**Epichlorohydrin**

| MAK value | – |
| Peak limitation | – |
| Absorption through the skin (1961) | H |
| Sensitization (2003) | Sh |
| Carcinogenicity (1979) | Category 2 |
| Prenatal toxicity | – |
| Germ cell mutagenicity (2003) | Category 3B |

**BAT value**

| Synonyms: | 1-Chlor-2,3-epoxypropane |
| 2-(Chloromethyl)oxirane |
| 3-Chloro-1,2-propylene oxide |
| α-Epichlorohydrin |
| Chemical name (CAS): | 1-Chlor-2,3-epoxypropane |
| CAS number: | 106-89-8 |
| Structural formula: | C₃H₅ClO |
| Molecular formula: | C₃H₅ClO H₂C–CH–CH₂C–O |
| Molecular weight: | 92.53 |
| Melting point: | – 48°C |
| Boiling point at 1013 hPa: | 116°C |
| Density at 20°C: | 1.183 g/cm³ |
| Vapour pressure at 20°C: | 17 hPa |
| log P_{OW} | 0.45 |
| 1 ml/m³ (ppm) ≙ 3.84 mg/m³ | 1 mg/m³ ≙ 0.260 ml/m³ (ppm) |
The present documentation is based mainly on a BUA report (BUA 1992) and an IARC assessment (1999) and has been supplemented by recent studies on DNA adduct formation in vivo and on fertility. Epichlorohydrin, which is colourless and poorly soluble in water and has a pungent, chloroform-like odour, is converted to 3-chloro-1,2-propanediol (α-chlorohydrin) in an aqueous milieu at a pH of 7 and 20°C. The specified half-lives are 5.3–8.2 days (BUA 1992). The hydrolysis rate increases in acidic and alkaline aqueous solutions.

1 Toxic Effects and Mode of Action

Epichlorohydrin is a directly acting alkylating agent. If it is attacked by nucleophiles, it reacts preferably with the epoxide group as well as with the chloride function. The substance is rapidly metabolized. In the preferred reaction, chloropropandiols are formed, which may lead to glycidyls and glycerol derivatives. Metabolism takes place either via hydrolytic formation of 3-chloro-1,2-propanediol (spontaneously or catalyzed by epoxide hydrolase) or alternatively via a coupling to glutathione, forming GSH and mercapturic acid derivatives.

The 4-hour LC$_{50}$ for rats is about 500 ml/m$^3$. Chronic and subchronic administration of epichlorohydrin in studies with rodents causes damage to the lungs, liver, kidneys, adrenals and the CNS and leads to a reduction of haemoglobin and lymphocytes in the peripheral blood. It has a corrosive effect on the skin, eyes and mucous membranes of the respiratory tract. It has a corrosive effect on the skin, eyes and mucous membranes of the respiratory tract. Several, although not always sufficiently documented clinical findings on the sensitizing effect of epichlorohydrin on the skin are available. Animal studies provide evidence of skin sensitization. Fertility disorders and a temporary – up to a permanent – sterility are induced in male rodents from 50 ml/m$^3$ or 3 mg/kg body weight administered intraperitoneally. In pregnant rodents, epichlorohydrin is foetotoxic, but not teratogenic at maternally toxic doses. The compound is genotoxic in numerous test systems in vitro even without metabolic activation. In vivo, it causes DNA adducts, is genotoxic in Drosophila and induces SCE and chromosomal aberrations in mice. The micronucleus and dominant lethal tests led to negative results. Epichlorohydrin is locally carcinogenic in rodents. DNA adducts, SCE and chromosome lesions were observed in the lymphocytes of exposed workers. Only a few useful studies with a small number of cases are available on the question of the carcinogenic effect on humans, but no reliable conclusions can be drawn from them.

2 Mechanism of Action

Epichlorohydrin induces malignant lymphomas, hyperplasias, forestomach papillomas and carcinomas, subcutaneous fibromas and lung and pituitary tumours in rodents (Konishi et al. 1980; Laskin et al. 1980; Stoner et al. 1986; Wester et al. 1985).
It has been shown to be an initiator in the two-stage experiment (Van Duuren et al. 1974) and directly binds to target organ DNA (Prodi et al. 1986), which explains the tumourigenicity. Local irritation is due to high reactivity with nucleophiles. Lethal doses lead to paralysis of the respiratory centre (Hine et al. 1981). Reduced fertility in male rodents might be related to a reduction of sperm ATP levels. The metabolite 3-chlorolactaldehyde inhibits enzymes of glycolysis (particularly glycer-aldehyde-3-phosphatedehydrogenase; Jelks et al. 2001). Proteins which are necessary for the interaction between sperm and ovum are also diminished after administration of epichlorohydrin (Klinefelter et al. 1997).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution and elimination

After both inhalation and oral administration, more than 90% epichlorohydrin was rapidly absorbed and distributed in the organism of rats within 2–4 hours (CMA 1979 a; Gingell et al. 1985; Weigel et al. 1978). The highest systemic tissue concentrations were reached in the kidneys, intestine, liver, lacrimal glands, pancreas and spleen after administration of radioactively labelled epichlorohydrin. The highest level of radioactivity was found in the stomach after oral administration and in the nasal mucosa after inhalation. Lower radioactivity was detected in the blood, lungs, brain and sex organs (Weigel et al. 1978). At different dose levels and with various types of administration of 14C-labelled epichlorohydrin, 90% of the activity was excreted within 72 hours, i.e. 46–54% in the urine, 25–40% via the lungs and maximally 4% via the faeces (CMA 1979 a; Gingell et al. 1985).

3.2 Metabolism

After initial reaction with glutathione, epichlorohydrin was metabolized at one of the two reactive centres (Fig. 1), leading to excretable metabolites that were detected in the urine. These were the mercapturic acid derivatives N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine, S-(2,3-dihydroxypropyl)-L-cysteine and N-acetyl-S-(2,3-dihydroxypropyl)-L-cysteine. In addition, another excretable 3-chloro-1,2-propanediol formed from hydrolysis. N-Acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine (36% of the dose) and 3-chloro-1,2-propanediol (4%) are considered to be the main metabolites (Gingell et al. 1985). According to Fakhouri and Jones (1979), 3-chloro-1,2-propanediol in vivo leads to the formation of β-chlorolactic acid, which in turn yields oxalic acid. The latter metabolite was however not detected in other studies.

N-(2,3-dihydroxypropyl)valine was described as a component of a haemoglobin adduct. The coupling product was also detected in rats after intraperitoneal
Figure 1  Metabolism of epichlorohydrin in rats (Gingell et al. 1985)
administration of 40 mg/kg body weight. An increased amount of it was found in smokers (Hindsø Landin et al. 1996). The authors’ findings provide a basis for future biomonitoring.

Incubation of epichlorohydrin in the presence of human cells of lung and bronchial parenchyma led to a decrease of mutagenicity (see below), which is assumed to have been caused by rapid inactivation, perhaps by thiol formation (De Flora et al. 1984; Petruzelli et al. 1989)

4 Effects in Humans

4.1 Single exposures

An airborne concentration of 20 ml/m³ epichlorohydrin caused corrosion to the eyes and nasal mucosa after one hour. 40 ml/m³ led to irritation to the eyes and throat, which lasted for 48 hours (no other details on exposure period). 100 ml/m³ was intolerable even for the shortest period. Exposure of the eyes to the liquid substance led to opacity and necrosis of the cornea (no other details; Lefaux 1966).

Cases of severe skin burns after contact with epichlorohydrin were described. Erythema, oedema and papules were observed during some days after direct skin contact. The persons affected complained about agonizing itching. The symptoms had subsided in all persons only after about two weeks (Ippen and Mathies 1970).

Schultz (1964) reported a person who had developed chronic asthmatic bronchitis after inhalation exposure to epichlorohydrin. Severe fatty degeneration of the liver was diagnosed bioptically.

A Russian study described EEC changes at 0.3 mg/m³ (0.08 ml/m³). No abnormalities were however detected at 0.2 mg/m³ (0.053 ml/m³). The relevance of these findings is questionable (HSE 1991).

4.2 Repeat exposure

There are no data available for repeated exposure to epichlorohydrin.

4.3 Local effects on skin and mucous membranes

A 46-year-old pharmaceutical company worker developed severe erythema and oedema on the face, neck, back and hands after having continuously been exposed to epichlorohydrin for 11 months. The symptoms subsided after the worker left the workplace for two weeks, but returned when he resumed work at his former workplace. They cannot be assigned to epichlorohydrin with certainty since there was co-exposure to other substances in the synthesis of propanolol and oxprenolol (Rebandel and Rudzki 1990).
4.4 Allergenic effects

In a Dutch plant for the production of epoxy resins, 26 cases of eczema were observed among 228 male workers. All workers were occupationally exposed to epichlorohydrin and bisphenol A, the starting materials of the manufacturing process. The authors reported that the workers had unintentional skin contact with bisphenol A epoxy resins, for example during maintenance operations, although closed systems were used for manufacturing the epoxy resins and protective measures such as wearing gloves had been taken. A patch test was carried out with 19 of the 26 workers. In addition to other substances, the two epoxy resins (molecular weight 385 and 980), which were the main production products, and bisphenol A, 1% epichlorohydrin in petrolatum and 1% in isopropanol, were tested. In the patch test, a positive reaction to 1% epichlorohydrin in petrolatum was obtained in 8 cases; it was isolated in 4 cases and occurred together with reactions to epoxy resins in 4 cases. The observed delayed-type sensitization to epichlorohydrin may have been caused by two routes of sensitization: first by direct skin contact and second aero-genically by increased airborne concentrations due to the volatility of epichlorohydrin (Prens et al. 1986).

The same research group reported another 6 cases (5 workers of a plant for the production of epoxy resins and a vehicle painter) of occupational contact dermatitis, which was considered to be caused by exposure to epichlorohydrin or bisphenol A epoxy resins. In addition to other substances, an epoxy resin with an average molecular weight of 385 as well as bisphenol A and 1% epichlorohydrin in petrolatum were patch tested. All patients showed delayed-type reactions to epichlorohydrin, two of them to epichlorohydrin alone (van Joost 1988).

Another publication by this research group focussed on 5 workers of a plant for the production of epoxy resins who had developed contact dermatitis at their workplace. Here, too, the authors saw a connection with the delayed-type reaction to 1% epichlorohydrin in petrolatum, which they detected in the patch test in all 5 patients. A reaction to epichlorohydrin alone was found in 2 patients (van Joost et al. 1990).

Moreover, other research groups described case reports of contact sensitization to epichlorohydrin that had not been acquired in epoxy resin production:

One worker in a pharmaceutical plant, in which epichlorohydrin was used as a starting material for the manufacture of propranolol hydrochloride and oxprenolol hydrochloride, repeatedly developed aerogenic contact dermatitis at the workplace. Patch testing showed reactions to 0.001% epichlorohydrin in water and to 1% propranolol in petrolatum (Rebandel and Rudzki 1990).

Beck and King (1983) described a 54-year-old man who developed allergic contact dermatitis in using cement. Patch testing of the cement (10% in acetone) and of 0.1% epichlorohydrin in alcohol and 1% in petrolatum showed positive reactions, whereas testing of the controls with cement was negative. Moreover, an incompletely documented communication reported 2 cases of sensitization to epichlorohydrin as a stabilizer in technical trichloroethylene and another 4 cases of sensitiza-
tion to epichlorohydrin. All patients showed a positive reaction to 1% epichlorohydrin in ethanol in the patch test (Lambert et al. 1978).

One of 95 patients who had been tested with epoxy resin components between 1981 and 1988 reacted positively to 0.1% epichlorohydrin in petrolatum (Holness and Nethercott 1993). In further studies, none of the 308 patch-tested patients showed any reaction to 0.1% epichlorohydrin in petrolatum that was assessed as allergic, whereas an irritant reaction was described in 2/308 patients (Kanerva et al. 1999); there was no positive reaction among 839 patients (Tarveinen 1995).

In a marble-processing plant, (aerogenic) contact eczema occurred among 10/22 workers after 20-day to 2-month handling of an epoxy resin product. All 10 workers showed reactions to individual components or epoxy resin, but not to 0.1% epichlorohydrin in petrolatum (Angelini et al. 1996).

A worker who had contact with epoxy resins and propylene oxide, among others, which was used as a solvent, showed a positive reaction in the patch test to 1% propylene oxide and 1% epichlorohydrin (each in acetone) and to 0.5% cycloaliphatic epoxy resin in petrolatum after 24 and 48 hours (Morris et al. 1998).

In one case, testing a worker who used trichloroethylene for degreasing metal parts with 10% technical trichloroethylene in vegetable oil led to a pronounced reaction, whereas testing with pure trichloroethylene caused no reaction. In a further test, the patient showed a twofold positive reaction to 0.01% epichlorohydrin in isopropanol and a simple positive reaction to 0.001% epichlorohydrin, 0.07% of which was included in technical trichloroethylene as a stabilizer. In another worker, who had previously shown a patch test reaction to 10% technical trichloroethylene, re-testing provoked a simple positive reaction to 0.01% epichlorohydrin, but not to 0.001% epichlorohydrin in isopropanol (Epstein 1974).

When the author re-examined the irritant effect of epichlorohydrin in a self-experiment, a 48-hour patch test with 0.1%, 0.5% and 1% epichlorohydrin in ethanol initially induced no reaction, a reaction only following after 8–11 days. Retesting showed a positive reaction to 0.1% as early as after 48 hours while 0.01% epichlorohydrin induced only an erythematos reaction (Fregert and Gruvberger 1970). Another, although undocumented case of sensitization caused by the patch test with 1% epichlorohydrin was reported (Jolanki 1991).

### 4.5 Reproductive toxicity

Two studies of possible fertility disorders after exposure to epichlorohydrin, and in some cases simultaneous exposure to allyl chloride and 1,3-dichloropropene, were negative (Milby and Whorton 1980; Venable et al. 1980).
4.6 Genotoxicity

The DNA adduct 7-(3-chloro-2-hydroxypropyl)guanine was detected at a concentration of 0.8–7.1 adducts/10^9 nucleotides in the lymphocytes of workers who were classified as exposed to epichlorohydrin on account of the fact that they worked in an epichlorohydrin-processing plant. No details are available about the level of exposure. This adduct was not found in non-exposed control persons (Plna et al. 2000).

Significantly increased SCE frequencies were detected in the lymphocytes of 21 workers with high exposure to epichlorohydrin (4.5 years; 1.1–3.9 ml/m^3) compared with 29 non-exposed control persons adjusted for age. Smoking was excluded as the only cause of the increase. The SCE frequency in 35 workers with low exposure (4.2–7.0 years; 0.1–0.2 ml/m^3) was not significantly increased compared with the control persons (Cheng et al. 1999).

The lymphocytes of workers who were exposed to 0.4–0.86 mg/m^3 (0.11–0.23 ml/m^3) during a 12-hour shift showed no increased frequency of hprt mutations, a slight increase of micronuclei and a significant increase of SCE and high frequency cells (> 10 SCE per cell) (Hindsø Landin et al. 1997).

Kucerová et al. (1977) found significantly increased frequencies of structural chromosomal aberrations (chromatid and chromosome breaks) in the lymphocytes of workers occupationally exposed to epichlorohydrin concentrations of 0.125 to 1.25 ml/m^3. The workers were examined before the beginning of exposure (1.37 aberrations/cell), one year (1.91 aberrations/cell) and two years (2.69 aberrations/cell; p < 0.001) after the beginning of exposure. Šrám et al. (1980) re-examined 23 of these workers after 4-year exposure (3.02 aberrations/cell) and compared them with an adjusted control group (for age, smoking and drinking habits; n = 34; 2.06 aberrations/cell; p < 0.01) and with the general population (n = 21; 1.33 aberrations/cell; p < 0.01). In another study of Picciano (1979), 93 exposed persons (no concentrations specified; presumably 5 ml/m^3 TWA; age 35.8 years) and 75 control persons (age 25.2 years) were examined. The frequencies of cells with chromatid breaks, chromosome breaks and marker chromosomes (rings, dicentric chromosomes and translocations), of severely damaged cells and of the total number of damaged cells were significantly higher (p < 0.005) in the exposed group than in the control group.

4.7 Carcinogenicity

4.7.1 Case-control studies

In a nested case-control study by Bond et al. (1986) among 19,608 workers of a chemical production facility who were examined for possible health damage caused by carbon tetrachloride, a lowering of lung cancer mortality was found for the very
small subcohort of persons ever exposed to epichlorohydrin (odds ratio 0.3; 95% CI 0.1–0.9; 5 cases).

Barbone et al. (1992, 1994) studied the frequency of lung cancer and CNS cancer in a nested case-control study based on a cohort previously examined by Delzell et al. (1989). A positive association was found between potential exposure to epichlorohydrin and lung cancer after adjustment for smoking habits (odds ratio 1.7; 95% CI 0.7–4.1; 51 cases), but not in the calculation with regard to exposure period and cumulative dose. An association with potential exposure to epichlorohydrin was detected in 11 cases with CNS cancer (7 with brain tumours, 2 with meningiomas and 2 with benign tumours) and 44 controls matched for age (odds ratio 4.2; 95% CI 0.7–26). Associations with the exposure period (p = 0.11) and cumulative exposure (p = 0.08) were also observed. These results are not statistically significant. The small number of cases must be considered.

4.7.2 Cohort studies

Delzell et al. (1989) reported an excess of lung cancer in a cohort study among 2642 male workers with at least six-month exposure to epichlorohydrin. At an expected level of 0.91 (p < 0.03), 4 of 44 persons exposed in the production of the substance developed lung cancer.

Tsai et al. (1996) reported a cohort of 863 workers who had previously been examined by Enterline (1982) and Enterline et al. (1990). The rate of workers affected by lung cancer did not increase (SMR 0.7; 95% CI 0.5–1.1; 23 cases). Increased incidence rates of prostate cancer (SMR 2.3; 95% CI 1.0–4.5; 8 cases) and malignant melanomas (SMR 3.2; 95% CI 0.7–9.4; 3 cases) were found among workers whose initial exposure had taken place at least 20 years before. No relation between the frequency of developing cancer and the estimated exposure level was obtained in this study.

Olsen et al. (1994) described results of a retrospective cohort study on cancer mortality among 1064 male workers in the production areas for epoxy resins, glycerol and allyl chloride/epichlorohydrin. Exposures to epichlorohydrin in glycerol production (highest exposures) were between 1 ml/m³ and 5 ml/m³ before 1970 and below 1 ml/m³ after 1970. A total of 66 cohort members died up to 1989, 10 of them from cancer (SMR 0.5; 95% CI 0.2–0.9).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

After exposure periods between 2 and 8 hours, the LC₅₀ was 3000 to 250 ml/m³ and the 4-hour LC₅₀ for rats was 500 ml/m³ (Hine et al. 1981; Pallade et al. 1967;
Pozzani and Carpenter 1960; Šrám et al. 1981). An oral LD$_{50}$ of about 220 mg/kg body weight was determined in rodents (Hine et al. 1981; Lawrence et al. 1972; Pozzani and Carpenter 1960), and the dermal LD$_{50}$ established in rabbits was 754 (Lawrence et al. 1972) and 1038 mg/kg body weight (Hine et al. 1981). CNS, respiratory tract or renal lesions were specified as causes of death depending on the type of administration (Laskin et al. 1980; Pallade et al. 1967; Weigel et al. 1978).

In an inhalation study, the respiratory rate of rats was clearly reduced within 15 minutes at a concentration of 363 ml/m$^3$, and halved at 1342 ml/m$^3$. Marked discharge from the nasal mucosa was observed at 1963 ml/m$^3$ (Gardner et al. 1985).

5.2 **Subacute, subchronic and chronic toxicity**

5.2.1 **Inhalation**

In a 90-day study (CMA 1979 b; Quast et al. 1979), 20 female and 20 male B6C3F1 mice, Fischer 344 rats and Sprague Dawley rats were exposed to epichlorohydrin for 6 hours on 5 days per week at concentrations of 5, 25 and 50 ml/m$^3$. Whereas no effects were recorded at 5 ml/m$^3$, hyperplasia, metaplasia and inflammatory infiltrates were found in the nose, the most sensitive organ, at the higher concentrations. Damage to the kidneys, liver and adrenals of varying severity was observed in the different animal strains.

In a study described by BUA (1992), continuous inhalation of 5 ml/m$^3$ by rats over 98 days led to weight loss and morphological changes to the liver, heart, kidneys and CNS, to increased urinary coproporphyrin and an increase of leukocytes in the peripheral blood. After inhalation of 0.05 and 0.5 ml/m$^3$, these effects were not found or were only slight as compared with the controls. The validity of this study is unclear.

See also Section 5.7

5.2.2 **Oral Uptake**

See Section 5.7

5.2.3 **Dermal absorption**

Four applications of 600 mg/kg body weight were fatal for 10/10 rats and three applications of 1200 mg/kg body weight were fatal for 4/10 rats (Freuder and Leake 1941). See also Section 5.7.
5.2.4 Intraperitoneal injection

After intraperitoneal injection of 11, 22 and 56 mg/kg body weight three times a week over a period of 12 weeks, there was a dose-dependent, significant decrease of haemoglobin in the blood, an increase of eosinophils in all treated animals and a reduction of lymphocytes in the two groups treated with the highest doses. The weights of heart, liver and kidneys increased in the animals treated with 56 mg/kg body weight (Lawrence et al. 1972).

5.3 Effects on skin and mucous membranes

5.3.1 Skin

Undiluted epichlorohydrin led to severe irritation up to necrosis on the skin of rabbits within 2 to 24 hours (Pallade et al. 1967). Marked irritation was also found with a 5% solution in cottonseed oil following a 24-hour period under an occlusive bandage, whereas solutions of less than 0.3% showed no effects (Lawrence et al. 1972).

5.3.2 Eyes

Concentrations of less than 10% epichlorohydrin in cottonseed oil induced slight irritation to the rabbit eye, whereas an 80% solution caused severe irritation and corneal damage (Lawrence et al. 1972).

5.4 Allergenic effects

Skin sensitization was examined in a guinea pig maximization test in 15 guinea pigs (20 animals in the control group). Intradermal and dermal inductions were carried out with 5% epichlorohydrin in ethanol, and 1% epichlorohydrin in ethanol was used for dermal challenge. A positive reaction was observed in 9 of 15 animals (Thorgeirsson and Fregert 1977).

No sensitization was found in another, insufficiently documented maximization test in 5 guinea pigs at a test concentration of 0.01% epichlorohydrin in vegetable oil (Lawrence et al. 1972). However, this study has only limited applicability for assessment since the number of animals was too small, the test substance concentration might have been too low and insufficient information was provided on range finding. Another study in which none of 18 guinea pigs reacted after 8 intracutaneous injections during challenge (Weil et al. 1963) cannot be assessed either because of inadequate documentation (e.g. test substance concentrations not specified).

In a modified test carried out according to Landsteiner in 10 guinea pigs dermally
treated four times with epichlorohydrin for induction (as well as a single intradermal treatment with Freund’s adjuvant), all 10 animals reacted positively in the dermal challenge (no other details for example on the test substance concentration used; Rao et al. 1981).

5.5 Reproductive toxicity

5.5.1 Fertility

John et al. (1983a) exposed 30 male Sprague Dawley rats and 10 New Zealand rabbits to concentrations of 0, 0.5, 25 and 50 ml epichlorohydrin/m³ over 10 weeks for 6 hours daily on 5 days per week. The male rats (25) were mated with non-exposed female rats during and up to 10 weeks after exposure. The rate of fertilized females was significantly reduced only in the rats exposed to 50 ml/m³ during the exposure phase (tested after 2, 4, 7 and 10 weeks), but not in the matings after the end of exposure (tested after 2, 5 and 10 weeks). The number of implantations was however significantly reduced during the exposure phase at 25 ml/m³. Histopathology or the weight of the reproductive organs revealed no changes compared with the control either during exposure or after the exposure period. The exposed rabbits were only mated in the tenth week of exposure and showed no reduced fertility.

Daily oral administration of 15 mg epichlorohydrin/kg body weight for 12 days led to sterility in male SD rats after one week. The animals were fertile again one week later (Hahn 1970). The histopathological examination of the testes, epididymides, prostate and seminal vesicles on day 12 of treatment revealed no differences from the control animals. This statement is based on an abstract without data and is therefore only of limited validity.

Cooper et al. (1974) observed sterility in male SD rats lasting up to 10 weeks after five oral administrations of 50 mg/kg body weight daily and reduced fertility for the same period after a single administration of 100 mg/kg body weight (5 males per dose). The histopathological examination of the complex of testes, epididymides and ductus deferens revealed no changes up to 8 weeks after the single treatment. The validity of the study is restricted since the number of animals used was small and there was no control group.

In a study carried out by Cassidy et al. (1983) in Wistar rats, a significant increase in morphologically abnormal sperm head counts in sonicated testicular homogenates was observed in the group with higher exposure 11 days after the single oral administration of 25 and 50 mg/kg body weight. Total sperm counts were clearly reduced only in the group with lower exposure. The testis weight was unchanged in both dose groups. The examination of testicular sperm head anomalies 11 days after exposure is not an evaluated method.

Toth et al. (1989) treated male Long-Evans rats orally with 0, 12.5, 25 and 50 mg epichlorohydrin/kg body weight daily for 21 days. Following the last exposure, the
males were mated with ovariectomized, hormone-treated females (1:1) for 3 hours to observe the mating behaviour and to obtain sperm samples for analysis. Two days later, the male rats treated with the highest dose were daily mated with one female in the pro-oestrus until all males had successfully copulated once within 5 days. After 48 hours, the male rats were sacrificed for histopathological examinations. Mating behaviour, the sperm count in ejaculates, the percentages of motile sperm or sperm morphology were not affected by the treatment with epichlorohydrin. Although all males treated with 50 mg/kg body weight and day had copulated (confirmed by the formation of a vaginal plug), none of the females was pregnant as opposed to 90% of the control group animals (examination of the implantations in the uteri 15 days after observation of the vaginal plug). The histopathological examination only showed a significant reduction of the sperm count in the caudaes epididymides at the highest dose. Various motility parameters were however changed in relation to the dose (vigour and swimming pattern). The authors discussed this change as the cause of the lack of fertilization of ova in the highest dose group. It may have been due to damage to the spermatozoa energy metabolism in the epididymis induced by the metabolite 3-chloro-1,2-propanediol.

After intraperitoneal treatment of rats with 3 (n = 3) and 6 (n = 7) mg epichlorohydrin/kg body weight and day for 4 days, sperm were obtained from the proximal region of the caudaes epididymides and introduced into the uterus of stimulated female rats on day 5. On day 9, corpora lutea on the ovaries and implantations in the uteri were counted. These fertility parameters were reduced at both dose levels (Klinefelter et al. 1997).

Two examinations with the metabolite 3-chloro-1,2-propanediol provide information about the cause of the antifertile effect of epichlorohydrin.

Slott et al. (1997) treated groups of 9 male Syrian hamsters with 0, 33, 49, 66 and 83 mg 3-chloro-1,2-propanediol/kg body weight and day for 4 consecutive days, mated them on day 5 and counted the foetuses in the uteri of the fertilized females on the day before parturition. There was a dose-dependent decrease in the pregnancy rate of the sperm-positive females (100%, 78%, 67%, 22% and 0%). Epididymal sperm from the same males showed unaffected percentages of motile sperm, but sperm motility was reduced in relation to the dose. The sperm from treated males were also less likely to support in vitro fertilization (IVF). The authors concluded that 3-chloro-1,2-propanediol impairs sperm function.

A single oral administration of 5, 10, 25, 50 and 75 mg 3-chloro-1,2-propanediol/kg body weight reduced the following fertility parameters in SD rats: sperm ATP levels (3 hours and 5 days after treatment with 10 mg/kg body weight and higher), sperm motility (3 hours after treatment with 25 mg/kg body weight) and binding and penetration rates of zona pelucida-free oocytes in vitro from 10 mg/kg body weight without further increases at higher doses (Jelks et al. 2001). The authors concluded that altered ATP levels induced by 3-chloro-1,2-propanediol impair the fertilizing ability of sperm and thus confirm the assumptions of Toth et al. (1989).
5.5.2 Developmental toxicity

No prenatal toxicity was found in an inhalation study with pregnant rats and rabbits at concentrations of 2.5 and 25 ml/m³ although food consumption and weight gain of the rats were reduced at the high concentration (CMA 1979 c; John et al. 1983 b).

No teratogenic effects were observed in studies with rats and mice after oral administration of up to 160 mg/kg body weight, not even at maternally toxic doses and doses that led to reduced foetal weights (Marks et al. 1982).

5.6 Genotoxicity

A review on the genotoxic effects of epichlorohydrin is available (IARC 1999). Its results are summarized below.

5.6.1 In vitro

In most of the in vitro test systems used, epichlorohydrin induced genotoxic effects that were almost always observed even in the absence of an added metabolic activation system.

Studies in bacterial test systems showed that epichlorohydrin led to DNA lesions in *E. coli* and *B. subtilis* and induced gene mutations in *S. typhimurium* and *E. coli* strains and in *Klebsiella pneumoniae*. It caused DNA lesions, recombinations, gene mutations and aneuploidies in yeasts. Epichlorohydrin induced DNA single strand breaks and SCE in mammalian cells. Induction of gene mutations at different loci and of chromosome mutations was detected in numerous studies.

5.6.2 In vivo

In a study on the ability of epichlorohydrin to bind covalently to macromolecules, the [2-14C]-labelled substance (6.35 μmol/kg body weight) was intraperitoneally injected into mice and rats. In mice, an association of radioactivity with the purified DNA from liver, lung, kidney and stomach, which was quantitatively similar for all organs, was observed 22 hours after administration. A covalent binding index (CBI) of 23 was determined for rat liver DNA. The corresponding value for benzene was 7 and that for 1,2-dibromoethane was 515 (Prodi et al. 1986).

In another study in rats, a quantitatively similar binding to the DNA of various organs was detected 6 and 24 hours after intraperitoneal injection of [2-3H]epichlorohydrin (0.97 μmol/kg body weight), and N7-(3-chloro-2-hydroxypropyl)guanine was identified as the main DNA adduct. A CBI value of 0.6 was determined. A CBI value of 2 was found by the same working group for the chemically less reactive
propylene oxide. This discrepancy was attributed to a relatively more rapid elimination of epichlorohydrin (Hindsø Landin et al. 1999).

Epichlorohydrin induced X chromosomal recessive lethal mutations in the fruit fly *Drosophila melanogaster* (Knaap et al. 1982; Vogel et al. 1981). A third test had a negative result (Würgler and Graf 1981).

Paika et al. (1981) reported sister chromatid exchanges (SCE) in bone marrow cells of CBA/J mice after partial hepatectomy and a single intraperitoneal injection of 6 mg/kg body weight. This effect was not found without prior partial hepatectomy or in liver cells. This test was carried out as part of an interlaboratory study with coded substances and a uniform, but unusual protocol, which was also intended to record SCE in regenerating liver cells. The results should therefore be assessed very critically.

Epichlorohydrin (50 and 100 mg/kg body weight) was administered intramuscularly or subcutaneously in a host-mediated assay with NMRI mice and the *Salmonella* strains G46, TA100, TA1950, TA1951 and TA1952 (Šrá́m et al. 1976). An increased rate of revertants was found for the strains G46, TA100 and TA1950. In another assay with *Schizosaccharomyces pombe* (after intraperitoneal administration of the yeast suspension and intraperitoneal treatment or intrasanguinous administration of the yeast suspension and intravenous treatment) and two different mouse strains [CD1 and (CD1×C57BL)F1], negative results were reported by Rossi et al. (1983 b) for doses between 2 and 100 mg/kg body weight.

A third assay with NMRI mice and *Escherichia coli* strains K-12 uvrB/recA (mainly cell death of the repair-deficient bacterial strains) yielded negative results after orally administered 240 mg/kg body weight or intraperitoneally injected 140 mg/kg body weight (Hellmér and Bolcsfoldi 1992).

Increased sperm head anomalies (see Section 5.5.1) were described in a study in mice (11 days after a single oral administration of 50 mg/kg body weight; Cassidy et al. 1983). This finding was however not confirmed in a second study with intraperitoneal injection of 0.025–0.2 ml/kg body weight and day for 5 days (Topham 1980). Since morphological sperm anomalies are generally not interpreted as mutations, these results are not relevant.

Epichlorohydrin induced chromosomal aberrations in the bone marrow of ICR mice in a dose range of 1–50 mg/kg body weight (in DMSO) after single or several (on 5 consecutive days) intraperitoneal and oral administrations (Šrá́m et al. 1976).

No significant increase in the incidence of chromosomal aberrations was found in the bone marrow of CD1 mice in another study after oral administration of 50 or 200 mg/kg body weight (Rossi et al. 1983 a). The authors attribute the negative result to the fact that epichlorohydrin was no longer detectable in the blood as early as 20 minutes after oral (in DMSO) or intraperitoneal (in water) administration.

Several authors obtained uniformly negative results in micronucleus tests with mice (Asita et al. 1992; Kirkhart 1981; Salamone et al. 1981; Tsuchimoto and Matter 1981).

Nor did epichlorohydrin induce any dominant lethal mutations (Epstein et al. 1972). The originally negative result was confirmed in detailed investigations (once
intraperitoneally 5, 10 and 20 mg/kg body weight; once orally 20 and 40 mg/kg body weight; five times intraperitoneally 1 and 4 mg/kg body weight; five times orally 4 and 16 mg/kg body weight) (Šrámk et al. 1976).

5.7 Carcinogenicity

5.7.1 Short-term studies

In a lung adenoma test with intraperitoneal administration of 20, 50 and 100 mg/kg body weight to an A/J strain of mice three times a week for 8 weeks, significantly more lung tumours were induced only in the males that had received the highest dose (Stoner et al. 1986).

5.7.2 Long-term studies

Initiation-promotion studies

In an initiation-promotion study, 2 mg epichlorohydrin in 0.1 ml acetone was applied once to the skin of 30 ICR/Ha Swiss mice. After 2 weeks, 2.5 μg phorbol myristate acetate in 0.1 ml acetone was applied three times a week for a period of 385 days. From the 92nd day, skin papillomas developed in 9 animals and a skin carcinoma in one animal. A skin papilloma was observed in 3 of the mice treated with phorbol myristate acetate alone after about 224 days, whereas the control group treated with acetone alone developed no tumours (Van Duuren et al. 1974). Another study carried out with epichlorohydrin as an initiator in 20 mice was negative (Van Duuren et al. 1972).

Studies with administration of epichlorohydrin alone

In a whole-body inhalation study carried out by Laskin et al. (1980), groups of 100 male Sprague Dawley rats were subjected to lifetime exposure to 0, 10 and 30 ml epichlorohydrin/m³ (purity 99%) for 5 hours daily on 5 days per week. Two further groups of 100 and 40 male rats were exposed to 100 ml/m³ 6 hours daily for 30 days and then observed during their entire lifespan. One group of 100 male controls was sham-exposed and another group of 50 control animals remained untreated. No tumours developed after exposure to 10 ml/m³. Exposure to 30 ml/m³ yielded a nasal papilloma in one rat after 40 days and a squamous cell carcinoma of the nasal cavity in a second rat after 752 days. Among the 140 rats that had been exposed to 100 ml/m³ for 30 days, 15 rats developed squamous cell carcinomas and 2 rats developed nasal papillomas between days 330 and 933 of the study. One bronchial papilloma was observed on day 583 after the beginning of the study. Four of the exposed rats developed pituitary adenomas; a squamous cell carcinoma in the forestomach and further tumours were found in one animal. A total of 5
tumours occurred in the 150 control animals: 3 subcutaneous fibromas, 1 forestomach papilloma and 1 malignant lymphoma. The authors regarded the respiratory tract tumours as being related to exposure, unlike the other tumours.

Konishi et al. (1980) administered 0, 375, 750 and 1500 mg epichlorohydrin/l (purity not specified) to 6-week-old Wistar rats with the drinking water over a period of 81 weeks. The animals were then sacrificed and the tissues examined histopathologically. Hyperplasias and forestomach tumours were found in the treated rats in relation to the dose in the order of the specified doses: hyperplasias: 0/10, 7/9, 9/10, 12/12; papillomas: 0/10, 0/9, 1/10, 7/12; carcinomas: 0/10, 0/9, 1/10, 2/12. No tumours were detected in other tissues.

Wester et al. (1985) administered daily doses of 0, 2 and 10 mg epichlorohydrin/kg body weight with a purity of 99.5% by gavage to groups of 50 newly weaned female and male Wistar rats daily on 5 days per week over a period of 2 years. Subsequently the animals were sacrificed. A dose-dependent increase of hyperplasias, papillomas and forestomach carcinomas was observed. In the order of the specified doses, the males showed 5/50, 24/49 and 6/49 hyperplasias, 1/50, 6/49 and 4/49 papillomas and 0/50, 6/49 and 35/49 carcinomas. The females revealed 3/47, 12/44 and 7/39 hyperplasias, 2/47, 3/44 and 0/39 papillomas and 0/47, 2/44 and 24/39 carcinomas.

Fifty mice that had been treated epicutaneously with epichlorohydrin (2 mg in 0.1 ml acetone, three times a week for 580 days) developed no tumours (Van Duuren et al. 1974). This observation is consistent with the findings of Weil et al. (1963), who observed no tumour formation after lifetime application of one brush filling each of undiluted epichlorohydrin to the shaved dorsal skin of 90-day-old CH3 mice three times a week.

After subcutaneous administration of 1 mg epichlorohydrin in 0.05 ml tricaprilin once a week for 580 days, 6/50 female IVR/HA Swiss mice developed local sarcomas and one developed an adenocarcinoma. The control incidence for local sarcomas was 1/50 (Van Duuren et al. 1974). Another, similar study yielded sarcomas in 2/50 mice (Van Duuren et al. 1972).

The intraperitoneal injection of 1 mg epichlorohydrin in 0.05 ml tricaprilin, once a week for 450 days, led to lung papillomas in 11 of 30 ICR/HA Swiss mice, whereas lung papillomas were observed in 10 of 30 control animals treated with tricaprilin and a local sarcoma was observed in one mouse (Van Duuren et al. 1974).

6 Manifesto (MAK value, classification)

In animal studies epichlorohydrin is a directly acting genotoxic carcinogen with a mainly local effect, which is manifest in respiratory tract tissues after inhalation. Additionally, pituitary tumours were induced. An epidemiological study showed possible associations between exposure to epichlorohydrin and the occurrence of CNS tumours. However, the data are not sufficient to derive a conclusive evaluation
of the carcinogenicity for humans. Nor can a safe concentration be specified for hu-
mans at present. The classification of epichlorohydrin in carcinogen Category 2 has
therefore been retained.

Several, although not always adequately documented, clinical findings on the sen-
sitizing effect of epichlorohydrin on the skin are available. Animal studies provided
evidence of skin sensitization. Epichlorohydrin is therefore designated with “Sh”.
Since the effect on the respiratory tract cannot be assessed because of the lack of
data, it is not designated with “Sa”.

Epichlorohydrin not only has local effects, but also shows systemic toxicity and is
lethal after repeated epicutaneous application. However here one must take into
account that the corrosive effect may have destroyed the skin barrier. Absorption of
diluted, no longer irritant solutions, via intact skin cannot be ruled out. The sub-
stance causes systemic genotoxicity. An additional genotoxic risk must therefore be
assumed even if small amounts are absorbed via the skin. The designation with “H”
has thus been retained.

On the basis of the data available for the genotoxicity of epichlorohydrin in vivo,
particularly the cytogenetic findings and the findings on the development of epi-
chlorohydrin-specific DNA adducts among persons exposed to epichlorohydrin,
epichlorohydrin is classified in Germ Cell Mutagen group 3B.

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