BIS(2-CHLOROETHYL)ETHER

Data were last reviewed in IARC (1975) 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.: 111-44-4

Systematic name: 1,1′-Oxybis(2-choro)ethane

1.1.2 *Structural and molecular formulae and relative molecular mass*

$C_4H_8Cl_2O$ Relative molecular mass: 143.02

1.1.3 *Physical properties* (for details, see IARC, 1975)

(*a*) *Boiling-point*: 178°C

(*b*) *Melting-point*: –50°C (Budavari, 1989)

(*c*) *Conversion factor*: $mg/m^3 = 5.85 \times ppm$

1.2 Production and use

It is not clear whether bis(2-chloroethyl)ether is still produced commercially. It has been used as a solvent, a chemical intermediate and as a soil fumigant (IARC, 1975; WHO, 1998).

2. Studies of Cancer in Humans

Two studies have examined the risk of cancer among chlorohydrin production workers potentially exposed to bis(2-chloroethyl)ether as well as 1,2-dichloroethane and ethylene chlorohydrin (see the monograph on 1,2-dichloroethane in this volume for a detailed description of the study methods). In one study there was an excess of pancreatic, lymphatic and haematopoietic cancers (Benson & Teta, 1993), while in the other there was not (Olsen *et al*., 1997). In neither study was it possible to link mortality to any particular chemical exposure.

3. Studies of Cancer in Experimental Animals

Bis(2-chloroethyl)ether produced an increased incidence of hepatomas in male mice of two strains following its oral administration at a dose of 100 mg/kg bw per day in a screening study. The hepatoma incidences were: (C57BL/6 × C3H/Anf)F_1 strain males, 8/79 in the control group and 14/16 in the treated group; (C57BL/6 × AKR)F_1 males, 5/90 in the control group and 9/17 in the treated group. Subcutaneous administration to mice produced a low incidence of sarcomas at the injection site (IARC, 1975).

3.1 Oral administration

Bis(2-chloroethyl)ether (purity 100% according to nuclear magnetic resonance analysis) was administered orally by gavage to groups of 26 male and female Sprague-Dawley rats at doses of 25 and 50 mg/kg bw per day twice a week for 78 weeks and then observed without further dosing up to 104 weeks. The test was conducted concurrently with several other chemicals, for which a common vehicle control group of 58 rats of each sex was used for comparison. Survival at 52 weeks among male and female rats was 96% and 96%, respectively, in the 25 mg/kg bw group and 100% and 65%, respectively, in the 50 mg/kg bw group. Apart from the high-dose female group, at least 81% of the rats were alive at 78 weeks. There were no increases in the incidence of tumours in either male or female rats (Weisburger *et al*., 1981). [Tumour incidence data for the treatment groups were not presented; the group sizes were smaller than contemporary recommendations. The Working Group noted the short duration of dosing.]

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*

Bis(2-chloroethyl)ether is rapidly absorbed through the skin of rabbits (IARC, 1975).

Young adult male Sprague-Dawley rats were given single oral doses of bis(2-chloro-[1-^{14}C]ethyl)ether (40 mg/kg bw) and the excretion of $^{14}CO_2$ and urinary ^{14}C was followed for 48 h. Half of the administered radioactivity was eliminated within 12 h. Recoveries of the administered radioactivity from the expired air, urine, faeces and body organs at 48 h were 11.5%, 64.7%, 2.4% and 2.3%, respectively. Unchanged bis(2-chloroethyl)ether would have contributed no more than 2% of the dose. The main body depots of radioactivity were blood (0.49%), liver (0.19%), kidney (0.56%) and muscle (0.96%). The major

urinary metabolite was thiodiglycolic acid, which accounted for about 75% of the radioactivity. Minor urinary metabolites were 2-chloroethoxyacetic acid (5%) and *N*-acetyl-*S*-[2-(2-chloroethoxy)ethyl]-L-cysteine (7%). The authors proposed that facile in-vivo cleavage at the ether linkage to form active metabolites may be important for adverse responses to the compound (Lingg *et al*., 1979, 1982).

4.2 Toxic effects

4.2.1 *Humans*

Brief exposure of volunteers to 550 ppm [3220 mg/m^3] bis(2-chloroethyl)ether was intolerably irritating to the eyes and nasal passages (IARC, 1975).

4.2.2 *Experimental systems*

Bis(2-chloroethyl)ether is rapidly lethal to rabbits upon skin application and to guinea-pigs upon inhalation (IARC, 1975).

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)

Bis(2-chloroethyl)ether is weakly mutagenic in *Salmonella typhimurium* TA1535. In one study, it produced sex-linked recessive lethal mutations in *Drosophila melanogaster* when administered by injection. It did not induce heritable translocations in *D. melanogaster* or mice. In rats, it formed covalent complexes with protein but not with DNA.

5. Evaluation

There is *inadequate evidence* for the carcinogenicity of bis(2-chloroethyl)ether in humans.

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

Overall evaluation

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

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

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, *Escherichia coli*, SOS induction	–	NT	NG	Quinto & Radman (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	?	5000	Mortelmans *et al*. (1986)[c]
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1250	JETOC (1997)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	(+)	5000	Mortelmans *et al*. (1986)[c]
SA5, *Salmonella typhimurium* TA1535, reverse mutation	(+)	(+)	1250	JETOC (1997)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	Mortelmans *et al*. (1986)[c]
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1875	JETOC (1997)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Mortelmans *et al*. (1986)[c]
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1875	JETOC (1997)
ECF, *Escherichia coli*, forward mutation	–	NT	NG	Quinto & Radman (1987)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	2500	JETOC (1997)
ECB, *Escherichia coli*, recombination	–	NT	NG	Quinto & Radman (1987)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	(+)		10 500 ppm inj	Foureman *et al*. (1994)
DMH, *Drosophila melanogaster*, heritable translocation test	–		13 000 ppm inj	Foureman *et al*. (1994)
MHT, Mouse heritable translocation test *in vivo*	–		100 po × 1, 8 wk	Jorgenson & Rushbrook (1977)
BIP, Binding (covalent) to RNA *in vitro*	–	NT	7150	Shooter (1975)
BVP, Protein binding, Wistar rat liver *in vivo*	+		125 inh 24 h	Gwinner *et al*. (1983)
BVD, Binding (covalent) to DNA, Wistar rat liver *in vivo*	–		125 inh 24 h	Gwinner *et al*. (1983)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

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

[c] Tested in two laboratories; results shown are for the one testing to higher doses; all results from the other laboratory were negative.

6. References

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