Recommendation from the Scientific Committee on Occupational Exposure Limits for epichlorohydrin

SCOEL/SUM/169
September 2011
Table of content

1 Occurrence/use and occupational exposure ................................................................. 4
2 Health significance .............................................................................................................. 4
   2.1 Toxicokinetics .............................................................................................................. 4
      2.1.1 Human data ............................................................................................................ 4
      2.1.2 Animal data ............................................................................................................ 4
      2.1.3 Biological monitoring ............................................................................................. 4
   2.2 Acute toxicity ................................................................................................................ 5
      2.2.1 Human data ............................................................................................................ 5
      2.2.2 Animal data ............................................................................................................ 5
   2.3 Irritation and corrosivity .............................................................................................. 5
      2.3.1 Human data ............................................................................................................ 5
      2.3.2 Animal data ............................................................................................................ 6
   2.4 Sensitisation .................................................................................................................. 6
      2.4.1 Human data ............................................................................................................ 6
      2.4.2 Animal data ............................................................................................................ 6
   2.5 Repeated dose toxicity ............................................................................................... 7
      2.5.1 Human data ............................................................................................................ 7
      2.5.2 Animal data ............................................................................................................ 7
   2.6 Genotoxicity .................................................................................................................. 7
      2.6.1 In vitro .................................................................................................................... 8
      2.6.2 In vivo - human data ............................................................................................... 8
      2.6.3 In vivo – animal data .............................................................................................. 8
   2.7 Carcinogenicity .............................................................................................................. 9
      2.7.1 Human data ............................................................................................................ 9
      2.7.2 Animal data ............................................................................................................ 10
      2.7.3 Mode of action and cancer risk assessment .......................................................... 11
   2.8 Reproductive toxicity .................................................................................................. 12
      2.8.1 Human data ........................................................................................................... 12
      4.9.2 Animal data ........................................................................................................... 12
Recommendation .................................................................................................................. 13
References ............................................................................................................................ 15
# Recommendation from the Scientific Committee on Occupational Exposure Limits for Epichlorohydrin

8-hour TWA: not assigned (see “Recommendation” page 11)

STEL (15 min): not assigned (see “Recommendation” page 11)

Additional classification: skin notation (see “Recommendation” page 11)

BLV: not assigned

SCOEL carcinogen group: A (non-threshold carcinogen)

Carcinogenic risk assessment: see “Recommendation” (page 11)

## Substance Identification

1-chloro-2,3-epoxypropane

## Synonyms

chloropropylene oxide, chloromethyl-oxirane

## Structural Formula

\[ \text{H}_2\text{C} \quad \begin{array}{c} \text{CH} \\ \text{O} \end{array} \quad \text{CH}_2\text{Cl} \]

## CAS no.

106-89-8

## Molecular Formula

C₃H₅ClO

## Molecular Weight

92.53

## Melting Point

-48°C

## Boiling Point

116°C

## EU-Classification

- Flammable liquid and vapour (H226)
- May cause cancer (H350)
- Toxic if inhaled (H331)
- Toxic in contact with skin (H311)
- Toxic if swallowed (H301)
- Causes severe skin burns and eye damage (H314)
- May cause an allergic skin reaction (H317)

## Conversion Factor

1 ppm = 3.84 mg/m³; 1 mg/m³ = 0.260 ppm (DFG 2009)

## Criteria Documents Used

This summary is mainly based on the recent documentation of DFG (2009), which includes data reported earlier by BUA (1992), IARC (1999) and DFG (2003). This was supplemented by a recent literature search by SCOEL.
1 Occurrence/use and occupational exposure

Epichlorohydrin is a major raw chemical for the production of epoxy and phenoxy resins. It and is also used in the manufacture of glycerine, in curing propylene-based rubbers, as a solvent for cellulose esters and ethers, and in resins with high wet-strength for the paper industry (IARC 1999, NTP 2002).

2 Health significance

Epichlorohydrin is a directly acting alkylating agent. With nucleophiles it reacts preferably with the epoxide ring, but also with the chlorine function. The biological properties of the compound are related to this reactivity.

2.1 Toxicokinetics

2.1.1 Human data

Incubation of epichlorohydrin in the presence of human cells of lung and bronchial parenchyma led to a decrease of mutagenicity, which is likely to be related to rapid metabolic inactivation (De Flora et al. 1984).

2.1.2 Animal data

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 1979a; Gingell et al. 1985; Weigel et al. 1978). After application of radiolabeled epichlorohydrine, the highest systemic tissue concentrations were reached in the kidneys, intestine, liver, lacrimal glands, pancreas and spleen. 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 1979a; Gingell et al. 1985).

After initial reaction with glutathione, epichlorohydrin is metabolized, leading to metabolites that are detected in the urine. These are 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, a likewise excretable 3-chloro-1,2-propanediol is 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.

2.1.3 Biological monitoring

The analysis of haemoglobin adducts derived from epichlorohydrin has been proposed as a means of biological monitoring. As epichlorohydrin is a bifunctional alkylating agent (Romano et al. 2007), the reaction with the N-terminal valine of haemoglobin occurs either with its chlorine or with its epoxide moiety. N-(2,3-Dihydroxypropyl)valine was first described as haemoglobin adduct. This was also detected in rats after intraperitoneal administration of 40 mg/kg body weight. An increased amount of it was found in smokers (Hindsø Landin et al. 1996).

Later, Bader et al. (2009) described a method of quantitation of the adduct N-(3-chloro-2-hydroxypropyl)valine in human haemoglobin. This adduct was found in the blood of persons exposed to epichlorohydrin at a freight train accident.
These methods could provide a basis for biomonitoring in the future. However, more detailed occupational field studies are lacking so far.

2.2 Acute toxicity

2.2.1 Human data

An airborne concentration of 20 ppm epichlorohydrin caused corrosion to the eyes and nasal mucosa after one hour. 40 ppm led to irritation to the eyes and throat, which lasted for 48 hours (no other details on exposure period). 100 ppm 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 biopictally.

2.2.2 Animal data

After exposure periods between 2 and 8 hours, the LC50 was 3000 to 250 ppm and the 4-hour LC50 for rats was 500 ppm (Hine et al. 1981; Pallade et al. 1967; Pozzani and Carpenter 1960; Sräm et al. 1981). An oral LD50 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 LD50 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 ppm, and halved at 1342 ppm. Marked discharge from the nasal mucosa was observed at 1963 ppm (Gardner et al. 1985).

2.3 Irritation and corrosivity

2.3.1 Human data

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 workstation. 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).

Luo et al. (2004) investigated the influence of the glutathione S-transferase hGSTM1 and hGSTT1 genes on the toxic effect of epichlorohydrin. In hGSTM1 null genotype workers, there was a dose-response of lung function tests (FEV1, FEV1/FVC, MMEF) for epichlorohydrin exposure, but not in the hGSTM1 non-null genotype workers. The exposure was found to be significantly associated with a decreased FEV1 value (p = 0.09) and a decreased MMEF value (p = 0.053) after adjusting for other factors. The hGSTM1 null genotype was found to be significantly associated with a decreased FEV1 value (p = 0.038), decreased FEV1/FVC value (p = 0.056), and decreased MMEF value (p = 0.012) after adjusting for other factors. The study was interpreted to indicate that obstructive lung abnormalities and small airway lung damage are associated with epichlorohydrin exposure.

The irritancy of epichlorohydrine to the respiratory tract is in accordance with human experience after an accidental release of epichlorohydrine (Basting et al. 2006)
2.3.2 Animal data

Experimental exposures of rats and rabbits to 25 or 50 ppm epichlorohydrine (6h/d, 5d/wk for 10 weeks) caused severe irritating effects to the nasal turbinates (John et al. 1983a). In mice, the RD50 concentration was assessed to be 687 ppm. In addition to the nasal cavity, this concentration induced lesions in the lower respiratory tract, when applied 6h/d for 5 days (Buckley et al. 1984).

2.4 Sensitisation

2.4.1 Human data

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 aerogenically 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 solvent 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 (for a detailed description, see DFG 2009).

2.4.2 Animal data

Skin sensitization was examined in a Guinea pig maximization test in 15 Guinea pigs (20 animals in the control group). Intra-dermal 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).

2.5 Repeated dose toxicity

2.5.1 Human data

No published data are available.

2.5.2 Animal data

In a 90-day study (CMA 1979b; 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 ppm. Whereas no effects were recorded at 5 ppm, 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 ppm by rats over 98 days led to weight loss and morphological changes to the liver, heart, kidneys and CNS, an increase in urinary coproporphyrin and an increase of leukocytes in the peripheral blood. After inhalation of 0.05 and 0.5 ppm, these effects were not found or were only slight as compared with the controls. The validity of this study is unclear.
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). 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).
Adult male and female Sprague-Dawley rats received epichlorohydrin via gavage in distilled water for 10 consecutive days at dose levels of 3, 7, 19, and 46 mg/kg per day, and for 90 days at dose levels of 1, 5, and 25 mg/kg per day. Epichlorohydrin did not adversely effect mortality, but toxicity, at the higher doses, was evident by losses in body weight gain and organ weights, reductions in food and water consumption, and in the hematological and microscopic examinations in both study periods. Significant decreases in erythrocyte count, hemoglobin, and hematocrit levels were found in the high dose level in males after 10 and 90 days. Dose-related increases in kidney and liver weights were observed in both sexes at 25 mg/kg per day in the 90-day study and in various organs for both 19 and 46 mg/kg per day in the 10-day study. Histopathological examination identified the forestomach as the primary target organ for both sexes and in both studies with significant dose-related increases in mucosal hyperplasia (acanthosis) and hyperkeratosis. Based on the data presented, a lowest observable adverse effect level (LOAEL) for oral exposure of Sprague-Dawley rats to epichlorohydrin was 3 mg/kg per day for 10 days and 1 mg/kg per day was suggested as the no observed adverse effect level (NOAEL) for a 90 day oral exposure (Daniel et al. 1996).

2.6 Genotoxicity

Detailed reviews on the genotoxic effects of epichlorohydrin are available by Giri (1997), IARC (1999) and Kolman et al. (2002). The main results are summarized below.
2.6.1 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 (IARC 1999). The main adduct obtained after reaction of epichlorohydrin with 2'-deoxynucleosides in vitro is 7-(3-chloro-2-hydroxypropyl)guanine, resulting from reaction of the epoxide ring of epichlorohydrine (Singh et al. 1996). Another aspect of DNA interaction is the formation of interstrand DNA-crosslinks (Romano et al. 2007).

Holzer et al. (2008) incubated rat and human nasal mucosa cells with epichlorohydrin and used the COMET assay as an endpoint of genotoxicity. In contrast to the cells derived from rats, pronounced interindividual differences in susceptibility were found with the human samples.

2.6.2 In vivo - human data

The DNA adduct 7-(3-chloro-2-hydroxypropyl)guanine (vs.) was detected at a concentration of 0.8–7.1 adducts/10⁹ 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 (Pina et al. 2000). Significantly increased sister chromatid exchange (SCE) frequencies were detected in the lymphocytes of 21 workers with high exposure to epichlorohydrin (4.5 years; 1.1–3.9 ppm) 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 ppm) 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/m³ (0.11–0.23 ppm) 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 ppm. 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 ppm 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.

2.6.3 In vivo – animal data

In a study on the ability of epichlorohydrin to bind covalently to macromolecules, the [2-¹⁴C]-labelled substance (6.35 micromol/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 (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 (Srám 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 (CD1xC57BL)F1], negative results were reported by Rossi et al. (1983b) 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 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 (Srám 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. 1983a). 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) (Srám et al. 1976).

2.7 Carcinogenicity

2.7.1 Human data

In a nested case-control study by Bond et al. (1986) among 19608 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.

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.

2.7.2 Animal data

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).

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).

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 ppm 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 ppm. Exposure to 30 ppm 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 ppm 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 was 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).

2.7.3 Mode of action and cancer risk assessment

Epichlorohydrin is reasonably anticipated to be a human carcinogen based on the experimental data (IARC 1999, NTP 2002). The primary experimental tumours are local. When administered by gavage, it induced forestomach tumours of rats. By inhalation (minimal effective concentration: 30 ppm), it induced tumours of the nasal cavity in rats. Subcutaneous injection produced local sarcomas in mice.

The local effect of epichlorohydrin on the rat nasal tissue has a parallel in the effect of the non-chlorinated compound, propylene oxide (for documentation, see SCOEL/SUM 161). Similar to propylene oxide, the induction of local cell proliferation appears to be a decisive factor (Girolamo et al. 2006). A particular impact of peak concentrations of epichlorohydrine for the local cancer risk is in-line with this view (Ginsberg et al. 1996).

In vitro, the genotoxicity (cell transformation tests and DNA strand break induction) of both chemically related compounds has been compared, and epichlorohydrine turned out to be about 10-times more genotoxic than propylene oxide (Kolman and Dusinská 1995, Kolman et al. 1997).

Similar to propylene oxide, the protective effect of a rapid metabolic detoxification of epichlorohydrin is of relevance (Hindskall et al. 1999).

By contrast to propylene oxide, epichlorohydrin is a bifunctional alkylating agent and induces DNA interstrand cross-links (Romao et al. 2007). Therefore, although there are similarities between epichlorohydrin and propylene oxide, differences in the modes of action ought to be considered.

The validity of the present database for the derivation of a quantitative assessment of human cancer risk has been a matter of debate. On the one hand, some authors consider the quantitative experimental data as not sufficient for such an assessment (Ginsberg et al. 1996, Kolman et al. 2002). On the other hand, the Dutch Expert Committee on Occupational Standards (DECOS) has used a linear extrapolation from the experimental data as a default method and estimated the additional lifetime cancer risk for epichlorohydrin to be $4 \times 10^{-3}$ for 40 years of human occupational exposure to 0.19 mg/m³, and accordingly $4 \times 10^{-3}$ for 40 years of occupational exposure to 19 mg/m³ (DECOS 2000).
2.8 Reproductive toxicity

2.8.1. Human data

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).

4.9.2 Animal data

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 ppm 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 ppm. 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 Sprague-Dawley 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 percentage 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 caudae 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 caudae 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).

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

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).

**Recommendation**

Epichlorohydrin is a directly acting genotoxic carcinogen in animal studies with a mainly local effect, with the target in the upper respiratory tract tissues after inhalation. Pituitary tumours were also induced experimentally. An epidemiological study showed possible associations between exposure to epichlorohydrin and the occurrence of CNS tumours. However, these data are not sufficient to derive a conclusive evaluation of the carcinogenicity for humans, nor can a safe concentration be specified for humans at present (2.7.3).

On the basis of the data on the genotoxicity of epichlorohydrin in vivo, particularly cytogenetic findings and findings on the development of epichlorohydrin-specific DNA adducts among persons exposed to epichlorohydrin, epichlorohydrin has been classified in germ cell mutagen.

In consequence of the clearcut direct genotoxicity, epichlorohydrin is categorised into the SCOEL carcinogen group A as a non-threshold carcinogen (Bolt and Huici-Montagud 2008). Accordingly, the derivation of a health-based OEL is not possible. An assessment of human cancer risk based on the available experimental data is accompanied with great uncertainties (2.7.3). The Dutch Expert Committee on Occupational Standards (DECOS) has applied a linear extrapolation from the experimental data as a default method and estimated the additional lifetime cancer risk for epichlorohydrin to be 4 x 10^-5 for 40 years of human occupational exposure to 0.19 mg/m^3, and accordingly 4 x 10^-3 for 40 years of occupational exposure to 19 mg/m^3 (DECOS 2000).
Although analytical methods have been described, which may serve as a basis for biological monitoring (2.3.1), occupational field studies are lacking, so that a recommendation for a biological monitoring guidance value cannot be given. Several, although not always adequately documented, clinical findings on the sensitizing effect of epichlorohydrin on the skin are available. Animal studies provided evidence of skin sensitization.

Epichlorohydrin not only has local effects, but also shows systemic toxicity and is lethal after repeated epicutaneous application. However, here the corrosive effect may have destroyed the skin barrier. Absorption of diluted, no longer irritant solutions via intact skin cannot be ruled out. Therefore, a skin notation is recommended.

In view of the above, SCOEL strongly recommends avoiding occupational exposure to epichlorohydrin.
References


BUA [Beratergremium für Altstoffe - Advisory Committee on Existing Chemicals of Environmental Relevance] (1992) Epichlorhydrin, BUA Stoffbericht 90, Hirzel Wissenschaftliche Verlagsgemeinschaft, Stuttgart


Cassidy SL, Dix KM, Jenkins T (1983) Evaluation of a testicular sperm head counting technique using rats exposed to dimethyloxethyl phthalate (DMEP), glycerol alpha-monomonochlorohydrid (GMCH), epichlorohydrin (ECH), formaldehyde (FA), or methyl methanesulfonate (MMS). Arch Toxicol 53:71–78


CMA [Chemical Manufacturers Association] (1979a) Pharmacokinetics of epichlorohydrin (EPI) administered to rats by gavage or inhalation. Toxicology Research Laboratory Health and Environmental Sciences, Dow Chemical USA, Midland, MI

CMA (1979b) Epichlorohydrin – subchronic studies. I. A 90-day inhalation study in laboratory rodents. Toxicology Research Laboratory Health and Environmental Sciences, Dow Chemical USA, Midland, MI

CMA (1979c) Epichlorohydrin – subchronic studies. IV. The effects of maternally inhaled epichlorohydrin on rat and rabbit embryonal and fetal development. Toxicology Research Laboratory Health and Environmental Sciences, Dow Chemical USA, Midland, MI


Epstein E (1974) Allergy to epichlorohydrin masquerading as trichloroethylene allergy. Contact Dermatitis Newslett 16: 475


Fregert S, Gruvberger P (1970) Sensitization to epichlorohydrin and cross-sensitization to propylene oxide. Contact Dermatitis Newsletter 8: 172


IARC (International Agency for Research on Cancer) (1999) IARC monographs on the evaluation of carcinogenicity of chemicals to man, ed. 71, IARC, Lyon, 603–628


van Joost T, Roëysanto ID, Satyawana I (1990) Occupational sensitization to epichlorohydrin (ECH) and bisphenol-A during the manufacture of epoxy resin. Contact Dermatitis 22: 125–126


Klinefelter GR, Laskey JW, Ferrell J, Suarez JD, Roberts NL (1997) Discriminant analysis indicates a single sperm protein (SP22) is predictive of fertility following exposure to epididymal toxicants. J Androl 18: 139–150


Lefaux R (1966) Chemie und Toxikologie der Kunststoffe, Krauskopf-Verlag für Wirtschaft, Mainz


Srám RJ, Zudová Z, Kuleshov NP (1980) Cytogenetic analysis of peripheral lymphocytes in workers occupationally exposed to epichlorohydrin. Mutat Res 70: 115–120