BROMODICHLOROMETHANE

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.: 75-27-4

Systematic name: Bromodichloromethane

1.1.2 *Structural and molecular formulae and relative molecular mass*

$CHBrCl_2$

$CHBrCl_2$ Relative molecular mass: 163.83

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

(*a*) *Boiling-point*: 90.1°C

(*b*) *Melting-point*: –57.1°C

(*c*) *Conversion factor*: $mg/m^3 = 6.70 \times ppm$

1.2 Production, use and human exposure

Bromodichloromethane is found in chlorinated drinking-water as a consequence of the reaction between chlorine, added during water treatment, and natural organic substances in the presence of bromide. The major route of human exposure is via drinking-water. Bromodichloromethane has also been detected in some untreated waters, but at much lower levels. It is a major component of the organohalides produced by marine algae (IARC, 1991).

2. Studies of Cancer in Humans

No data were available to the Working Group regarding exposure to bromodichloromethane alone. Exposure to this compound as a contaminant of drinking-water is treated in Volume 52 of the *IARC Monographs* (IARC, 1991).

3. Studies of Cancer in Experimental Animals

Bromodichloromethane was tested for carcinogenicity in two-year studies in male and female Fischer 344 rats and B6C3F_1 mice by oral gavage, in life-span studies in male and female Wistar rats and in CBA × C57BL/6 hybrid mice by administration in drinking-water. In the gavage studies, bromodichloromethane increased the incidences of adenomatous polyps and adenocarcinomas of the large intestine and of tubule-cell adenomas and adenocarcinomas of the kidney in male and female rats, of tubule-cell adenomas and adenocarcinomas of the kidney in male mice and of hepatocellular adenomas and carcinomas in female mice. When administered in drinking-water, it induced neoplastic nodules and adenofibrosis of the liver in rats; no increase in tumour incidence was seen in mice. In a screening test for lung adenomas by intraperitoneal injection, bromodichloromethane did not increase the incidence of lung tumours in strain A mice (IARC, 1991).

3.1 Oral administration

Rat: Groups of 40 male and 40 female Wistar rats, five weeks of age, were administered microencapsulated bromodichloromethane (purity, 98%) at dietary concentrations of 0.014, 0.055 or 0.22% (equivalent to 6.1, 25.5 or 138 mg/kg bw per day for males and 8.0, 31.7 or 168.4 mg/kg bw per day for females) for 24 months. A concurrent control group of 70 male and 70 female rats received the same diet containing the starch-gelatin microcapsules alone. The microencapsulated diets were prepared every four months and the bromodichloromethane concentrations were verified. Ten rats of each sex from the control group and six rats of each sex from each of the dosed groups were killed at six months, while nine rats of each sex from the control group and five rats of each sex of the dosed groups were killed at 12 and 18 months. The remaining survivors were killed at 24 months. Body weight gain was suppressed in the 0.22% group for both males and females, while absolute liver weights were increased in the same groups. Dose-related changes included fatty degeneration in the livers of the 0.014% or higher-dose male groups, and fatty degeneration and granuloma in the 0.055 and 0.22% group females, as well as bile duct proliferation and cholangiofibrosis in the 0.22% group for both males and females. No significant differences in incidences or numbers of neoplastic changes were seen between the controls and any of the treatment groups. The numbers of cholangiocarcinomas of the liver in the controls and the low-, medium- and high-dose groups, respectively, were, for males, 0, 0, 0, 1 and, for females, 0, 0, 0, 3 (Aida *et al.*, 1992a; Yasuhara *et al*., 1995). [The Working Group noted that a maximum of 24 rats per sex per group were permitted to remain on the experiment beyond 18 months.]

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*

After oral administration to rats, bromodichloromethane is rapidly absorbed; part of the dose is exhaled as unchanged bromodichloromethane and as CO_2, and only minor fractions of the dose are found in the urine. Absorbed bromodichloromethane is rapidly eliminated from experimental animals, mainly by exhalation (IARC, 1991).

The disposition of bromodichloro[^{14}C]methane was studied in male Fischer rats after single oral doses of 1, 10, 32 or 100 mg/kg bw and oral dosing of 10 or 100 mg/kg bw every day for 10 days. Bromodichloromethane was extensively (approximately 80–90%) metabolized within 24 h after dosing, with approximately 70–80% of the administered dose appearing as $^{14}CO_2$ and approximately 3–5% as ^{14}CO. At all dose levels, urinary and faecal elimination of ^{14}C accounted for only 4% and 1–3% of the dose, respectively. Oral administration of bromodichloromethane at a concentration of 10 mg/kg bw per day for 10 days did not result in bioaccumulation or altered disposition of the test chemical, but during the course of the repeated dosing at 100 mg/kg bw per day, the rate of production of $^{14}CO_2$ increased, suggesting that this dose of bromodichloromethane induced its own metabolism. Persistence of radiolabelled residues in tissues collected 24 h after single-dose administration was low (3–4% of dose), with the most marked accumulation (1–3% of dose) in liver. Kidney tissue, particularly the cortical region, also contained significant concentrations of residues (Mathews *et al.*, 1990).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Repeated exposure of rats and mice to bromodichloromethane resulted in toxic effects in several organs, including the liver and kidney (IARC, 1991).

Biochemical and histopathological signs of hepatic damage were observed in rats at dose levels of 150–300 mg/kg bw per day after five days; in mice serum alanine aminotransferase and sorbitol dehydrogenase activities were elevated at a dose level of 150 mg/kg, but no histopathological lesions were observed. In rats, but not in mice, the total hepatic cytochrome P450 levels were decreased. As a sign of kidney damage, serum creatinine and blood urea nitrogen were elevated in rats dosed with 300 mg/kg but not in mice (Thornton-Manning *et al.*, 1994). Histopathological liver damage was observed in

female and male rats after dietary administration of 0.014% or more of bromodichloromethane; the changes were observed after six months and were accentuated after 12 and 18 months of administration. No histopathological changes were observed in the kidneys. A dose-dependent increase in the frequency of fatty degeneration and increased frequency of bile duct proliferation and cholangiofibrosis at the highest dose level were observed (Aida *et al.*, 1992a). In a similar one-month experiment, hepatic—but not renal—damage was observed in males at a dose level of 0.215% and in females at a dose level of 0.076% or higher (Aida *et al.*, 1992b). Pretreatment of Fischer 344 rats with buthionine sulfoximine, which decreased the hepatic glutathione content by 86%, markedly accentuated the hepatic and renal toxicity of bromodichloromethane administered as a single dose (400 mg/kg bw) by gavage (Gao *et al.*, 1996).

In a carcinogenicity study, liver cell proliferation in Wistar rats measured using immunostaining with a monoclonal antibody to proliferating cell nuclear antigen in the highest-dose group was maximal at six months of treatment (Yasuhara *et al.*, 1995).

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

In rats given bromodichloromethane throughout the period of major organogenesis, skeletal variations were observed in the presence of maternal toxicity, but no teratogenic effect was seen (IARC, 1991).

Bromodichloromethane, given in the drinking-water to Fischer 344 rats for one year (39 mg/kg bw per day), decreased the velocity of epididymal sperm, but had no effect on testicular morphology (Klinefelter *et al.*, 1995).

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)

Bromodichloromethane induced gene mutations in most studies with bacteria, which included various *Salmonella typhimurium* strains and *Escherichia coli* PQ 37 (SOS chromotest). Gene mutations were obtained with mouse lymphoma L5178Y cells in the presence of an exogenous metabolic system in one study. Sister chromatid exchanges were observed in rat erythroblastic leukaemia cells and human lymphocytes *in vitro* but not in a Chinese hamster cell line *in vitro*.

Chromosomal aberrations were observed *in vitro* except in two studies with Chinese hamster ovary cells. The single study on polyploidy induction in Chinese hamster lung fibroblasts reported no effect.

Table 1. Genetic and related effects of bromodichloromethane

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, *Escherichia coli* PQ 37, SOS chromotest	(+)	+	3	Le Curieux *et al.* (1995)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	NG	Simmon *et al.* (1977)[c,d]
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Mortelmans *et al.* (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Khudoley *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	5	Strobel & Grummt (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	170	Varma *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	NG	Mersch-Sunderman (1989)[e]
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	+	NG	Khudoley *et al.* (1989)[c]
SA0, *Salmonella typhimurium* TA100, reverse mutation, fluctuation test	–	–	3000	Le Curieux *et al.* (1995)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	–	NG	Mersch-Sunderman (1989)
SA4, *Salmonella typhimurium* TA104, reverse mutation	(+)	(+)	125	Strobel & Grummt (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500	Mortelmans *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	170	Varma *et al.* (1988)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	(+)[f]	NT	110	Pegram *et al.* (1997)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	–	130	Varma *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Mortelmans *et al.* (1986)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Khudoley *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	(+)	500	Strobel & Grummt (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	170	Varma *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	NG	Mersch-Sunderman (1989)[e]
SA9, *Salmonella typhimurium* TA98, reverse mutation	NT	+	NG	Khudoley *et al.* (1989)[c]
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	+	5	Strobel & Grummt (1987)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	+	NG	Mersch-Sunderman (1989)[e]

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SZG, *Saccharomyces cerevisiae* D7, gene conversion	(+)		10	Nestmann & Lee (1985)
SGR, *Saccharomyces cerevisiae* XV185-14C, reverse mutation	(+)		20	Nestmann & Lee (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	+	180	McGregor *et al*. (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	?	1000	Sofuni *et al*. (1996)
SIC, Sister chromatid exchange, Chinese hamster FAF cell line *in vitro*	–	NT	8	Strobel & Grummt (1987)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	5000	US National Toxicology Program (1987)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	?	5000	Anderson *et al*. (1990)
SIR, Sister chromatid exchange, rat erythroblastic leukaemia K_3D cells *in vitro*	+	+	33	Fujie *et al*. (1993)
CIC, Chromosomal aberrations, Chinese hamster FAF cell line *in vitro*	+	NT	8	Strobel & Grummt (1987)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	5000	US National Toxicology Program (1987)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	(+)	+	240	Ishidate (1987)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	5000	Anderson *et al*. (1995)
CIC, Chromosomal aberrations, Chinese hamster lung fibroblast (CHL/IU) cells *in vitro*	(+)	+	1250	Matsuoka *et al*. (1996)
AIA, Aneuploidy, Chinese hamster lung fibroblast (CHL/IU) cells, polyploidy *in vitro*	–	–	2500	Matsuoka *et al*. (1996)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	65	Morimoto & Koizumi (1983)
UPR, Unscheduled DNA synthesis, CD-1 rat hepatocytes *in vivo*	–		450 po × 1	Stocker *et al*. (1997)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SVA, Sister chromatid exchange, male ICR/SJ mouse bone-marrow cells *in vivo*	+		50 po × 4	Morimoto & Koizumi (1983)
MVM, Micronucleus test, ddY mouse bone-marrow cells *in vivo*	?		500 ip × 1	Hayashi *et al*. (1988)
MVM, Micronucleus test, ddY mouse bone-marrow cells *in vivo*	–		200 ip × 4	Hayashi *et al*. (1988)
Micronucleus test, *Pleurodeles waltl* larvae *in vivo*	(+)		50 feed	Le Curieux *et al.* (1995)

[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; po, oral; ip, intraperitoneal
[c] Closed container
[d] Closed container +, standard –
[e] Spot test +, standard –
[f] *Salmonella typhimurium* transfected with rat θ-class GST T1-1 positive at 4.6 μg/mL

A micronucleus induction study gave inconclusive or negative results in the bone-marrow cells of mice treated *in vivo* and weakly positive results in *Pleurodeles waltl*. Bromodichloromethane did not induce unscheduled DNA synthesis in rat hepatocytes *in vivo*, while sister chromatid exchanges were increased in the bone marow of mice dosed *in vivo*.

5. Evaluation

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

There is *sufficient evidence* in experimental animals for the carcinogenicity of bromodichloromethane.

Overall evaluation

Bromodichloromethane is *possibly carcinogenic to humans (Group 2B).*

6. References

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