BIS(2-CHLORO-1-METHYLETHYL)ETHER

Data were last reviewed in IARC (1986) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

1. Exposure Data

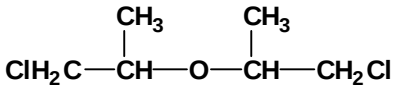
1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Services Reg. No.: 108-60-1

Systematic name: 2,2′-Oxybis(1-chloropropane)

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_6H_{12}Cl_2O$ Relative molecular mass: 171.7

1.1.3 *Physical properties* (for details, see IARC, 1986)

(*a*) *Boiling-point*: 187°C

(*b*) *Melting-point*: –100°C

(*c*) *Conversion factor*: $mg/m^3 = 7.02 \times ppm$

1.2 Production, use and human exposure

Bis(2-chloro-1-methylethyl)ether has been produced as a solvent and soil fumigant and is also formed in large quantities as a by-product in some propylene oxide/propylene glycol production processes. Low levels have been found in water. Thus, both occupational and environmental exposures may occur (IARC, 1986).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Bis(2-chloro-1-methylethyl)ether, containing 2-chloro-1-methylethyl(2-chloro-*n*-propyl)ether and bis(2-chloro-*n*-propyl)ether, was tested for carcinogenicity orally by gavage in one experiment in mice and in one experiment in rats. In mice, increased incidences of lung adenomas in males and females and of hepatocellular carcinomas in males were observed. In rats, no increase in tumour incidence was observed (IARC, 1986).

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

4.1 Absorption distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

In rats receiving a single oral dose of bis(2-chloro-1-methylethyl)ether of 0.0002–300 mg/kg bw, peak blood levels of radioactivity were reached at about 2–4 h. Following administration of a dose of 30 mg/kg bw, elimination was biphasic in rhesus monkeys, with half-lives of 5 h and two days, and monophasic in rats, with a half-life of two days. In rats, total recovery of radioactivity was 75% of an oral dose of the 1-^{14}C-labelled compound and 90% after an intraperitoneal dose with the 2-^{14}C-labelled compound; approximately 20% of the oral dose was exhaled as $^{14}CO_2$ in 48 h. Also in rats, urinary excretion of radioactivity accounted for 48% of a 90 mg/kg bw oral dose of the 1-^{14}C-labelled compound within 48 h and for 60% of a 30 mg/kg bw intraperitoneal dose of the 2-^{14}C-labelled compound within 24 h. Urinary metabolites identified after administration of an oral dose of 90 mg/kg bw of the 1-^{14}C-labelled compound to rats were 2-(2-chloro-1-methylethoxy)propanoic acid (17% of the dose) and *N*-acetyl-*S*-(2-hydroxypropyl)-cysteine (approximately 9% of the dose); following an intraperitoneal dose of the 2-^{14}C-labelled compound, metabolites identified were 1-chloropropan-2-ol, propylene oxide and 2-(2-chloro-1-methylethoxy)propanoic acid (IARC, 1986).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Inhalation exposure of rats to 350 ppm [2450 mg/m^3] for 5 h per day on eight consecutive days caused respiratory distress, reduced body weight gain, irritation to the

eyes, nose and lung and hepatic and renal injury. Dietary exposure of mice also caused anaemia (IARC, 1986).

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)

[Some experiments reported in the previous monograph (IARC, 1986) were not, in fact, done with this compound.]

Bis(2-chloro-1-methylethyl)ether is weakly mutagenic in *Salmonella typhimurium* TA1535 in the presence of an exogenous metabolic system. It induced mutations at the *tk* locus in mouse lymphoma cells. It did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* (as reported in an abstract: Mirsalis *et al.*, 1985).

5. Evaluation

No epidemiological data relevant to the carcinogenicity of bis(2-chloro-1-methylethyl)ether were available.

There is *limited evidence* in experimental animals for the carcinogenicity of bis(2-chloro-1-methylethyl)ether.

Overall evaluation

Bis(2-chloro-1-methylethyl)ether is *not classifiable as to its carcinogenicity to humans (Group 3)*.

6. References

IARC (1986) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 41, *Some Halogenated and Pesticide Exposures*, Lyon, pp. 149–160

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Supplement 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, p. 59

McGregor, D.B., Brown, A., Cattanach, P., Edwards, I., McBride, D., Riach, C. & Caspary, W.J. (1988) Responses of the L5178Y $tk^{+/-}$ mouse lymphoma cell forward mutation assay: III. 72 coded chemicals. *Environ. mol. Mutag.*, **12**, 85–154

Table 1. Genetic and related effects of bis(2-chloro-1-methylethyl)ether

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Mortelmans *et al.* (1986)[c]
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	(+)	166	Mortelmans *et al.* (1986)[c]
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	Mortelmans *et al.* (1986)[c]
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	166	Mortelmans *et al.* (1986)[c]
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	166	Mortelmans *et al.* (1986)[c]
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		1600 ppm inj[d]	Valencia *et al.* (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	250	McGregor *et al.* (1988)

[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; inj, injection

[c] Results from two independent laboratories

[d] Negative also when exposed to 283 ppm in the diet

Mirsalis, J., Tyson, K., Loh, E., Baake, J., Hamilton, C., Spak, D., Steinmetz, K. & Spalding, J. (1985) Induction of unscheduled DNA synthesis (UDS) and cell proliferation in mouse and rat hepatocytes following in vivo treatment (Abstract). *Environ. Mutag*., **7** (Suppl. 3), 73

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B. & Zeiger, E. (1986) *Salmonella* mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ. Mutag*., **8** (Suppl. 7), 1–119

Valencia, R., Mason, J.M., Woodruff, R.C. & Zimmering, S. (1985) Chemical mutagenesis testing in *Drosophila*. III. Results of 48 coded compounds tested for the National Toxicology Program. *Environ. Mutag*., **7**, 325–348