CHLOROETHANE

Data were last evaluated in IARC (1991).

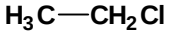
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Services Reg. No.: 75-00-3
Systematic name: Chloroethane
Synonym: Ethyl chloride

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_2H_5Cl Relative molecular mass: 64.52

1.1.3 *Physical properties* (for details, see IARC, 1991)

(*a*) *Melting-point*: –136.4°C
(*b*) *Boiling-point*: 12.3°C
(*c*) *Conversion factor*: $mg/m^3 = 2.64 \times ppm$

1.2 Production, use and human exposure

Chloroethane is produced by the hydrochlorination of ethylene. It is used in the manufacture of tetraethyllead, as an industrial ethylating agent, as a blowing agent in the production of polystyrene foam and as a local anaesthetic. Occupational exposure occurs during the production of tetraethyllead, and industrial emissions have led to detectable levels of chloroethane in ambient air (IARC, 1991).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Chloroethane was tested for carcinogenicity in a two-year study in male and female Fischer 344 rats and B6C3F$_1$ mice by inhalation at a single concentration of 15 000 ppm [39 600 mg/m^3]. It induced uterine carcinomas in mice; marginal increases occurred in the incidence of hepatocellular tumours in female mice and in the incidence of alveolar/bronchiolar tumours in male mice. There was a marginal increase in the incidence of skin tumours in male rats, and a few uncommon glial cell tumours occurred in female rats (IARC, 1991).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Human volunteers exhaled approximately 30% of an inhaled dose within 1 h (IARC, 1991).

4.1.2 *Experimental systems*

There was little dechlorination (< 0.5%) of chloroethane when it was incubated with rat hepatic microsomes and NADPH (IARC, 1991).

Cytochrome P450-dependent metabolism was examined in microsomal preparations from male and female Fischer 344 rats and B6C3F$_1$ mice exposed to 15 000 ppm [39 600 mg/m^3] chloroethane for 6 h per day for five days. Chloroethane is oxidatively dechlorinated in an NADPH- and oxygen-dependent reaction, yielding acetaldehyde. The involvement of CYP2E1 is indicated by its inhibition by 3-amino-1,2,4-triazole. This activity is inducible by chloroethane itself in mice and female rats and correlates with increased *para*-nitrophenol hydroxylation, an indicator of CYP2E1 metabolism (Fedtke *et al*., 1994a). Chloroethane is also conjugated with glutathione in hepatic cytosolic preparations and generally to a higher extent in mouse than in rat. Glutathione was depleted in the lungs and uterus of both species after exposure, but not in the liver and kidneys. The initial conjugate *S*-ethylglutathione was excreted as the mercapturic acid, *S*-ethyl-*N*-acetyl-L-cysteine, in the urine of both species. *S*-Ethyl-L-cysteine was also excreted in the urine of mice, but not rats. The combined quantities of these metabolites excreted in five days were up to five-fold higher for mice than for rats. Excretion of *S*-ethyl-*N*-acetyl-L-cysteine occurred mainly during the exposure period for mice, but after the exposure period for rats (Fedtke *et al*., 1994b).

4.2 Toxic effects

4.2.1 *Humans*

Allergic sensitization to chloroethane can occur as a consequence of its use as a local anaesthetic in medical practice (Aberer & Zonzits, 1989; Bircher *et al*., 1994). Chloro-

ethane has also been observed to produce severe neurological impairment, including hallucinations and ataxia after direct inhalation two to three times per week over a four-month period of abuse of this specific solvent by the patient (Soult & Walker, 1993).

4.2.2 *Experimental systems*

In 13-week studies, male and female Fischer 344 rats and $B6C3F_1$ mice were exposed to 2500–19 000 ppm [6600–50 200 mg/m^3] chloroethane for 6 h per day on five days per week. In rats and mice, no adverse effects except for reduced body weight gain were observed. Increases in liver weight were observed in male rats and female mice exposed to 19 000 ppm (IARC, 1991).

In response to the unusual observation of increased uterine tumours in mice (see above), possible changes in blood concentrations of sex hormones were investigated. Female $B6C3F_1$ mice (77–83 days of age) were exposed to 15 000 ppm [39 600 mg/m^3] chloroethane for 6 h per day for 21 days. No consistent changes were found in oestrous cyclicity or in serum concentrations of oestradiol and progesterone. Thus, none of the measured parameters emerged as a mechanistic factor that might contribute to the high incidence of endometrial tumours (Bucher *et al*., 1995).

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

Chloroethane was mutagenic to bacteria and at the *hprt* locus in a study with the Chinese hamster ovary cell line, but not did not induce transformation in BALB/c 3T3 cells. In $B6C3F_1$ mice exposed by inhalation, it did not induce either unscheduled DNA synthesis in hepatocytes or micronuclei in bone-marrow cells.

5. Evaluation

No epidemiological data relevant to the carcinogenicity of chloroethane were available.

There is *limited evidence* in experimental animals for the carcinogenicity of chloroethane.

Overall evaluation

Chloroethane is *not classifiable as to its carcinogenicity to humans (Group 3)*.

Table 1. Genetic and related effects of chloroethane

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	NG	US National Toxicology Program (1989)
SA0, *Salmonella typhimurium* TA100, reverse mutation (gas exposure)	+	+	1% in air	Araki *et al.* (1994)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	NG	US National Toxicology Program (1989)
SA5, *Salmonella typhimurium* TA1535, reverse mutation (gas exposure)	+	+	3% in air	Araki *et al.* (1994)
SA7, *Salmonella typhimurium* TA1537, reverse mutation (gas exposure)	–	–	17% in air	Araki *et al.* (1994)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	US National Toxicology Program (1989)
SA9, *Salmonella typhimurium* TA98, reverse mutation (gas exposure)	–	–	17% in air	Araki *et al.* (1994)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation (gas exposure)	+	+	1% in air	Araki *et al.* (1994)
GCO, Gene mutation, Chinese hamster ovary CHO cells *hprt* locus *in vitro*	+	(+)	940	Ebert *et al.* (1994)
TBM, Cell transformation, BALB/c 3T3 C11-13 mouse cells *in vitro*	–	NT	467	Tu *et al.* (1985)
UVM, Unscheduled DNA synthesis, B6C3F_1 mouse hepatocytes *in vivo*	–		25 500 inh. 6h/d × 3 d	Ebert *et al.* (1994)
CBA, Micronucleus test, B6C3F_1 mouse bone-marrow cells *in vivo*	–		25 500 inh. 6h/d × 3 d	Ebert *et al.* (1994)

[a] +, positive; (+), weak 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; inh, inhalation

6. References

Aberer, W. & Zonzits, E. (1989) Allergy to ethyl chloride does occur, and might frequently be misdiagnosed. *Contact Derm.*, **21**, 352–353

Araki, A., Noguchi, T., Kato, F. & Matsushima, T. (1994) Improved method for mutagenicity testing of gaseous compounds by using a gas sampling bag. *Mutat. Res.*, **307**, 335–344

Bircher, A.J., Hampl, K., Hirsbrunner, P., Buechner, S.A. & Schneider, M. (1994) Allergic contact dermatitis from ethyl chloride and sensitization to dichlorodifluoromethane (CFC 12). *Contact Derm.*, **31**, 41–44

Bucher, J.R., Morgan, D.L., Adkins, B., Jr, Travlos, G.S., Davis, B.J., Morris, R. & Elwell, M.R. (1995) Early changes in sex hormones are not evident in mice exposed to the uterine carcinogens chloroethane or bromoethane. *Toxicol. appl. Pharmacol.*, **130**, 169–173

Ebert, R., Fedtke, N., Certa, H., Wiegand, H.J., Régnier, J.F., Marshall, R. & Dean, S.W. (1994) Genotoxicity studies with chloroethane. *Mutat. Res.*, **322**, 33–44

Fedtke, N., Certa, H., Ebert, R. & Wiegand, H.J. (1994a) Species differences in the biotransformation of ethyl chloride. I. Cytochrome P450-dependent metabolism. *Arch. Toxicol.*, **68**, 158–166

Fedtke, N., Certa, H., Ebert, R. & Wiegand, H.J. (1994b) Species differences in the biotransformation of ethyl chloride. II. GSH-dependent metabolism. *Arch. Toxicol.*, **68**, 217–223

IARC (1991) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 52, *Chlorinated Drinking-Water; Chlorination By-Products; Some Other Halogenated Compounds; Cobalt and Cobalt Compounds*, Lyon, pp. 315–335

Soult, T.A. & Walker, J.S. (1993) Ethyl chloride intoxication [Letter to the Editor]. *Am. J. emerg. Med.*, **11**, 313–315

Tu, A.S., Murray, T.A., Hatch, K.M., Sivak, A. & Milman, H.A. (1985) In vitro transformation of BALB/c-3T3 cells by chlorinated ethanes and ethylenes. *Cancer Lett.*, **28**, 85–92

United States National Toxicology Program (1989) *Toxicology and Carcinogenesis Studies of Chloroethane (Ethyl chloride) (CAS No. 75-00-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies)* (NTP Technical Report Series No. 346), Research Triangle Park, NC, United States Department of Health and Human Services