemical known to be toxic to the testes. In one of these plants, most of the employees were exposed to epichlorohydrin concentrations below 3.8 mg/m$^3$ air. The rate of non-participating employees was high in both plants and amounted to a total of 172 workers (Milby et al., 1981).

## 9. EVALUATION OF HEALTH RISKS FOR MAN

On the basis of observations following short-term exposures to epichlorohydrin, human beings are likely to begin to experience eye and upper respiratory tract irritation at concentrations of approximately 76 mg/m³ (Wexler, 1971).

If man were equally as sensitive to epichlorohydrin as animals, lethal inhalation doses for human beings, calculated on the results of animal studies (Lawrence et al., 1972; Grigorowa et al., 1974; Laskin et al., 1980), would be likely to range from 1360 to 3000 mg/m³, with exposure lasting a few hours. At such doses, it is expected that the target organs would be the lungs, kidneys, and liver. However, such concentrations could be obtained only in the event of massive accidental spills.

Epichlorohydrin can sensitize the skin of human beings (Jirasek & Kalénsky, 1962; Von Ippen & Mathies, 1970; Fregert & Gruvberger, 1970; Beck & King, 1983).

Observations on laboratory animals have indicated that short-term exposures to epichlorohydrin for periods of from weeks to months are likely to induce kidney damage (Gage, 1959; Lawrence et al., 1972; Grigorowa et al., 1974; Quast et al., 1979b; Van Esch, 1981). Kidney damage has not been reported in man so far.

In male rodents, exposure to epichlorohydrin induced sterility (Jones, 1969; Hahn, 1970; Van Esch, 1981; John et al., 1983b). If human beings were as sensitive to epichlorohydrin as rodents, reversible decreased male fertility would occur with exposures to about 90 mg/m³ air for a few months. Such exposures are not likely to be tolerated by man for extended periods because of the irritation of the eyes and respiratory tract that occur below this level. Much higher doses are required to induce permanent sterility or sperm head abnormalities (Cooper et al., 1974; Cassidy et al., 1983). Limited epidemiological studies did not reveal effects on the fertility status of male workers exposed to epichlorohydrin (Venable et al., 1980; Milby et al., 1981).

In animals, epichlorohydrin is carcinogenic when administered by inhalation, orally, or by subcutaneous injection. The site of tumour induction has been localized to the site of administration, i.e., the nasal epithelium after inhalation, stomach epithelium after gavage and drinking-water administration, and the site of injection after injection (Konishi et al., 1980; Laskin et al., 1980; Van Esch & Wester, 1982a,b). On the basis of this evidence, together with the mutagenic effects observed in several short-term test systems, it can be concluded that epichlorohydrin could be carcinogenic

for human beings. Epidemiological studies to date have not provided evidence of malignant neoplasms in human beings, due to exposure to epichlorohydrin. However, the epidemiological data do not have a sufficient number of recorded deaths to detect a weak carcinogenic response. A longer observation time is needed before a final assessment can be made (Enterline & Henderson, 1978; Shellenberger et al., 1979; Enterline & Hartley, 1981; Tassignon et al., 1983).

# 10. SOME CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

## 10.1 Occupational Exposure

Legal maximum allowable cconcentrations[a] range from 1 mg/m³ (0.25 ppm, ceiling value) in the USSR and 2 mg/m³ (0.5 ppm, TWA) in Sweden to 4 mg/m³ (1 ppm, TWA) and a peak value of 19 mg/m³ (5 ppm) in the Netherlands and 8 mg/m³ (2 ppm, TWA) in the United Kingdom. In the USA, the American Conference of Governmental Industrial Hygienists recommends 10 mg/m³ (2 ppm, TWA). Short-term exposure limits are 20 mg/m³ (5 ppm) in the United Kingdom and 4 mg/m³ (1 ppm) in Sweden. In most regulations and guidelines, warnings are given concerning the carcinogenic nature of, and the possibility of skin penetration by, epichlorohydrin (IRPTC, 1984).

## 10.2 Ambient Air Levels

In the USSR, the maximum allowable concentration is an average of 0.2 mg/m³ per day (IRPTC, 1984).

## 10.3 Surface Water Levels

In the USSR, the maximum allowable concentration is 0.01 mg/litre (IRPTC, 1984).

## 10.4 Levels in Food

In the USA, the substance is exempted from tolerance requirements in plant products, when used according to good agricultural practice as an inert (or occasionally active) ingredient of pesticides applied to growing crops for some specified purposes (IRPTC, 1984).

## 10.5 Labelling and Packaging

The European Economic Commission regulations require that the label should state that epichlorohydrin is flammable and toxic by inhalation, in contact with skin, and if swallowed; that a container must be kept tightly closed in a well-ventilated place; that contact with the eyes should be avoided; and that medical advice should be sought, when a person is feeling unwell (IRPTC, 1984).

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[a] Values quoted in national lists.

## 10.6 Storage and Transport

The United Nations Committee of Experts on the Transport of Dangerous Goods (1984) qualifies epichlorohydrin as a toxic substance (Class 6.1) with medium danger for packing purposes (Packing Group II). Packing methods and a label are recommended. The label is:


The Inter-Governmental Maritime Consultative Organization[a] (1981) also qualifies epichlorohydrin as a toxic substance and recommends packing, stowage, and labelling method for maritime transport. The recommended labels are:



Background: red

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[a] Now the International Maritime Organization.

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