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VOLUME 101

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

1,3-DICHLORO-2-PROPANOL

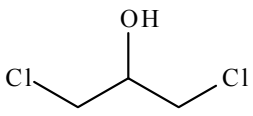
1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

From Merck Index (2010) and SciFinder (2010)
Chem. Abstr. Serv. Reg. No.: 96-23-1
Chem. Abstr. Name:
1,3-Dichloro-2-propanol
IUPAC Systematic Name:
1,3-Dichloropropan-2-ol
Synonyms: 1,3-DCP; α-dichlorohydrin; 1,3-dichlorohydrin; 1,3-dicloro-2-hydroxypropane; 1,3-dichloroisopropanol; 1,3-dichloroisopropyl alcohol; 1,3-dichloropropanol; enodrin; glycerol α,γ-dichlorohydrin; 2-glycerol 1,3-dichlorohydrin; propanol, 1–3-dichloro-; α-propenyldichlorohydrin; sym-glycerol dichlorohydrin
EINECS No.: 202-491-9

1.1.2 Structural and molecular formulae and relative molecular mass



$C_3H_6Cl_2O$
Relative molecular mass: 128.99

1.1.3 Chemical and physical properties of the pure substance

From Beilstein (2010), Merck Index (2010), and SciFinder (2010)
Description: Liquid with an ethereal odour
Boiling-point: 174.3 °C at 760 mm Hg
Melting-point: -4 °C
Density: 1.3530–1.3670 g/cm^3 at 20 °C
Refractive index: 1.4830 at 20 °C
Solubility: Soluble in water (up to 1:9); miscible with alcohol, ether and acetone

1.1.4 Technical products and impurities

No data were available to the Working Group.

1.1.5 Analysis

A review of the analysis of chloropropanols in general is provided in the *IARC Monograph* on 3-monochloro-1,2-propanediol (3-MCPD) in this volume and in Wenzl *et al.* (2007). 1,3-Dichloro-2-propanol (1,3-DCP) cannot be analysed by phenylboronic acid derivatization, which is the most commonly applied procedure for the analysis of 3-MCPD, because phenylboronic acid only reacts with diols.

Similarly to that of 3-MCPD, trace analysis of 1,3-DCP is difficult, especially because its volatility hampers the concentration of solvent extracts without loss of analyte. The solvent extracts frequently include several compounds that potentially co-elute with 1,3-DCP on gas

chromatography (GC), and might not be identified correctly when using electron capture detection (ECD). The major problem of these approaches is that they are time-consuming and require a considerable degree of skill and experience in laboratory manipulations (Crews *et al.*, 2002). Steam distillation with extraction into co-distilled petroleum ether:ethyl acetate was therefore proposed to determine 1,3-DCP with subsequent GC/ECD of the underivatized analyte (Van Rillaer & Beernaert, 1989), and an automated headspace (HS) sampling procedure for the analysis of 1,3-DCP was developed (Crews *et al.*, 2002). The advantages of this method are its rapidity, sensitivity and the need for little sample preparation. It provides accurate identification of 1,3-DCP using mass spectrometry (MS), and precise quantification using a deuterium-labelled internal standard. It requires almost no sample preparation or reagents and a large batch of samples can be processed unattended overnight (Crews *et al.*, 2002). Nyman *et al.* (2003) judged this HS-GC-MS method to be very fast and simple but with the disadvantage that simultaneous analysis of 3-MCPD and 1,3-DCP is not possible because the analysis of the underivatized compounds requires different GC columns. In addition, the low-molecular-weight ion fragments of the underivatized compounds render this method susceptible to interference and less reliable for confirmation of the identity of the analyte.

Analysis of heptafluorobutyrate derivatives was found to be more labour-intensive but had the advantage of analysing both 1,3-DCP and 3-MCPD during the same GC-MS run (Hamlet & Sutton, 1997). Moreover, the heptafluorobutyrate derivative produced higher-molecular-weight ion fragments that were less susceptible to interference.

Methods for the analysis of 1,3-DCP in different matrices are summarized in Table 1.1.

1.2 Production and use

1.2.1 Production

1,3-DCP can be synthesized in a continuous process by the reaction of hydrochloric acid with epichlorohydrin (Richey, 2000). The hypochlorination of allyl chloride generates a mixture of the glycerol dichlorohydrins, 2,3- and 1,3-DCP, at a ratio of approximately 7:3 (Richey, 2000; Liu *et al.*, 2005).

1,3-DCP is listed in the CHEMCATS database (SciFinder, 2010) as being available from 88 suppliers worldwide in amounts up to bulk quantities. Data summarized by the National Toxicology Program (NTP, 2005) of the United States of America showed that the production volume in 1998 was reported to be between more than 453 600 kg and 4.5 million kg. Unconfirmed information stated that, from the point of view of volume, almost all of the chlorohydrins produced are immediately converted into epoxides, such as epichlorohydrin, and the small quantities sold on the commercial market are used in specialty applications. It was reported that the compound is not produced for the commercial market in the USA (Richey, 2000).

1.2.2 Use

1,3-DCP is used in large quantities as an intermediate in epichlorohydrin production (NTP, 2005). Dehydration of 1,3-DCP with phosphoryl chloride forms 1,3-dichloropropene, a soil fumigant. Chlorination of 1,3-DCP (or 2,3-DCP) with phosphorous pentachloride gives 1,2,3-trichloropropane. Hydrolysis of dichlorohydrins has been used in the production of synthetic glycerol (NTP, 2005). 1,3-DCP has been used as solvent for hard resins and nitrocellulose, in the manufacture of photographic and Zapon lacquer, as a cement for celluloid and as a binder for water colours (Merck Index, 2010). Its use as a dye fixative/anti-fading agent in detergent formulations appears to be historical, based on a limited patent survey (NTP, 2005).

Table 1.1 Selected methods for the analysis of 1,3-dichloro-2-propanol in various matrices

Matrix	Analytes	Pre-treatment	Clean up	Derivatization	Detection	LOD for 1,3-DCP (µg/kg)	Reference
HVP	1,3-DCP	Micro-steam distillation, solvent extraction	-	None	GC-ECD	10	Van Rillaer & Beernaert (1989)
Seasonings	2-MCPD, 3-MCPD, 1,3-DCP, 2,3-DCP	Water, pH adjustment	Extrelut	None	GC-MS SIM	50	Wittmann (1991)
Paper	3-MCPD, 1,3-DCP	Acetonitrile extraction	-	BSTFA	GC-MS SIM	40	Bodén *et al.* (1997)
Soya sauce	1,3-DCP, 2,3-DCP	Ammonium sulfate	HS Extraction	None	GC-MS	3	Crews *et al.* (2002)
HVP	2-MCPD, 3-MCPD, 1,3-DCP, 2,3-DCP	5M NaCl solution	Extrelut, two-stage extraction	HFBI	GC-ECD, GC-MS	10	van Bergen *et al.* (1992)
Water	3-MCPD, 1,3-DCP (and bromo-propanediols)	Ethyl acetate extraction	-	HFBA	GC-ECD	1.7	Matthew & Anastasio (2000)
Soya sauce	1,3-DCP, 3-MCPD	5M NaCl solution	Silica gel (60 mesh)	HFBA	GC-MS SIM	5	Chung *et al.* (2002)
Soya sauce, flavouring	2-MCPD, 3-MCPD, 1,3-DCP, 2,3-DCP	5M NaCl solution	Extrelut	HFBA-Et_3N	GC-MS EI SIM or NCI SIM	3 (EI), 0.6 (NCI)	Xu *et al.* (2006)
Various foods	1,3-DCP, 3-MCPD	Saturated NaCl solution	Aluminium oxide	HFBA	GC-MS SIM	1	Abu-El-Haj *et al.* (2007)
Water	1,3-DCP	Adjustment to pH 4, addition of NaCl for salting out	HS-SPME	BSTFA	GC-MS/MS	0.4	Carro *et al.* (2009)
Water	1,3-DCP	$(NH_4)_2SO_4$ addition	LLE with ethyl acetate	None	GC-MS SIM	0.1	Schuhmacher *et al.* (2005)
Seasoning	3-MCPD, 1,3-DCP, 2,3-DCP	No data	No data	TSIM	GC-MS SIM	0.20	Cao *et al.* (2009)
Soya sauce	1,3-DCP, 3-MCPD	NaCl addition	HS-SPME	MSTFA	GC/MS SIM	0.41	Lee *et al.* (2007)
Soya and related sauces	1,3-DCP	5M NaCl solution	Extrelut	HFBI	GC/MS SIM	0.06	Nyman *et al.* (2003)

BSTFA, bis(trimethylsilyl)trifluoroacetamide; DCP, dichloropropanol; 1,3-DCP, 1,3-dichloro-2-propanol; 2,3-DCP, 2,3-dichloro-1-propanol; EI, electron-impact ionization; GC-ECD, gas chromatography with electron capture detection; GC-MS, gas chromatography-mass spectrometry; GC-MS/MS, gas chromatography-tandem mass spectrometry; HFBA, heptafluorobutyric anhydride; HFBI, heptafluorobutyrylimidazole; HS, headspace; HS-SPME, headspace solid phase microextraction; HVP, acid-hydrolysed vegetable protein; LLE, liquid liquid extraction; LOD, limit of detection; MCPD, monochloropropanediol; 2-MSTFA, *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide; NaCl, sodium chloride; NCI, negative chemical ionization; SIM, selected ion monitoring; TSIM, 1-trimethylsilylimidazole

Updated from Wenzl *et al.* (2007)

1.3 Occurrence

1.3.1 Natural occurrence

1,3-DCP is not known to occur as a natural product.

1.3.2 Occupational exposure

1,3-DCP may occur as a hydrolysis product of epichlorohydrin, which is a major raw material in the chemical and paper industry (see IARC, 1999). Concerns have therefore been raised that 1,3-DCP may be present in products made with epichlorohydrin as well as in workplace air. However, it was reported that 1,3-DCP is not usually detected, except in the headspace of improperly vented storage tanks (Dulany *et al.*, 2000). Industrial accidents may result in fatal intoxications (see Section 4.1.1; Iwasa *et al.*, 1992; Haratake *et al.*, 1993; Shiozaki *et al.*, 1994).

Workers using acrylic paint in spray-painting operations may be exposed to low concentrations of 1,3-DCP present as an impurity in the paint (NTP, 2005). 1,3-DCP may also be present as an impurity in bis(2-chloro-1-methylethyl)ether and the quaternary ammonium compound, *N*-(3-chloro-2- hydroxypropyl) trimethylammonium chloride (Dextrosil, Dowquat 188). Workers may be exposed indirectly to 1,3-DCP, which is a metabolite of 1,2,3-trichloropropane and tris(1,3-dichloro-2-propyl)phosphate (NTP, 2005).

1.3.3 Occurrence in food

1,3-DCP is a foodborne contaminant that can be formed during the processing of different foodstuffs (Wenzl *et al.*, 2007). It was first recognized in 1978 at the Institute of Chemical Technology in Prague (Velíšek *et al.*, 1978) in acid-hydrolysed vegetable protein, a seasoning ingredient that is widely used in a variety of processed and prepared foods. It generally occurs together with 3-MCPD, which is regarded as the most abundant chloropropanol found in foodstuff (Wenzl *et al.*, 2007) (see the *IARC Monograph* on 3-MCPD in this volume for details on the mechanisms of their formation in food). Limited data have shown a linear relationship between the concentrations of 1,3-DCP and 3-MCPD in food (JECFA, 2007).

In general, 1,3-DCP occurs at lower concentrations than 3-MCPD, except in meat products. Due to the analytical problems described above, and especially because 1,3-DCP cannot be detected by many of the methods developed for the analysis of 3-MCPD, data on the occurrence of 1,3-DCP worldwide are more sparse than those for 3-MDPC (Table 1.2). Similarly to 3-MCPD, 1,3-DCP occurs most abundantly in soya sauce and soya sauce-based products.

The international, representative average dietary exposure of the general population was estimated to be 0.051 μg/kg body weight (bw) per day, while an exposure of 0.136 μg/kg bw per day was estimated for high consumers (including children). Intakes were calculated by linking data on individual consumption with those on mean occurrence, using the actual body weight of consumers reported in consumption surveys (JECFA, 2007).

For secondary school students in China, Hong Kong Special Administrative Region, the average exposure was estimated to be 0.003–0.019 μg/kg bw per day, while that for high consumers was 0.009–0.040 μg/kg bw per day (Yau *et al.*, 2008).

Further exposure may occur when paper treated with epichlorohydrin-based wet resins are used in contact with food, such as tea bag paper, coffee filters, absorbent paper packaged with meats and cellulose casings (for ground meat products such as sausages) (NTP, 2005). Similar to bound 3-MCPD, bound 1,3-DCP may also be present in foods in the form of esters (Seefelder *et al.*, 2010).

Table 1.2 Summary of the distribution-weighted concentration of 1,3-dichloro-2-propanol in soya sauce and soya sauce-based products, in other foods and in food ingredients from various countries, 2001–06[a]

Product	LOQ (mg/kg)	No.	*n* < LOQ	Mean[b] (mg/kg)	Maximum (mg/kg)
Soya sauce and soya sauce-based products	0.002–0.15	484	371	0.110	9.84
Meat and meat products	0.005	99	51	0.019	0.11
Fish and sea food	0.005	29	26	0.0025	0.024
Food ingredients (including HVPs and malt extracts)	0.010	56	13	0.008	0.070

[a] Includes data of surveys before intervention to reduce occurrence had been undertaken by government or industry.
[b] Data below the level of detection or LOQ have been assumed to be half of those limits and the mean was weighted according to the number of samples per country.
HVP, acid-hydrolysed vegetable protein; LOQ, limit of quantification
Data summarized from JECFA (2007)

1.3.4 Environmental occurrence

1,3-DCP and related contaminants can be found in epichlorohydrin polyamine polyelectrolytes used in drinking-water treatment chemicals (coagulation and flocculation products) (NTP, 2005).

Similar to occupational exposure, environmental exposure to 1,3-DCP predominantly occurs from wastes containing epichlorohydrin. Single studies reported that 1,3-DCP was present in pulp mill effluents and spent kraft paper bleaching liquors, as well as in a municipal waste landfill leachate (NTP, 2005). Each of more than 300 river water samples from 32 sites in Austria that were analysed contained 1,3-DCP at concentrations of less than 1.0 µg/L, which was the quantification limit of the study (Schuhmacher *et al.*, 2005).

1.4 Regulations and guidelines

The current regulation of the US Food and Drug Administration for the use of dimethylamine epichlorohydrin copolymer resin establishes a limit for residues of 1,3-DCP in the resin of 1000 ppm (Code of Federal Regulations, 2010).

Fewer limits have been set for the levels of 1,3-DCP in food than for those of 3-MCPD (see the *Monograph* in this volume), because its concentration is generally lower than that of 3-MCPD (NTP, 2005). Hence, the regulatory control of 3-MCPD decreases the need for specific limits on 1,3-DCP, although some countries have imposed maximum limits (Australia/New Zealand, 0.005 mg/kg in soya/oyster sauces; Switzerland, 0.05 mg/kg in savoury sauces; USA, 0.05 mg/kg in acid-hydrolysed vegetable protein) (Hamlet & Sadd, 2009).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

3.1 Oral administration

See Table 3.1

3.1.1 Rat

Groups of 80 male and 80 female Wistar KFM/Han rats were administered 0 (control), 27 (low dose), 80 (mid dose) or 240 (high dose) mg/L [0, 0.21, 0.62 or 1.86 mmol/L] 1,3-DCP in the drinking-water for up to 104 weeks. These

Table 3.1 Carcinogenicity study of 1,3-dichloro-2-propanol administered in the drinking-water to rats

Strain (sex) Duration	Dosing regimen Animals/group at start	Incidence and/or multiplicity of tumours	Significance (Peto trend test)	Comments
Wistar (M) up to 104 wk	0, 27, 80 and 240 mg/L (0, 2.1, 6.3 and 19 mg/kg bw per d) 80/group	Liver (hepatocellular adenoma): 1/80, 0/80, 1/80, 0/80		Ten rats per group were killed after 26, 52 and 78 wk of treatment
		Liver (hepatocellular carcinoma): 0/80, 0/80, 2/80, 11/80***	***$P < 0.001$	
		Kidney (renal tubule adenoma): 0/80, 0/80, 3/80, 10/80***	***$P < 0.001$	
		Kidney (renal tubule carcinoma): 0/80, 0/80, 0/80, 1/80		
		Kidney (renal tubule adenoma or carcinoma): 0/80, 0/80, 3/80, 10/80***	***$P < 0.001$	
		Tongue/oral cavity (papilloma): 0/80, 1/80, 0/79, 6/80***	***$P < 0.001$	
		Tongue/oral cavity (squamous-cell carcinoma): 0/80, 0/80, 1/79, 6/80***	***$P < 0.001$	
		Thyroid (follicular-cell adenoma): 0/80, 0/80, 3/80*, 3/78*	*$P < 0.05$	
		Thyroid (follicular-cell carcinoma): 0/80, 0/80, 2/80, 1/78		
		Thyroid (follicular-cell adenoma or carcinoma): 0/80, 0/80, 5/80*, 4/78*		
Wistar (F) up to 104 wk	0, 27, 80 and 240 mg/L (0, 3.4, 9.6 and 30 mg/kg bw per d) 80/group	Liver (hepatocellular adenoma): 1/80, 1/80, 1/80, 6/80**	**$P < 0.01$	Ten rats per group were killed after 26, 52, and 78 wk of treatment
		Liver (hepatocellular carcinoma): 0/80, 0/80, 1/80, 44/80***	***$P < 0.001$	
		Kidney (renal tubule adenoma): 0/80, 0/80, 0/80, 1/79		
		Kidney (renal tubule carcinoma): 0/80, 0/80, 0/80, 0/79		
		Tongue/oral cavity (papilloma): 0/80, 0/80, 0/80, 7/79***	***$P < 0.001$	
		Tongue/oral cavity (squamous-cell carcinoma): 0/80, 1/80, 1/80, 4/79**	**$P < 0.01$	
		Thyroid (follicular-cell adenoma): 1/79, 0/80, 3/80, 4/79		
		Thyroid (follicular-cell carcinoma): 0/79, 0/80, 0/80, 2/79*	*$P < 0.05$	

bw, body weight; d, day or days; F, female; M, male; wk, week or weeks
From Research & Consulting Co. (1986), JECFA (2002), and Williams *et al.* (2010)

doses were reported to provide exposures equal to 0, 2.1, 6.3 or 19 and 0, 3.4, 9.6 or 30 mg/kg body weight (bw) per day for males and females, respectively. Ten rats of each sex per group were killed after 26, 52 and 78 weeks of treatment. The mortality rates of the 50 animals per group that were exposed for 104 weeks were higher in males (32/50, $P < 0.05$) and females (27/50, $P < 0.05$) in the high-dose groups than in controls (males, 18/50; females, 13/50). Those in the low- and mid-dose groups were 11/50 males and 9/50 females and 16/50 males and 14/50 females, respectively. Statistically significant increases in the incidence of the following tumours were observed: in the liver, hepatocellular carcinoma in males and hepatocellular carcinoma and adenoma in females; in the tongue/oral cavity, squamous-cell carcinoma and papilloma in males and females; in the kidney, renal tubule adenoma in males; and in the thyroid, follicular-cell carcinoma in females and follicular-cell adenoma or carcinoma combined in males. With the exception of follicular-cell adenoma of the thyroid in the mid-dose males, the increases in tumour incidence were only statistically significant in the high-dose groups (Research & Consulting Co., 1986; JECFA, 2002; Williams *et al.*, 2010).

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

The study of toxicity in humans has been restricted to industrial accidents, in which workers were exposed by inhalation to 1,3-DCP. A consistent finding was acute hepatitis, which was fatal in several cases (Iwasa *et al.*, 1992; Haratake *et al.*, 1993; Shiozaki *et al.*, 1994). [Confounding by co-exposure to other compounds, including epichlorohydrin, could not be excluded.]

4.1.2 Experimental systems

The limited available data on absorption, distribution, excretion and metabolism of 1,3-DCP in experimental systems have been reviewed previously (JECFA, 2002; NTP, 2005).

(a) Degradation in bacteria

Two pathways for the degradation of 1,3-DCP have been found in *Corynebacterium* sp. strain N-1074 (Natarajan *et al.*, 2008), which are catalysed by two groups of two isoenzymes (Nakamura *et al.*, 1992). One group of two enzymes catalyses the non-stereospecific dechlorination and subsequent hydrolyzation of 1,3-DCP. Both enzymes accept (*R*)- and (*S*)-enantiomers as substrates and convert them to racemic mixtures (Yu *et al.*, 1994). The second group of enzymes also accepts (*R*)- and (*S*)-enantiomers, but converts them to (*R*)-rich products (Nakamura *et al.*, 1992).

Although *Arthrobacter* sp. strain AD2 can dechlorinate 1,3-DCP and 3-chloro-1,2-propanediol, it has no epoxide hydrolase activity and therefore cannot use either compound as a sole source of carbon (Nagasawa *et al.*, 1992).

Another species, *Agrobacterium radiobacter* strain AD1, can use 1,3-DCP or epichlorohydrin as a sole source of carbon. The pathway of degradation is non-enantioselective and similar to that of the *Corynebacterium* strain (Rink *et al.*, 1997).

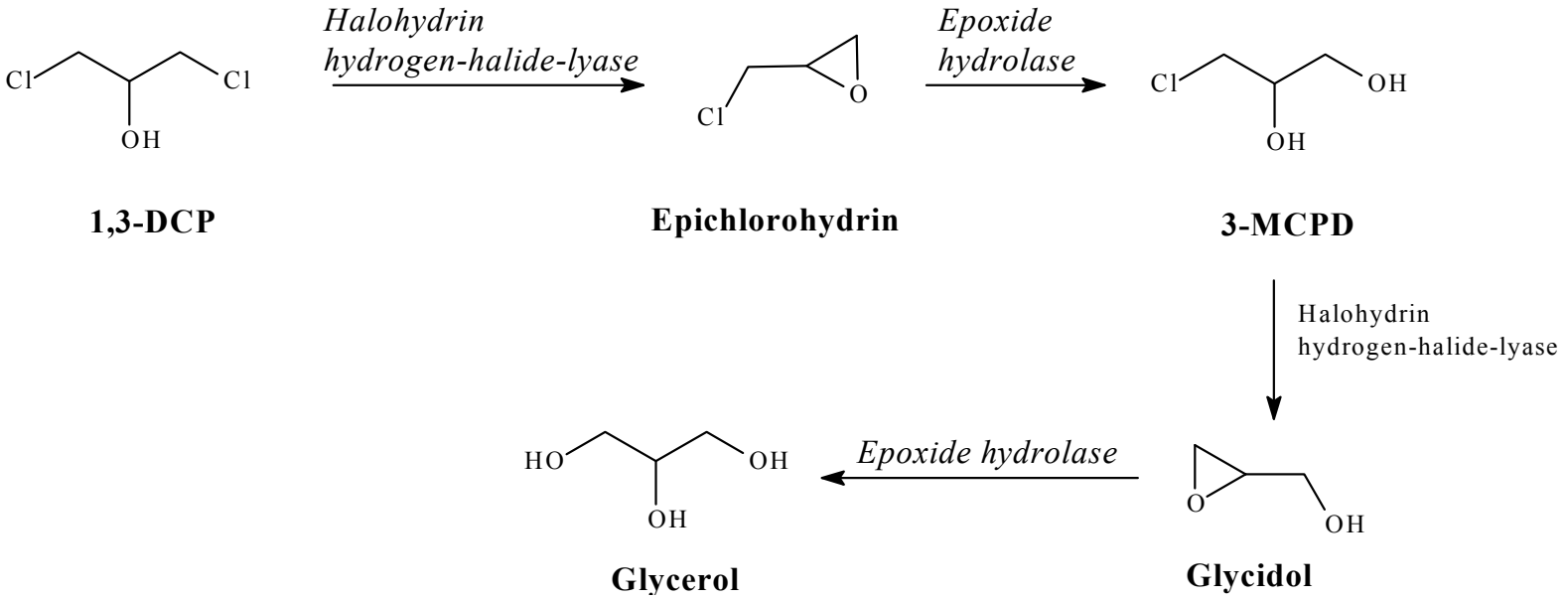
Epichlorohydrin was formed in media used for Ames and SOS chromotest assays with 1,3-DCP (Hahn *et al.*, 1991).

The proposed bacterial metabolism of 1,3-DCP is summarized in Fig. 4.1.

(b) Metabolism in mammalian systems

Few studies have investigated the metabolism of 1,3-DCP in mammalian systems, although it has been reported to induce and/or

Fig. 4.1 Proposed microbial metabolism of 1,3-dichloro-2-propanol



1,3-DCP, 1,3-dichloro-2-propanol; 3-MCPD, 3-monochloro-1,2-propanediol
Adapted from Natarajan *et al.* (2008)

be metabolized by the cytochrome P450 (CYP) enzyme isoform CYP2E1 (Garle *et al.*, 1997; Hammond & Fry, 1997; Fry *et al.*, 1999). Studies in rat hepatocytes in culture (Hammond & Fry, 1999) and in rat liver *in vivo* (Fry *et al.*, 1999) have indicated that 1,3-DCP is metabolized by CYP2E1 to an aldehyde intermediate that depletes glutathione (GSH). Under basal conditions, this metabolite appears to be effectively detoxified, but increased CYP2E1 activity and/or decreased aldehyde dehydrogenase activity promotes accumulation of the metabolite and thus GSH depletion and toxicity. Other factors, such as nutrition status (Fouin-Fortunet *et al.*, 1990), that modify GSH levels in humans may alter susceptibility to 1,3-DCP toxicity.

The metabolites identified in the urine of rats treated orally with 50 mg/kg bw 1,3-DCP per day for 5 days were β-chlorolactate (approximately 5% of the dose), *N*,*N*′-bis-acetyl-*S*,*S*′-(1,3-bis-cysteinyl)propan-2-ol (1%) and *N*-acetyl-*S*-(2,3-dihydroxypropyl)cysteine (Jones & Fakhouri, 1979). It was proposed that epoxychloropropane (epichlorohydrin, IARC Group 2A, IARC, 1999) is formed as an intermediate, and may either undergo conjugation with GSH to form mercapturic acid or be hydrolysed to 3-MCPD. The latter undergoes oxidation to β-chlorolactate, which is further oxidized to oxalic acid (see also the *Monograph* on 3-MCPD in this volume). The formation of other epoxides from α-chlorohydrins has been postulated but only at high pH (Jones & Fakhouri, 1979; JECFA, 2002).

Ethyl acetate-extractable metabolites were found in the 24-hour urine of male Wistar rats given a single subcutaneous injection of about 62 mg/kg bw 1,3-DCP. The parent compound accounted for 2.4% of the dose, 3-MCPD for 0.35% and 1,2-propanediol for 0.43%. 2,3-DCP was also found (0.16% of the dose), but the authors attributed this to its presence as an impurity (1.7%) in the 1,3-DCP administered to the rats. Metabolites that were not extractable in ethyl acetate were not analysed (Koga *et al.*, 1992; JECFA, 2002).

Alcohol dehydrogenase might be responsible for the oxidation of 1,3-DCP to dichloroacetone, a DNA-reactive metabolite, that can also be formed by rearrangement of the epichlorohydrin intermediate (Eder & Dornbusch, 1988; Weber & Sipes, 1992; JECFA, 2002). 1,3-Dichloroacetone is known to deplete GSH (Garle *et al.*, 1999), and may also be produced by CYP2E1-mediated metabolism (Hammond & Fry, 1997).

Because of selective extraction procedures and limited attempts at their identification, only a small percentage of administered doses have been accounted for as metabolites (JECFA, 2002).

1,3-DCP has been reported to deplete GSH both *in vitro* and *in vivo* (Hammond *et al.*, 1996; Garle *et al.*, 1997; Fry *et al.*, 1999; Garle *et al.*, 1999; Hammond & Fry, 1999). 1,3-DCP (up to 1000 µM [129 µg/mL]) depleted GSH dose-dependently when incubated with co-factors (i.e. a nicotinamide adenine dinucleotide phosphate-generating system) and liver microsomes from untreated rats. Inclusion of pyridine or omission of the co-factor, however, inhibited the depletion (Garle *et al.*, 1999). In rat hepatocyte cultures, isoniazid (an inducer of CYP) was found to increase the rate and extent of GSH depletion by 1,3-DCP, as well as its toxicity, whereas cyanamide (an aldehyde dehydrogenase inhibitor) did neither. Pretreatment of cultures with 1-aminobenzotriazole (an inhibitor of CYP) prevented the toxicity of 1,3-DCP, while pretreatment with diethyl maleate or buthionine sulfoximine (GSH inhibitors) increased its toxicity (Hammond & Fry, 1996, 1997, 1999).

A dose of 5 mg/kg bw diethyldithiocarbamate significantly protected against the hepatotoxicity induced in rats by intraperitoneal injection of 70 mg/kg bw 1,3-DCP, and also inhibited enzyme markers for CYP2E1 activity. At a dose of 25 mg/kg bw, diethyldithiocarbamate afforded complete protection. It was therefore concluded that the hepatotoxicity of 1,3-DCP was mediated

principally through its metabolism by CYP2E1 (Stott *et al.*, 1997).

In rats treated with 0.3 mg/kg bw 1,3-DCP, significantly increased hepatic levels of malondialdehyde were associated with decreases in liver GSH *S*-transferase activity and GSH content. Lipid peroxidation was suggested as a mechanism of the reported hepatotoxicity [diffuse massive necrosis] (Katoh *et al.*, 1998; Kuroda *et al.*, 2002).

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

Genotoxicity studies of 1,3-DCP *in vitro* and *in vivo* have recently been reviewed (JECFA, 2002), and are summarized in Table 4.1.

In vitro, 1,3-DCP induced reverse mutation in various strains of *Salmonella typhimurium*. It induced mutations and influenced DNA repair in *Escherichia coli*. 1,3-DCP induced sister chromatid exchange in Chinese hamster V79 cells. It was also mutagenic in HeLa cells and induced malignant transformation of mouse fibroblasts.

In the only available study *in vivo*, 1,3-DCP had no effect on the induction of wing spots in *Drosophila melanogaster* (Frei & Würgler, 1997).

4.3 Mechanistic data

4.3.1 Effects on cell physiology

Data *in vitro* suggested that 1,3-DCP-induced apoptosis was dependent on Ca^{2+} and that reactive oxygen species were also induced by exposure of B16F10 murine melanoma cells to 1,3-DCP (Park *et al.*, 2010).

Exposure of A549 lung adenocarcinoma cells to 1,3-DCP was reported to inhibit cell growth, generate reactive oxygen species and to activate p53 and $p21^{CIP1/WAF1}$ (Jeong *et al.*, 2007).

Six groups of rats received a single intraperitoneal injection of 0.2 mL 20% ethanol (control), or 1/8, 1/4, or 1/2 of the dose that was lethal in 50% of animals (LD_{50}), the LD_{50} or double the LD_{50} (LD_{50} = 149 µg/kg bw) of 1,3-DCP diluted in 20% ethanol. Rats administered ethanol only or 1/8 (18.6 µg/kg bw) and 1/4 (37 µg/kg/bw) of the LD_{50} showed no serological or histopathological abnormalities. Marked elevation of serum glutamate pyruvate transaminase and diffuse massive necrosis of the liver cells were noted in all rats treated with both the LD_{50} (149 µg/kg bw) and double the LD_{50} (298 µg/kg bw), and irregular zonal necroses were found in three of four rats injected with 1/2 the LD_{50} (74.5 µg/kg bw). No serious toxic changes occurred in other organs. In a second experiment in which rats were exposed to ethanol alone or the LD_{50}, hepatic malondialdehyde levels were significantly increased, associated with decreases in liver GSH *S*-transferase activity and reduced GSH content in the LD_{50}-treated group. The authors concluded that the hepatotoxicity was dose-dependent and that one of its mechanisms might be lipid peroxidation (Katoh *et al.*, 1998). [Lipid peroxidation was not shown to be dose-dependent.]

4.3.2 Structure-activity relationships relevant to an evaluation of carcinogenicity and structural analogies with known carcinogens

Carcinogenicity, genotoxicity and toxic effects on reproduction and development were compiled for a limited group of C3-compounds and their derivatives related to 1,3-DCP (NTP, 2005). Oxygen-containing compounds that induced malignancies in rodents included epichlorohydrin [106-89-8] (Group 2A, IARC, 1999), 2,3-dibromo-1-propanol [96-13-9] and tris(2,3-dibromopropyl) phosphate [126-72-7] (Group 2A, IARC, 1999). Oxygen-containing compounds that induced only benign tumours were 3-MCPD [96-24-2] and 1,3-dichloro-2-propanol

Table 4.1 Genetic and related effects of 1,3-dichloro-2-propanol

Test system	Results		Dose (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, reverse mutation	-	+	0.05 mg/plate	Gold *et al.* (1978)
Salmonella typhimurium TA100, TA1535, reverse mutation	+	+	0.39 mg/plate	Nakamura *et al.* (1979)
Salmonella typhimurium TA100, reverse mutation	+	+	0.13 mg/plate	Stolzenberg & Hine (1980)
Salmonella typhimurium TA100, reverse mutation	+	-	0.1 mg/plate	Lynn *et al.* (1981)
Salmonella typhimurium TA100, TA1537, TA1538, reverse mutation	-	-	26 mg/plate	Silhánková *et al.* (1982)
Salmonella typhimurium TA100, reverse mutation	NT	+	≤ 0.5 mg/plate	Majeska & Matheson (1983)
Salmonella typhimurium TA100, TA1535, reverse mutation	+	+	0.3–3.33 mg/plate	Zeiger *et al.* (1988)
Salmonella typhimurium TA100, reverse mutation	+	+	3.4 mg/plate	Hahn *et al.* (1991)
Salmonella typhimurium TA100, TA1535, reverse mutation	+	+	≤ 1.2 mg/plate	Ohkubo *et al.* (1995)
Salmonella typhimurium TA1535, reverse mutation	+	+	0.26 mg/plate	Silhánková *et al.* (1982)
Salmonella typhimurium TA1535, reverse mutation	+	+	0.72 mg/plate	Hahn *et al.* (1991)
Salmonella typhimurium TA97, reverse mutation	-	+	3.33 mg/plate	Zeiger *et al.* (1988)
Salmonella typhimurium TA98, reverse mutation	-	+	6.7 mg/plate	Zeiger *et al.* (1988)
Salmonella typhimurium TA98, reverse mutation	-	-	1.2 mg/plate	Ohkubo *et al.* (1995)
Salmonella typhimurium TM677, forward mutation	-	+	≤ 0.1 mg/plate	Ohkubo *et al.* (1995)
Escherichia coli WP2, TM930, TM1080, reverse mutation	-	+	0.26 mg/plate	Silhánková *et al.* (1982)
Prophage induction, SOS repair, DNA strand breaks or cross-links (*Escherichia coli* PM21, GC4798)	-	+	1.3–3.9 mg/sample	Hahn *et al.* (1991)
Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	+	0.032–0.13 mg/mL	von der Hude *et al.* (1987)
Mutation, inhibition of DNA synthesis, HeLa S3 cells *in vitro*	NT	+	0.32 mg/mL	Painter & Howard (1982)
Transformation assay, mouse fibroblasts, M2 clone *in vitro*	+	NT	0.1 mg/mL	Piasecki *et al.* (1990)
Drosophila melanogaster, somatic mutation, wing-spot test	-		1.3 mg/mL	Frei & Würgler (1997)

+, positive; -, negative; HID, highest ineffective dose; LED, lowest effective dose; NT, not tested

[13674-87-8]. Two related chlorinated hydrocarbons, 1,3-dichloropropene [542-75-6] (Group 2B, IARC, 1999) and 1,2,3-trichloropropane [96-18-4] (Group 2A, IARC, 1995), were also rodent carcinogens.

No long-term study was available for 2,3-dichloropropanol [616-23-9]. The compounds that caused tumours, including 1,3-DCP, were genotoxic in at least some mammalian systems *in vitro*. The metabolism of all of these compounds has not been explored, but their conversion to epichlorohydrin or epibromohydrin [3132-64-7] might be involved in their mode of action of tumour induction.

Brominated analogues evaluated by IARC include 1,2-dibromo-3-chloropropane [96-12-8] (Group 2B, IARC, 1999) and 2,3-dibromo-1-propanol [96-13-9] (Group 2B, IARC, 2000).

4.4 Mechanisms of carcinogenesis

While no studies have evaluated the genotoxicity of 1,3-DCP in intact mammalian organisms or humans, the results of in-vitro studies demonstrated that 1,3-DCP can readily interact with chromosomal material in cells. Therefore, 1,3-DCP or its metabolites can be expected to have genotoxic activity in target tissues *in vivo* (JECFA, 2002). Nevertheless, no clear mode of action was established for tumours observed in experimental animals (i.e. of the liver, kidney and tongue).

5. Summary of Data Reported

5.1 Exposure data

1,3-Dichloro-2-propanol is used as an intermediate in the production of epichlorohydrin. Hydrolysis of epichlorohydrin, which is a major raw material in industry, may contribute to occupational exposure to 1,3-dichloro-2-propanol. 1,3-Dichloro-2-propanol may be formed as a heat-induced contaminant during food processing. The levels in food are usually below 100 µg/kg with the exception of soya sauce and soya sauce-based products, which may contain levels up to the milligram per kilogram range. Levels in food have been regulated in some jurisdictions, and indirect regulation also occurs in jurisdictions where 3-monochloro-1,2-propanediol is regulated, because both compounds are formed by similar mechanisms and their concentrations were correlated.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

In a 2-year study in rats, administration of 1,3-dichloro-2-propanol in the drinking-water increased the incidence of tongue carcinoma, tongue papilloma and hepatocellular carcinoma in males and females. The incidence of renal tubule adenoma in males, thyroid follicular-cell carcinoma in females and thyroid follicular-cell adenoma or carcinoma (combined) in males was also increased.

Tumours of the tongue and thyroid are rare spontaneous neoplasms in experimental animals.

5.4 Other relevant data

1,3-Dichloro-2-propanol may be metabolized in bacteria by two consecutive steps of halohydrin hydrogen-halide-lyase followed by epoxide hydrolase, which generates the metabolites epichlorohydrin and glycidol, both of which are classified by IARC as *probably carcinogenic to humans (Group 2A)*. The metabolism in mammals is not fully elucidated but may be similar.

β-Chlorolactate was detected in the urine of rats treated orally with 1,3-dichloro-2-propanol.

The compound is assumed to be formed by oxidation of 3-monochloro-1,2-propanediol, which may arise as a hydrolysis product of the epichlorohydrin metabolite.

1,3-Dichloro-2-propanol is mutagenic *in vitro*, but the limited data available from in-vivo assays were negative. At high doses, it exhibits hepatoxicity in experimental animals and evidence for acute hepatitis was also detected in cases of human intoxication. A possible mechanism for the carcinogenicity of 1,3-dichloro-2-propanol is the induction of DNA damage by the agent itself or its metabolites, and the production of reactive oxygen species.

Overall, the available mechanistic data are considered to be weak. However, the relevance of the tumour response in experimental animals to humans cannot be excluded.

6. Evaluation

6.1 Cancer in humans

No data were available to the Working Group.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,3-dichloro-2-propanol.

6.3 Overall evaluation

1,3-Dichloro-2-propanol is *possibly carcinogenic to humans (Group 2B).*

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