EPICHLOROHYDRIN

Data were last reviewed in IARC (1976) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

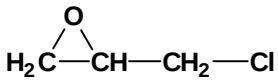
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 106-89-8
Chem. Abstr. Name: (Chloromethyl)oxirane
IUPAC Systematic Name: 1-Chloro-2,3-epoxypropane
Synonym: Chloropropylene oxide

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_3H_5ClO Relative molecular mass: 92.53

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid (Verschueren, 1996)
(*b*) *Boiling-point*: 117°C (Verschueren, 1996)
(*c*) *Melting-point*: –48°C (Verschueren, 1996); –25°C (Lewis, 1993; Budavari, 1996)
(*d*) *Solubility:* Insoluble in water; miscible with ethanol, diethyl ether, chloroform, trichloroethylene and carbon tetrachloride; immiscible with petroleum hydrocarbons (Budavari, 1996)
(*e*) *Vapour pressure:* 1.6 kPa at 20°C; relative vapour density (air = 1), 3.3 (Verschueren, 1996)
(*f*) *Flash-point:* 40°C, open cup (Budavari, 1996)
(*g*) *Explosive limits:* upper, 21.0%; lower, 3.8% (American Conference of Governmental Industrial Hygienists, 1991)
(*h*) *Conversion factor:* $mg/m^3 = 3.78 \times ppm$

1.2 Production and use

Total world production figures for epichlorohydrin are not available. In the United States, production increased from 156 thousand tonnes in 1973 to 250 thousand tonnes in 1975 and 213 thousand tonnes in 1978. Epichlorohydrin was also produced in Czechoslovakia, France, Germany, the Netherlands and the USSR (WHO, 1984).

Epichlorohydrin is a major raw material for epoxy and phenoxy resins, and is 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 (Lewis, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1990–93 CAREX database for 15 countries of the European Union (Kauppinen *et al.*, 1998) and the 1981–83 National Occupational Exposure Survey (NOES) in the United States (NOES, 1997), approximately 25 000 workers in Europe and as many as 80 000 workers in the United States were potentially exposed to epichlorohydrin (see General Remarks). Occupational exposures to epichlorohydrin may occur in its use as a solvent and in resin production and use, the manufacture of glycerine and use of propylene-based rubbers.

1.3.2 *Environmental occurrence*

Epichlorohydrin may be released to the atmosphere and in wastewater during its production and use in manufacture of epoxy resins, glycerine and other chemicals and other uses. It has been detected at low levels in wastewater, groundwater and ambient water samples (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 1.9 mg/m^3 as the 8-h time-weighted average threshold limit value for occupational exposures to epichlorohydrin in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

The World Health Organization has established a provisional international drinking-water guideline for epichlorohydrin of 0.4 µg/L (WHO, 1993).

2. Studies of Cancer in Humans

2.1 Industry-based studies

Delzell *et al*. (1989) conducted a cohort study of workers at a dye and resin manufacturing plant. The full cohort consisted of 2642 male workers who had been employed at the facility for at least six months between 1952 and 1985. The study follow-up was from 1952 to 1985 and was 94% complete; 106 cancer deaths were observed (97 expected).

Seven cancers were observed (7.3 expected) among 230 workers in the plastics and additives production area where there was potential for exposure to epichlorohydrin. An excess of lung cancer was observed among the 44 workers who had been employed in the production of epichlorohydrin, which had been manufactured at the plant between 1961 and 1965 (levels of exposure not reported) (standardized mortality ratio (SMR), [4.4]; 4 observed versus 0.91 expected; $p = 0.03$).

Tsai *et al.* (1996) reported on a small cohort of workers in the United States who were potentially exposed to epichlorohydrin and isopropanol. Enterline (1982) and Enterline *et al.* (1990) had previously reported on this cohort, which consisted of 863 workers employed at two chemical manufacturing facilities between 1948 and 1965. Exposure was classified by a panel of industrial hygienists and current and former employees as nil, light, moderate or heavy. Exposures during 'early production periods' were estimated to be 10–20 ppm [38–76 mg/m^3]. Results from the latest follow-up were reported for 1960–93 with comparisons made with local county mortality rates. There were 175 deaths (SMR, 0.6; 95% confidence interval (CI), 0.5–0.7) and 60 cancer deaths observed (SMR, 0.8; 95% CI, 0.6–1.0). A number greater than expected of cancers of the prostate (SMR, 2.3; 95% CI, 1.0–4.5; $n = 8$) and malignant melanomas (SMR, 3.2; 95% CI, 0.7–9.4; $n = 3$) were observed among workers at least 20 years after first exposure, but the relative risks did not vary with estimated level of exposure. The SMR for lung cancer was 0.7 (95% CI, 0.5–1.1; 23 cases) in the total population and did not increase with level of exposure or time since first exposure.

Olsen *et al*. (1994) reported on the results of a retrospective cohort mortality study of workers in the United States with potential exposure to epichlorohydrin and allyl chloride (see this volume). The cohort consisted of 1064 men employed in the epoxy resin, glycerine and allyl chloride/epichlorohydrin production areas of a large chemical facility between 1957 and 1986. Follow-up was carried out until 1989. Mortality was compared with national rates and company rates for other facilities. Average exposures to epichlorohydrin were estimated to be generally below 1 ppm [3.8 mg/m^3] in the epoxy resin area, in the allyl chloride/epichlorohydrin area and, after 1970, in the glycerine area. Exposures to epichlorohydrin were estimated to be between 1 and 5 ppm [3.8 and 18.9 mg/m^3] in the glycerine area before 1970 and occasionally in some jobs in the allyl chloride/epichlorohydrin area, although respiratory protection may have been worn by these workers. There were 66 deaths (SMR, 0.8; 95% CI, 0.6–1.0). Ten cancers were observed (SMR, 0.5; 95% CI, 0.2–0.9, compared with national rates) in the entire cohort and no associations between site-specific cancer risks and exposure to epichlorohydrin were observed.

Nested case–control studies for lung (Barbone *et al*., 1992) and central nervous system (Barbone *et al*., 1994) neoplasms were conducted using the full cohort of dye and resin manufacturing workers reported on by Delzell *et al*. (1989). Exposure was assessed on an ordinal scale based on job titles, work areas, and potential for contact. When the work histories of 51 lung cancer cases were compared with those of 102 controls matched for year of birth, an association was observed with potential epichlorohydrin

exposure (odds ratio, 1.7; 95% CI, 0.7–4.1) after adjustment for smoking. However, no association was observed with duration or cumulative level of exposure. For 11 central nervous system tumour cases compared with 44 similarly matched controls, an association was observed with potential exposure to epichlorohydrin (odds ratio, 4.2; 95% CI, 0.7–26) and the magnitude of this association increased with both duration of exposure (p = 0.11 for trend test) and cumulative level of exposure (p = 0.08 for trend test). Two of the four epichlorohydrin-exposed central nervous system tumour cases had meningiomas.

Bond *et al*. (1986) conducted a nested case–control study of lung cancer among a cohort of 19 608 male chemical workers in the United States (Bond *et al*., 1985). Further details of the study are reported in Section 2.2 of the monograph on carbon tetrachloride in this volume. Ever having been exposed to epichlorohydrin was associated with a decreased risk of lung cancer (odds ratio, 0.3; 95% CI, 0.1–0.9; 5 exposed cases).

3. Studies of Cancer in Experimental Animals

Epichlorohydrin was tested for carcinogenicity in mice by subcutaneous injection: it produced local sarcomas. It was active as an initiator in a two-stage carcinogenesis study in mice (IARC, 1976).

3.1 Oral administration

Rat: Groups of 18 male outbred Wistar rats, six weeks of age, were administered 0, 375, 750 or 1500 mg/L (ppm) epichlorohydrin [purity unspecified] in the drinking-water for 81 weeks, at which time the experiment was terminated. All rats were necropsied and tissues examined histologically. Forestomach lesions ranging from hyperplasia or papilloma to carcinoma occurred in treated rats: hyperplasia, 0/10, 7/9, 9/10 and 12/12; papilloma, 0/10, 0/9, 1/10 and 7/12; carcinoma, 0/10, 0/9, 1/10 and 2/12 in the control, low-dose, mid-dose and high-dose groups, respectively. Tumours at other sites were not reported (Konishi *et al*., 1980).

Groups of 50 female weanling Wistar rats were administered 0, 2 or 10 mg/kg bw epichlorohydrin (purity, 99.5%) daily by gavage on five days per week for two years. All surviving animals were killed. The incidence of forestomach hyperplasia, papilloma and carcinoma was increased in both sexes (Table 1). The incidence of tumours at other sites was not increased (Wester *et al*., 1985).

3.2 Inhalation exposure

Rat: Groups of 100 male Sprague-Dawley rats, eight weeks of age, were exposed by whole-body inhalation to 0, 10 or 30 ppm (0, 38 or 113 mg/m^3) epichlorohydrin (99% pure) for 6 h per day on five days per week for lifetime. Two further groups of 100 and 40 male rats were exposed to 100 ppm (380 mg/m^3) for 6 h per day on 30 days followed by observation for lifetime. A group of 100 male controls was sham-exposed and a group

Table 1. Incidence of forestomach lesions in Wistar rats treated with epichlorohydrin

Sex	Lesion	Control	Dose of epichlorohydrin	
			2 mg/kg bw	10 mg/kg bw
Males	Hyperplasia	5/50	24/40	6/49
	Papilloma	1/50	6/49	4/49
	Carcinoma		6/49	35/49
Females	Hyperplasia	3/47	12/44	7/39
	Papilloma	2/47	3/44	
	Carcinoma		2/44	24/39

From Wester *et al*. (1985)

of 50 controls was untreated. In rats exposed to 10 ppm epichlorohydrin, no neoplastic changes were reported. In the 30-ppm group, one rat had a nasal papilloma and one a squamous-cell carcinoma of the nasal cavity after 402 and 752 days, respectively. In rats exposed 30 times to 100 ppm and observed for lifespan, 17 rats developed 15 squamous-cell carcinomas and two papillomas of the nasal epithelium between 330 and 933 days from the start of exposure. 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. No tumour of these types was found in controls (Laskin *et al*., 1980).

3.3 Intraperitoneal administration

Mouse: In a strain A lung adenoma assay, intraperitoneal injection of total doses of 20, 50 or 100 mg/kg bw epichlorohydrin given three times per week for eight weeks significantly increased the number of lung tumours per mouse in males treated with the highest dose (0.80 ± 0.68, compared with 0.47 ± 0.63 in controls; $p < 0.01$) but not in other groups (Stoner *et al*., 1986).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Incubation of epichlorohydrin in the presence of human bronchial and lung parenchymal tissues led to a decrease in its mutagenicity, suggesting rapid inactivation (Petruzzelli *et al*., 1989), probably via thiol binding (De Flora *et al*., 1984).

Recently, a biomonitoring method for epichlorohydrin by measuring *N*-(2,3-dihydroxypropyl)valine in haemoglobin has been developed. The adduct level is increased in cigarette smokers. The same adduct can be detected in rats after intraperitoneal administration of 40 mg/kg bw epichlorohydrin (Landin *et al*., 1996).

4.1.2 *Experimental systems*

Early toxicokinetic studies were summarized by Šrám *et al*. (1981). In rats, epichlorohydrin is rapidly absorbed via oral or inhalation routes and practically all of the compound is eliminated via urine as metabolites or via lungs as CO_2.

After an oral dose of 6 mg/kg bw to rats, approximately 38% of the dose was exhaled as CO_2, 50% was excreted as metabolites in the urine and 3% was present in faeces (Gingell *et al*., 1985). Concentrations were highest in liver, kidney and forestomach. The initial metabolic reactions are conjugation of the epoxide with glutathione, which is probably a chemical, not enzymatic, reaction, and hydration of the epoxide by epoxide hydrolase. The major metabolites in urine are *N*-acetyl-*S*-(3-chloro-2-hydroxypropyl)-L-cysteine (36% of the dose) and 3-chloro-1,2-propanediol (α-chlorohydrin) (4%).

The absorption and elimination of epichlorohydrin in mice are rapid after oral administration. The diol metabolite, 3-chloro-1,2-propanediol, was detected in plasma (Rossi *et al*., 1983a).

4.2 Toxic effects

4.2.1 *Humans*

Fomin (1966) found that exposure to epichlorohydrin at a concentration of 0.3 mg/m^3, which represents a threshold value for the smell of that substance for the most sensitive human subjects, produced changes in the electroencephalogram pattern, whereas a concentration of 0.2 mg/m^3 was inactive.

Several cases of severe skin burns have resulted from local contact with epichlorohydrin (Hine & Rowe, 1963). Six workers with occupational exposure to epichlorohydrin, four of whom worked in an epoxy resin plant, were diagnosed with contact dermatitis, apparently due to epichlorohydrin (van Joost, 1988). A 46-year-old worker in a pharmaceutical plant quickly developed pronounced swelling and erythema of the face, dorsum of the hands and neck after 11 months of epichlorohydrin exposure, which regressed completely after a two-week absence from work (Rebandel & Rudzki, 1990). There was a recurrence of the skin changes three days after returning to work. The patient was also exposed to other reagents in the process of propranolol and oxprenolol synthesis. One case of severe epichlorohydrin poisoning occurred in a 39-year-old laboratory assistant; initial irritation of the eyes and throat was followed by chronic asthmatic bronchitis; successive biopsies established a high degree of fatty infiltration of the liver (Schultz, 1964).

Several hours after having been exposed for about 30 min to fumes of epichlorohydrin, a 53-year-old worker complained of burning of the nose and throat, coughing, chest congestion, running nose, eye tenderness and headache, followed by nausea (United States National Institute for Occupational Safety and Health, 1976).

Studies of effects of co-exposures to epichlorohydrin and allyl chloride on heart disease mortality are described in the monograph on allyl chloride (see this volume).

4.2.2 *Experimental systems*

The intraperitoneal LD_{50} values of epichlorohydrin range from 120 to 170 mg/kg bw for rats, mice, guinea-pigs and rabbits. Oral LD_{50} values in mice and rats are 240 and 260 mg/kg bw, respectively. The LD_{50} following oral percutaneous administration to rabbits is 760 mg/kg bw. The median time to death of mice inhaling an air–vapour mixture containing 7200 mg/m^3 epichlorohydrin was 9 min (Lawrence *et al*., 1972).

Epichlorohydrin can cause central nervous depression and irritation of the respiratory tract; death is generally due to depression of the respiratory centre (Hine & Rowe, 1963). Nephrotoxicity is a cumulative effect of epichlorohydrin poisoning (Hine & Rowe, 1963; Pallade *et al*., 1968); renal insufficiency occurred within 24–48 h in approximately 80% of rats that had been given 125 mg/kg bw of the compound (Pallade *et al*., 1968). Epichlorohydrin produces extreme irritation when tested intradermally, dermally or intraocularly in rabbits (Lawrence *et al*., 1972). It caused skin sensitization in 60% (9/15) of female albino guinea-pigs tested using a 24-h occluded patch test with a 1.0% concentration in ethanol applied two weeks after a sensitivity induction protocol that consisted of three intradermal injections (5% w/v in ethanol) and one topical application using a 48-h occluded patch (5% w/v in ethanol) (Thorgeirsson & Fregert, 1977).

In a 12-week, subacute toxicity test in rats given intraperitoneal injections of epichlorohydrin, treatment led to a dose-related decrease in haemoglobin values; an increase in segmented neutrophils was seen with doses of 56 mg/kg bw and a reduction in the proportion of lymphocytes occurred at doses of 22 and 56 mg/kg bw (Lawrence *et al*., 1972). An increased leukocyte count was observed in animals exposed chronically to vapours of epichlorohydrin in air at concentrations of 2 mg/m^3 (Fomin, 1966). The maximum tolerated dose in a 13-week subacute study in rats following oral administration of epichlorohydrin was 45 mg/kg bw per day (Oser *et al*., 1975).

Daniel *et al*. (1996) treated adult male and female Sprague-Dawley rats with epichlorohydrin by gavage at dose levels of 3, 7, 19 and 46 mg/kg bw per day for 10 consecutive days and dose levels of 1, 5 and 25 mg/kg bw per day for 90 days. Although mortality was not affected by treatment, other adverse effects were observed. Significant decreases in both final mean body weight and total body weight gain were observed for both sexes at the highest dose level (46 mg/kg bw/day) in the 10-day dosing study; however, this was not observed in the 90-day study. Significant increases in relative kidney weights were seen at the two highest doses (19 and 46 mg/kg bw/day) for both sexes at the end of the 10-day dosing study and in the high-dose group (25 mg/kg bw/day) of each sex at the end of the 90-day study. Relative liver weights were significantly increased in the female high-dose group (46 mg/kg bw/day) and in the two highest-dose groups (19 and 46 mg/kg bw/day) for males in the 10-day dosing study. Increased relative liver weights were also observed in the highest-dose group of each sex at the end of the 90-day dosing study. In addition, relative testis weights were

increased in males at the highest dose in the 10-day study. All other relative organ weights were unchanged in both sexes relative to controls. Significant decreases in erythrocyte count, haemoglobin and haematocrit levels were found in the male high-dose group after 10 and 90 days of epichlorohydrin dosing. In both sexes and in both the 10- and 90-day gavage studies, induction of dose-related lesions of the forestomach was observed. Histopathological examination revealed a range of inflammatory and epithelial alterations in both sexes. The most pronounced effect was a dose-related increase in mucosal hyperplasia and hyperkeratosis. The authors suggested that the lowest observable adverse effect level (LOAEL) for oral exposure for both sexes of Sprague-Dawley rats to epichlorohydrin is 3 mg/kg bw per day for 10 days and 1 mg/kg bw per day for a 90-day oral exposure.

Groups of 20 male and 20 female B6C3F_1 mice, Fischer 344 rats and Sprague-Dawley rats were exposed for 6 h per day on five days per week during a 90-day period to 0, 5, 25 or 50 ppm [0, 19, 95 or 189 mg/m^3] epichlorohydrin vapour. The following clinical signs were evaluated: body weight, haematology, urine analysis, blood serum urea nitrogen, serum alkaline phosphatase activity, serum glutamic pyruvic transaminase activity, serum glutamic oxaloacetic transaminase activity, serum glucose and gross pathology. In addition to histological examination, organ weights and organ:body weight ratios of brain, heart, liver, kidneys, testes, spleen and thymus were determined; the nasal turbinates were the most sensitive organ. Dose-related microscopic changes were seen in the nasal turbinates at 25 and 50 ppm. Other parameters evaluated showed minimal treatment-related effects at the 50 ppm level. No treatment-related effect was detected at the 5 ppm level of exposure (Quast *et al.*, 1979).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

Venable *et al*. (1980) studied the fertility status of male employees engaged in the manufacture of glycerine (exposure to epichlorohydrin, allyl chloride and 1,3-dichloropropene). This study included 64 exposed workers and 63 control volunteers. Reproductive medical histories were taken, and laboratory studies included blood hormone analysis and analysis of semen specimens (volume, viscosity, percentage progressive sperm, percentage motile sperm, sperm count (MM/cc), percentage viable sperm and percentage normal sperm forms). The results showed no detrimental effect on fertility due to exposure to epichlorohydrin. Milby and Whorton (1980) also reported no sperm-count suppression among workers exposed to epichlorohydrin, in contrast to parallel observations on workers exposed to 1,2-dibromo-3-chloropropane.

4.3.2 *Experimental systems*

Repeated oral administration of 15 mg/kg bw epichlorohydrin produced reversible infertility in male rats within seven days: fertility was restored after dosing had been discontinued for approximately one week (Hahn, 1970). In male mice given single intraperitoneal doses of 5, 10 or 20 mg/kg bw epichlorohydrin, single oral doses of 20 or

40 mg/kg bw, five daily intraperitoneal doses of 1 and 5 mg/kg bw or five daily oral doses of 4 and 20 mg/kg bw, fertility was reduced in some groups but no dose–response relationship was observed (Šrám *et al*., 1976). Toth *et al*. (1989) found that male Long-Evans rats exposed by gavage to 50 mg/kg bw per day for 21 days (a period covering development of the late-stage spermatids and their transit through the cauda epididymis) had totally impaired fertility. Fertility was not evaluated at lower doses. This effect was said to be consistent with the spermatozoal metabolic lesions reported for α-chlorohydrin, a metabolite of epichlorohydrin.

Marks *et al*. (1982) evaluated the teratogenic effect of epichlorohydrin administered by gavage to CD-1 mice and CD rats during days 6–15 of gestation. Rats were given doses of 40, 80 and 160 mg/kg bw per day and mice were given 80, 120 and 160 mg/kg bw per day. Epichlorohydrin caused a significant reduction in the weight gain of pregnant rats at 80 mg/kg per day compared with the control group. However, there was no evidence of teratogenicity in the rat fetuses even at the highest dose level (160 mg/kg bw/day), which caused the death of some of the treated dams. Epichlorohydrin did not produce a significant increase in the average percentage of malformed mouse fetuses even at 160 mg/kg bw per day, a dose that killed three of 32 treated dams. The highest two doses in the mouse study (120 and 160 mg/kg bw per day) caused a significant ($p < 0.05$) reduction in average fetal weight compared with controls.

4.4 Genetic and related effects

4.4.1 *Humans*

Chromosomal aberrations were observed in three studies of lymphocytes of workers occupationally exposed to concentrations of epichlorohydrin ranging from 0.5 to 5.0 mg/m^3 (Kučerová *et al.*, 1977; Šrám *et al.*, 1980) and in one other study in which epichlorohydrin concentrations were not given (Picciano, 1979).

4.4.2 *Experimental systems* (see Table 2 for references)

The genetic and related effects of epichlorohydrin have been reviewed (Giri, 1997).

Epichlorohydrin induced DNA damage in *Escherichia coli* and *Bacillus subtilis*. It was mutagenic to *Salmonella typhimurium* and *E. coli* in the presence and absence of exogenous metabolic activation. Epichlorohydrin induced gene mutation in *Krebsiella pneumoniae* without exogenous metabolic activation. It induced DNA damage, gene conversion, recombination, aneuploidy and mutation in *Saccharomyces cerevisiae* and gene mutations in *Schizosaccharomyces pombe* and *Neurospora crassa*. It was mutagenic in the *Drosophila melanogaster* sex-linked recessive lethal mutation assay.

Epichlorohydrin induced DNA single-strand breaks but not unscheduled DNA synthesis in mammalian cell cultures. It induced gene mutations in mouse lymphoma L5178Y cells and gene mutations, sister chromatid exchanges and chromosomal aberrations in Chinese hamster cells *in vitro*.

Diphtheria toxin-resistant mutants were observed in human epithelial type EUE cells but not in human lung fibroblasts exposed to epichlorohydrin *in vitro*. Epichlorohydrin

Table 2. Genetic and related effects of epichlorohydrin

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
PRB, Induction of SOS response in *S. typhimurium* TA1535/pSK1002	+	NT	60	Nakamura *et al*. (1987)
ECD, *Escherichia coli pol A*, differential toxicity	+	+	250	Tweats (1981)
ECL, *Escherichia coli pol A*, differential toxicity	+	NT	10	Rosenkranz & Leifer (1980)
BSD, *Bacillus subtilis rec* strains, differential toxicity	–	NT	10500	Elmore *et al*. (1976)
BSD, *Bacillus subtilis rec* strains, differential toxicity	–	(+)	92300	Laumbach *et al*. (1977)
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	–	0.1	Kada *et al*. (1980)
SAF, *Salmonella typhimurium*, forward mutation	NT	+	1000	Skopek *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	92.5	Elmore *et al*. (1976)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	100	Šrám *et al*. (1976)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	220	Laumbach *et al*. (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	13.9	Andersen *et al*. (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	0.04	Bridges (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	0.03	Simmon (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	250	Wade *et al*. (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	462	Bartsch *et al*. (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	27.8	Hemminki & Falck (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	46.2	Stolzenberg & Hine (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	25	Connor *et al*. (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	90	Eder *et al*. (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	25	Martire *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	31	Nagao & Takahashi (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	0.5	Richold & Jones (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	–	9.25	Voogd *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	46	Bartsch *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	+	200	Imamura *et al*. (1983)

Table 2 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	250	Hughes *et al*. (1987)
SA2, *Salmonella typhimurium* TA102, reverse mutation	+	+	250	Hughes *et al*. (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	11.7	Andersen *et al*. (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	NT	0.06	Biles *et al*. (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	NT	0.2	Bridges (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	NT	250	Wade *et al*. (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	46.2	Stolzenberg & Hine (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	25	Rowland & Severn (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	5	Simmon & Shepherd (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	–	250	Richold & Jones (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	NT	46	Bartsch *et al*. (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	250	De Flora *et al*. (1984)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	(+)	–	250	Richold & Jones (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	(+)	–	250	Richold & Jones (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	4625	Stolzenberg & Hine (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	50	Richold & Jones (1981)
SAS, *Salmonella typhimurium* G46, reverse mutation	+	NT	1000	Šrám *et al*. (1976)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	+	NT	27.8	Hemminki & Falck (1979)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	+	NT	NG	Hemminki *et al*. (1980)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	+	+	10	Gatehouse (1981)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	+	+	120	Matsushima *et al*. (1981)
EC2, *Escherichia coli* WP2, reverse mutation	+	+	295	Matsushima *et al*. (1981)
ECR, *Escherichia coli* WP2 *uvrA*/pkM101, reverse mutation	+	+	120	Matsushima *et al*. (1981)
ECR, *Escherichia coli* 3431M31 *uvrB*, reverse mutation	+	+	200	Mohn *et al*. (1981)
KPF, *Klebsiella pneumoniae*, forward mutation	+	–	18	Voogd *et al*. (1981)

Table 2 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
KPF, *Klebsiella pneumoniae*, forward mutation	+	NT	9	Knaap *et al*. (1982)
SSD, *Saccharomyces cerevisiae* rad strains, differential toxicity	+	+	100	Sharp & Parry (1981a)
SCG, *Saccharomyces cerevisiae* D7, gene conversion	+	NT	6010	Vashishat *et al*. (1980)
SCG, *Saccharomyces cerevisiae* D4, gene conversion	–	–	166	Jagannath *et al*. (1981)
SCG, *Saccharomyces cerevisiae* JD1, gene conversion	+	NT	50	Sharp & Parry (1981b)
SCG, *Saccharomyces cerevisiae* D7, gene conversion	+	NT	100	Zimmermann & Scheel (1981)
SCH, *Saccharomyces cerevisiae* D7, homozygosis	+	NT	6010	Vashishat *et al*. (1980)
SCH, *Saccharomyces cerevisiae* 'race XII', homozygosis	–	(+)	100	Kassinova *et al*. (1981)
SCR, *Saccharomyces cerevisiae* D7, reverse mutation	+	NT	6010	Vashishat *et al*. (1980)
SCR, *Saccharomyces cerevisiae* XV185-14C, reverse mutation	+	NT	48	Mehta & von Borstel (1981)
SZF, *Schizosaccharomyces pombe*, forward mutation	+	+	18.5	Migliore *et al*. (1982)
SZF, *Schizosaccharomyces pombe*, forward mutation	+	NT	92	Rossi *et al*. (1983a)
SZF, *Schizosaccharomyces pombe*, forward mutation	–	+	1	Loprieno (1981)
SZF, *Schizosaccharomyces pombe*, forward mutation	+	+	74	Rossi *et al*. (1983b)
SZR, *Schizosaccharomyces pombe*, reverse mutation	+	NT	180	Heslot (1962)
NCR, *Neurospora crassa*, reverse mutation	(+)	NT	14000	Kolmark & Giles (1955)
SCN, *Saccharomyces cerevisiae* D6, aneuploidy	+	NT	50	Parry & Sharp (1981)
ASM, *Arabidopsis* species, mutation	+	NT	NG	Acedo & Rédei (1982)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		472	Vogel *et al*. (1981)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		0.2%	Wurgler & Graf (1981)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		472 inj × 1	Knaap *et al*. (1982)
DIA, DNA single-strand breaks, rat hepatocytes *in vitro*	+	NT	28	Sina *et al*. (1983)
DIA, DNA single-strand breaks, mouse lymphoma L5178Y cells *in vitro*	+	NT	96	Garberg *et al*. (1988)

Table 2 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	NT	4.6	Probst *et al*. (1981)
GCO, Gene mutation, Chinese hamster ovary CHO cells *in vitro*	+	NT	25	Amacher & Zelljadt (1984)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	NT	100	Nishi *et al*. (1984)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	+	68.3	Jotz & Mitchell (1981)
G51, Gene mutation, mouse lymphoma L5178Y cells, *hprt* locus *in vitro*	+	NT	46	Knaap *et al*. (1982)
G51, Gene mutation, mouse lymphoma L5178Y cells, ouabain resistance *in vitro*	+	NT	24	Amacher & Dunn (1985)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	+	4.8	Evans & Mitchell (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	+	100	Natarajan & van Kesteren-van Leeuwen (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	–	10	Perry & Thomson (1981)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	NT	500	Nishi *et al*. (1984)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	(+)	9.25	von der Hude *et al*. (1987)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	NT	23	von der Hude *et al*. (1991)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	NT	9.2	Sasaki *et al*. (1980)
CIC, Chromosomal aberrations, Chinese hamster lung CHL fibroblasts *in vitro*	+	NT	47	Ishidate *et al*. (1981)

Table 2 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	+	100	Natarajan & van Kesteren-van Leeuwen (1981)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	NT	15	Asita (1989)
CIA, Chromosomal aberrations, rat epithelial-like liver cells *in vitro*	–	NT	20	Dean & Hodson-Walker (1979)
GIH, Gene mutation, human HSC172 lung fibroblasts, diphtheria toxin resistance *in vitro*	–	–	100	Gupta & Goldstein (1981)
GIH, Gene mutation, human epithelial-type EUE cells, diphtheria toxin resistance *in vitro*	+	NT	46	Perocco *et al*. (1983)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	+	9	White (1980)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	0.0009	Carbone *et al*. (1981)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	4.6	Norppa *et al*. (1981)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	0.09	Kucerová & Polívková (1976)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	0.009	Šrám *et al*. (1976)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	18.5	Norppa *et al*. (1981)
HMM, Host-mediated assay, *Salmonella typhimurium* TA60, G46 in ICR mouse peritoneal fluid	+		100 im × 1	Šrám *et al*. (1976)
HMM, Host-mediated assay, *Schizosaccharomyces pombe* in CD1 and C57BL × CD1 mice	–		200 ip × 1	Rossi *et al*. (1983c)
HMM, Host-mediated assay, *Escherichia coli* K12 in NMRI mice	–[c]		240 po × 1	Hellmér & Bolcsfoldi (1992)
SVA, Sister chromatid exchange, CBA/J mouse bone marrow *in vivo*	+[d]		6 ip × 1	Paika *et al*. (1981)

Table 2 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
MVM, Micronucleus test, ICR mice *in vivo*	–		100 ip × 2	Kirkhart (1981)
MVM, Micronucleus test, $B6C3F_1$ mice *in vivo*	–		160 ip × 2	Salamone *et al*. (1981)
MVM, Micronucleus test, CD-1 mice *in vivo*	–		100 ip × 2	Tsuchimoto & Matter (1981)
MVM, Micronucleus test, ddY mice *in vivo*	–		200 ip × 2	Asita *et al*. (1992)
CBA, Chromosomal aberrations, ICR mouse bone marrow *in vivo*	+		1 ip × 1	Šrám *et al*. (1976)
CBA, Chromosomal aberrations, CD-1 mouse bone marrow *in vivo*	–		200 po × 1	Rossi *et al*. (1983a)
DLM, Dominant lethal test, ICR/Ha Swiss mice	–		150 ip × 1	Epstein *et al*. (1972)
DLM, Dominant lethal test, ICR mice	–[e]		20 po × 5	Šrám *et al*. (1976)
BID, DNA binding (covalent), calf thymus DNA *in vitro*	+	NT	15	Hemminki (1979)
BVD, DNA binding, BALB/c mouse and Wistar rat liver, lung, kidney and stomach *in vivo*	+		0.6 ip × 1	Prodi *et al*. (1986)
SPM, Sperm morphology, CBA × BALB/c mice *in vivo*	–		200 ip × 5	Topham (1980)
SPR, Sperm morphology, Wistar rats *in vivo*	+		50 po × 1	Cassidy *et al*. (1983)

[a] +, positive; (+), weakly positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; NG, not given; im, intramuscular; inj, injection; ip, intraperitoneal; po, oral

[c] Positive when mice were treated intraperitoneally with 180 mg/kg bw/day epichlorohydrin

[d] Positive only when mice received partial hepatectomy before treatment

[e] Negative also after a single intraperitoneal dose of 20 mg/kg bw or a single oral dose of 40 mg/kg bw

also increased the frequency of sister chromatid exchanges and chromosomal aberrations in cultures of human lymphocytes.

In a single study, epichlorohydrin bound to DNA of mice and rats treated *in vivo*. One study reported that sister chromatid exchanges were induced in the bone marrow of partially hepatectomized CBA/J mice treated with epichlorohydrin by a single intraperitoneal injection. Sister chromatid exchange frequencies in mice that did not receive partial hepatectomy before treatment with epichlorohydrin were comparable to the control frequencies. One of two studies reported that epichlorohydrin induced chromosomal aberrations in mouse bone marrow. Positive results were also reported for epichlorohydrin in the mouse host-mediated assay in one of three studies. In single studies, epichlorohydrin caused sperm head abnormalities in rats but not mice. It did not induce micronuclei or dominant lethal mutations in mice *in vivo*.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to epichlorohydrin may occur during the production and use of resins, glycerine and propylene-based rubbers and its use as a solvent. It has been detected at low levels in water.

5.2 Human carcinogenicity data

The risk of cancer has been investigated among four populations exposed to epichlorohydrin. In one cohort study, an excess of lung cancer was observed among the small number of workers employed in the production of epichlorohydrin. A nested case–control study within this population found a weak association between epichlorohydrin and lung cancer but risk was not related to level of exposure. In another nested case–control study based on the same cohort, a weak association with central nervous system tumours was observed which appeared to be related to the level of exposure. A small excess of lung cancer was observed in another cohort, but in a third no excess of cancer was observed. In a case–control study of lung cancer nested within a further cohort of chemical workers, a significantly decreased risk of lung cancer was associated with epichlorohydrin exposure. All results were based on relatively small numbers.

5.3 Animal carcinogenicity data

Epichlorohydrin was tested in rats by oral administration, inducing papillomas and carcinomas of the forestomach, and by inhalation, inducing papillomas and carcinomas of the nasal cavity. It was also tested in mice by skin application and by subcutaneous and intraperitoneal injection; it gave negative results after continuous skin painting but was active as an initiator on skin. It produced local sarcomas after subcutaneous injection and was active in a mouse-lung tumour bioassay by intraperitoneal injection.

5.4 Other relevant data

Epichlorohydrin is itself a reactive epoxide and is metabolized by binding to glutathione and by hydration via epoxide hydrolase. The same haemoglobin adduct has been detected in humans and rats. In man, epichlorohydrin causes local damage upon contact exposure. In rodents, toxicity to kidneys, liver and forestomach has been observed. After inhalation, the most sensitive target organ is the nasal turbinates. Epichlorohydrin induces genetic damage in most bacterial and mammalian tests *in vitro* or *in vivo*, not requiring the presence of a metabolic activation system.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of epichlorohydrin.

There is *sufficient evidence* in experimental animals for the carcinogenicity of epichlorohydrin.

Overall evaluation

Epichlorohydrin is *probably carcinogenic to humans (Group 2A)*.

In making the overall evaluation, the Working Group took into consideration the known chemical reactivity of epichlorohydrin and its direct activity in a wide range of genetic tests.

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