CHLORODIBROMOMETHANE

Data were last evaluated in IARC (1991).

1. Exposure Data

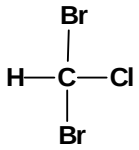
1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Services Reg. No.: 124-48-1

Systematic name: Chlorodibromomethane

1.1.2 *Structural and molecular formulae and relative molecular mass*



$CHBr_2Cl$ Relative molecular mass: 208.29

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

(*a*) *Boiling-point*: 119–200°C at 99 kPa

(*b*) *Melting-point*: < –20°C

(*c*) *Conversion factor*: $mg/m^3 = 8.52 \times ppm$

1.2 Production, use and human exposure

Chlorodibromomethane has limited commercial use but is used industrially as a chemical intermediate. It is found in chlorinated drinking-water as a consequence of the reaction between chlorine, added during drinking-water treatment, and natural organic substances in the presence of bromide. The major route of human exposure is via drinking-water. Chlorodibromomethane is not normally present in untreated water. It is a major component of organohalide emissions from marine algae (IARC, 1991).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Chlorodibromomethane was tested for carcinogenicity in two-year studies by oral gavage in male and female B6C3F_1 mice and Fischer 344 rats and in a lifetime study in CBA × C57BL/6 hybrid mice by administration in the drinking-water. In B6C3F_1 mice, it produced a significant increase in the incidence of hepatocellular neoplasms in females and a marginal increase in males. Chlorodibromomethane did not increase the proportion of rats with tumours at any site relative to that in controls. There was no increase in tumour incidence in CBA × C57BL/6 hybrid mice given chlorodibromomethane in the drinking-water (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*

No data were available to the Working Group.

4.1.2 *Experimental systems*

Chlorodibromomethane administered in corn oil orally by gavage to rats was eliminated in the expired air as unchanged chlorodibromomethane (approx. 48% of the dose) and CO_2 (18%) within 8 h. Only 1% appeared in urine and about 1% was retained in tissues. In contrast, after oral dosing to mice, unchanged chlorodibromomethane in expired air accounted for approximately 12% of the dose and CO_2 for approximately 72% within 8 h. About 2% of the dose was excreted in urine and 5% was retained in tissues (IARC, 1991).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Liver and kidney are target organs in rats and mice for chlorodibromomethane toxicity following oral gavage dosing. In a 13-week study, male and female Fischer 344/N rats and B6C3F_1 mice were administered 15–250 mg/kg bw chlorodibromomethane by gavage on five days per week. The highest dose was lethal for 9/10 male and 9/10 female rats and resulted in fatty changes and centrilobular necrosis in the liver and proximal tubule-cell degeneration and regeneration in the kidney. Inflammation and squamous metaplasia were observed in the salivary glands. Mice were less sensitive. Fatty changes of the liver and

tubule degeneration of the kidney were observed in 5/10 of the males but not in the females of the highest dose group. In the subsequent carcinogenicity study in which the doses used were 40 or 80 mg/kg bw for rats and 50 or 100 mg/ kg bw for mice, fatty changes occurred in the liver of all dose groups, whereas cytomegaly and necrosis of the liver were observed only in the high-dose male mice. Nephrosis was observed in female rats and male mice and follicular-cell hyperplasia of the thyroid gland was observed in female mice in all dose groups (IARC, 1991).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Chlorodibromomethane can cause maternal toxicity in the absence of fetal or embryo toxicity in orally dosed rats. No teratogenic effects have been observed (IARC, 1991).

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)

Chlorodibromomethane induced DNA damage and mutation in bacteria. In single studies, it induced gene conversion and aneuploidy, but not mutation, in fungi. It induced chromosomal aberrations, sister chromatid exchanges and mutations in mammalian cell lines and sister chromatid exchanges in cultured human lymphocytes. Sister chromatid exchanges, but not micronuclei, were increased in mice treated *in vivo*. Unscheduled DNA synthesis was not induced in hepatocytes from rats treated *in vivo*.

5. Evaluation

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

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

Overall evaluation

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

Table 1. Genetic and related effects of chlorodibromomethane

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS chromotest, *Escherichia coli* PQ37	+	+	10	Le Curieux *et al.* (1995)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	NG	Simmon *et al.* (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	US National Toxicology Program (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Khudoley *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	8	Varma *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	+	NG	Khudoley *et al.* (1989)[c]
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Mersch-Sundermann (1989)[d]
SA0, *Salmonella typhimurium* TA100, reverse mutation (fluctuation test)	–	–	3000	Le Curieux *et al.* (1995)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	US National Toxicology Program (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	8	Varma *et al.* (1988)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1667	US National Toxicology Program (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	+	8	Varma *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1667	US National Toxicology Program (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+	8	Varma *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Khudoley *et al.* (1989)
SA9, *Salmonella typhimurium* TA98, reverse mutation	NT	+	NG	Khudoley *et al.* (1989)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Mersch-Sundermann (1989)[d]
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	–	NG	Mersch-Sundermann (1989)[d]

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	NG	Mersch-Sundermann (1989)[d]
SCG, *Saccharomyces cerevisiae* D7, gene conversion	+	(+)	245	Nestmann & Lee (1985)
SCR, *Saccharomyces cerevisiae* XVI85-14C, reverse mutation	–	–	1225	Nestmann & Lee (1985)
ANN, *Aspergillus nidulans*, aneuploidy	+	NT	360	Benigni *et al.* (1993)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–[e]		2000 ppm inj.	Foureman *et al.* (1994)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	100	McGregor *et al.* (1991)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	(+)[f]	+[f]	25	Sofuni *et al.* (1996)
SIR, Sister chromatid exchange, rat erythroblastic leukaemia K_3D cells *in vitro*	+	+	420	Fujie *et al.* (1993)
CIC, Chromosomal aberrations, Chinese hamster lung (CHL)cells *in vitro*	–	+	100	Ishidate (1988)
CIC, Chromosomal aberrations, Chinese hamster lung fibroblast (CHL/IU) cells *in vitro*	–	(+)	1680	Matsuoka *et al.* (1996)
AIA, Aneuploidy, Chinese hamster lung fibroblast (CHL/IU) cells, polyploidy *in vitro*	+	–	720	Matsuoka *et al.* (1996)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	80	Morimoto & Koizumi (1983)
UPR, Unscheduled DNA synthesis, male Sprague-Dawley rat hepatocytes *in vivo*	–		2000 po × 1	Stocker *et al.* (1997)
SVA, Sister chromatid exchange, ICR/SJ mouse bone-marrow cells *in vivo*	+		25 po × 4	Morimoto & Koizumi (1983)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Micronucleus test, *Pleurodeles waltl* erythrocytes *in vivo*	–		50	Le Curieux *et al.* (1995)
MVM, Micronucleus test, ddY mouse bone-marrow cells *in vivo*	–		1000 ip × 1	Hayashi *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; NG, not given; inj., injection; po, oral; ip, intraperitoneal
[c] Closed container
[d] Standard assay, closed container or spot test
[e] Sex-linked recessive lethal mutations also negative with 1500 ppm chlorodibromomethane in the diet
[f] One of two laboratories reported positive results

6. References

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