BROMOFORM

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.: 75-25-2

Systematic name: Tribromomethane

1.1.2 *Structural and molecular formulae and relative molecular mass*

$CHBr_3$ Relative molecular mass: 252.75

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

(*a*) *Boiling-point*: 149.5°C

(*b*) *Melting-point*: 8.3°C

(*c*) *Conversion factor*: $mg/m^3 = 10.34 \times ppm$

1.2 Production, use and human exposure

Bromoform has a limited number of industrial uses. It 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 ion. It has also been detected in untreated water, but at lower levels. Bromoform is the major organohalide produced by chlorination of seawater during desalination. 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.

3. Studies of Cancer in Experimental Animals

Bromoform was tested for carcinogenicity in two-year studies by oral gavage in male and female B6C3F$_1$ mice and Fischer 344 rats. It induced a low incidence of adenomatous polyps and adenocarcinomas of the large intestine in male and female rats. Bromoform did not increase the proportion of mice with tumours. In a screening study by intraperitoneal injection, there was no dose-related increase in the average number of lung tumours in strain A mice given bromoform (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*

Bromoform administered in corn oil orally by gavage to rats is rapidly absorbed and distributed to the liver, brain, kidney and adipose tissue. In the expired air of dosed rats, unchanged bromoform accounted for approximately 67% of the dose and CO_2 for 4% within 8 h. Only 2% appeared in urine and 2% was retained in tissues. In contrast, in mice that were dosed orally, unchanged bromoform in expired air accounted for about 6% of the dose and CO_2 for about 40% within 8 h. About 5% of the dose was excreted in urine and 12% was retained in tissues. Bromoform is metabolized to carbon monoxide and dibromocarbonyl, the bromine analogue of phosgene (IARC, 1991).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

The liver is the primary target organ in rats and mice for bromoform toxicity following oral gavage dosing; hepatic fatty changes were observed in both short-term studies and carcinogenicity studies. A single dose of bromoform did not increase the incidence of γ-glutamyltranspeptidase-positive foci in rat liver in a two-stage carcinogenicity model experiment (IARC, 1991). However, bromoform induces S-phase DNA synthesis in male mouse liver at 48 h following a single oral dose of 600 mg/kg bw (Mirsalis *et al*., 1989).

In mice, bromoform has been observed to produce tubular hyperplasia and glomerular degeneration after an oral dose of 289 mg/kg bw daily for 14 days (IARC, 1991). A single

intraperitoneal dose of 3 mmol/kg bw given to Sprague-Dawley rats has also been shown to produce renal dysfunction, characterized by a reduction in glomerular filtration rate, reduced renal concentrating ability and elevated blood urea nitrogen levels (Kroll *et al*., 1994).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

There was some evidence that bromomethane can cause developmental toxicity in the absence of maternal toxicity in orally dosed rats (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)

Bromoform induced DNA damage and mutation in bacteria, particularly if exposures were in closed containers. In single studies, it induced aneuploidy in fungi, sex-linked recessive lethal mutations, but not heritable translocations, in *Drosophila melanogaster,* and micronuclei in the peripheral erythrocytes of larvae of the newt, *Pleurodeles waltl*. Results were inconsistent from tests in mammalian cell lines for the induction of chromosomal aberrations and sister chromatid exchanges, while mutations were induced in a single study with mouse lymphoma L5178Y cells. Sister chromatid exchanges were induced in cultured human lymphocytes and in mice treated *in vivo*. Micronuclei were increased in one of three studies with mice treated *in vivo*. Unscheduled DNA synthesis was not induced in hepatocytes and binding to DNA was not observed in the liver and kidney of rats treated *in vivo*.

5. Evaluation

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

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

Overall evaluation

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

Table 1. Genetic and related effects of bromoform

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)
SAF, *Salmonella typhimurium* BA13/BAL13, forward mutation, arabinose resistance test (Ara test)	?	–	353	Roldán-Arjona & Pueyo (1993)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	NG	Simmon *et al.* (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	–	300	Haworth *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1667	US National Toxicology Program (1989)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	NT	500	Rapson *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	–	250	Varma *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Mersch-Sundermann (1989)[c]
SA0, *Salmonella typhimurium* TA100, reverse mutation (fluctuation test)	+	–	300	Le Curieux *et al.* (1995)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	–	NG	Mersch-Sundermann (1989)[c]
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	NT	NG	Simmon *et al.* (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	300	Haworth *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1667	US National Toxicology Program (1989)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	NG	Varma *et al.* (1988)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	300	Haworth *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1667	US National Toxicology Program (1989)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Varma *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	300	Haworth *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	US National Toxicology Program (1989)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Varma *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	–	NG	Mersch-Sundermann (1989)[c]
SAS, *Salmonella typhimurium* TA97, reverse mutation	+	–	NG	Mersch-Sundermann (1989)[c]
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	1667	US National Toxicology Program (1989)
ANN, *Aspergillus nidulans*, aneuploidy	+	NT	870	Benigni *et al.* (1993)
ACC, *Allium cepa*, c-mitosis	+	NT	250	Östergren (1944)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		3000 feed	Woodruff *et al.* (1985)
DMH, *Drosophila melanogaster*, heritable translocations	–		3000 feed	Woodruff *et al.* (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	+	70	US National Toxicology Program (1989)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–[d]	–	968	Galloway *et al.* (1985)
SIR, Sister chromatid exchange, rat erythroblastic leukaemia K_3D cells *in vitro*	+	+	5.1	Fujie *et al.* (1993)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	(+)	+	116	Ishidate (1988)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–[d]	–	1600	Galloway *et al.* (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	20	Morimoto & Koizumi (1983)
UPR, Unscheduled DNA synthesis, male Sprague-Dawley rat hepatocytes *in vivo*	–		1080 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		
SVA, Sister chromatid exchange, B6C3F$_1$ mouse bone-marrow cells *in vivo*	+		800 ip × 1	US National Toxicology Program (1989)
Micronucleus test, *Pleurodeles waltl* erythrocytes *in vivo*	+		2.5	Le Curieux *et al.* (1995)
MVM, Micronucleus test, ddY mouse bone-marrow cells *in vivo*	–		1400 ip × 1	Hayashi *et al.* (1988)
MVM, Micronucleus test, B6C3F$_1$ mouse *in vivo*	+		800 ip × 2	US National Toxicology Program (1989)
MVM, Micronucleus test, Swiss CD-1 mouse bone-marrow cells *in vivo*	–		1000 po × 1	Stocker *et al.* (1997)
CBA, Chromosomal aberrations, B6C3F$_1$ mouse bone-marrow cells *in vivo*	–		800 ip × 1	US National Toxicology Program (1989)
BVD, DNA binding, Sprague-Dawley rat liver and kidney *in vivo*	–		380 po × 1	Pereira *et al.* (1982)

[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] Standard assay, closed container or spot test

[d] Weak positive response in one or two laboratories at a single dose

6. References

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