METHYL BROMIDE

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

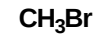
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 74-83-9
Chem. Abstr. Name: Bromomethane
IUPAC Systematic Name: Bromomethane
Synonym: Monobromomethane

1.1.2 *Structural and molecular formulae and relative molecular mass*



CH_3Br Relative molecular mass: 94.94

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless gas with a chloroform-like odour at high concentrations (Budavari, 1996)
(*b*) *Boiling-point*: 3.5°C (Lide, 1997)
(*c*) *Melting-point*: –93.7°C (Lide, 1997)
(*d*) *Solubility*: Slightly soluble in water, very soluble in organic solvents (American Conference of Governmental Industrial Hygienists, 1992)
(*e*) *Vapour pressure*: 166 kPa at 20°C; relative vapour density (air = 1), 3.27 (Lewis, 1993)
(*f*) *Explosive limits*: Upper, 15%; lower, 10% by volume in air (American Conference of Governmental Industrial Hygienists, 1992)
(*g*) *Conversion factor*: $mg/m^3 = 3.88 \times ppm$

1.2 Production and use

Production of methyl bromide in the United States was estimated to be 20 400 tonnes in 1984 (United States National Library of Medicine, 1997). Information available in 1995 indicated that it was produced in 10 countries (Chemical Information Services, 1995).

Methyl bromide is used as a soil and space fumigant; as a pesticide on potatoes, tomatoes and other crops; in organic synthesis; and as an extraction solvent for vegetable oil (Lewis, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 5000 workers in the United States were potentially exposed to methyl bromide (see General Remarks). Occupational exposures may occur in its production, in pest control for vegetables and fruits and in fumigation of soil.

1.3.2 *Environmental occurrence*

Methyl bromide is produced by a variety of marine organisms. The bulk of the methyl bromide detected in the environment is believed to be released from oceans. Release to the environment also results from the use of methyl bromide as a soil and space fumigant and its occurrence in vehicle exhaust. Methyl bromide is frequently detected in ambient air and, at low levels, in surface water, drinking water and groundwater (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 3.9 mg/m^3 as the 8-h time-weighted average threshold limit value, with a skin notation, for occupational exposures to methyl bromide in workplace air. Values of 1–60 mg/m^3 have been used as standards or guidelines in other countries (International Labour Office, 1991).

No international guideline for methyl bromide in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

Wong *et al.* (1984) studied the mortality of a cohort of 3579 white male workers with potential exposure to brominated compounds at three chemical manufacturing plants and at a research establishment between 1935 and 1976. The exposures included 1,2-dibromo-3-chloropropane (DBCP) (see this volume), tris(2,3-dibromopropyl)phosphate (Tris) (see this volume), polybrominated biphenyls (PBBs) (IARC, 1987b), various organic and inorganic bromides and DDT (IARC, 1991). Among a subgroup of 665 men exposed to organic brominated compounds other than DBCP, Tris and PBBs, and with potential exposure to methyl bromide, 51 deaths occurred versus 44.77 expected (standardized mortality ratio (SMR), 1.1; 95% confidence interval (CI), 0.9–15.0). Ten deaths from cancer were observed versus 7.86 expected, yielding a SMR of 1.3 (95% CI, 0.6–2.3). In this group of workers, there were two deaths from testicular cancer versus 0.11 expected

(SMR, 17.8; 95% CI, 2.0–64.9). An investigation of the work histories showed that methyl bromide was the only common potential exposure of these two cases. These men died at the ages of 17 and 33 years, respectively. [The Working Group noted that no information was available on duration of exposure or on time between first exposure and death from testicular cancer.]

A number of studies have analysed cancer mortality or incidence in pesticide applicators, some of whom may have been exposed to methyl bromide. However, none have provided estimates of risk in relation to methyl bromide specifically.

3. Studies of Cancer in Experimental Animals

In one 90-day study, methyl bromide was tested in rats by oral administration. An increased incidence of squamous-cell carcinomas of the forestomach was observed in animals of each sex (IARC, 1986).

3.1 Oral administration

Rat: In a study to investigate further the findings of a previously reported 90-day study, groups of 15 male Wistar rats, six weeks of age, were administered 50 mg/kg bw methyl bromide (purity, > 99%) in arachis oil by gavage on five days per week for 13, 17, 21 or 25 weeks, at which times the surviving animals were killed. Further groups received methyl bromide for 13, 17 or 21 weeks followed by observation up to 25 weeks. Control animals received arachis oil for 13 or 25 weeks. In rats exposed for 25 weeks, one squamous-cell carcinoma of the forestomach occurred. Hyperplasia of the forestomach occurred in all treated groups but the hyperplasia regressed by 25 weeks in the groups in which treatment stopped earlier (Boorman *et al*., 1986).

3.2 Inhalation exposure

3.2.1 *Mouse*

Groups of 70 male and 70 female B6C3F_1 mice, six weeks of age, were administered methyl bromide (purity, 99.8%) by whole-body inhalation at concentrations of 0 (controls), 10, 33 or 100 ppm [0, 4, 129 or 389 mg/m^3] for 6 h per day on five days per week. The control, low- and mid-dose groups were exposed for 103 weeks. In the high-dose group, exposure to methyl bromide was stopped after 20 weeks because of high mortality in this group and the remaining mice were exposed to air only for the rest of the study. Ten mice of each sex from each group were killed at six and 15 months. All surviving animals were killed at weeks 105–106. Necropsy was performed on all animals and all organs were examined histologically. Survival at termination was 40/50, 37/50, 40/50 and 16/70 in males and 36/50, 41/50, 45/49 and 40/60 in females in the control, low-, mid- and high-dose groups, respectively. No treatment-related increase in the incidence of tumours was observed in males or females (United States National Toxicology Program, 1992).

Groups of 50 male and 50 female BDF_1 (C57BL/6 × DBA/2) mice, six weeks of age, were administered methyl bromide (purity, > 99.9%) by whole-body inhalation at concentrations of 0 (controls), 4, 16 or 64 ppm [0, 16, 62 or 249 mg/mg^3] for 6 h per day on five days per week for 104 weeks. At 105 weeks, all surviving animals were killed. Necropsy was performed on all animals and all organs were examined histologically. Survival at 104 weeks was 41/50, 36/50, 33/50 and 45/50 in males and 32/50, 23/50, 24/49 and 35/49 in females in the control, low-, mid- and high-dose groups, respectively. No increased incidence of tumours related to treatment was observed (Gotoh *et al*., 1994).

3.2.2 *Rat*

Groups of 50 male and 50 female Wistar rats, six weeks of age, were administered methyl bromide (purity, 98.8%) by whole-body inhalation at concentrations of 0 (controls), 3, 30 or 90 ppm [0, 12, 117 or 350 mg/m^3] for 6 h per day on five days per week for 29 months. Additional satellite groups of 10 males and 10 females were used for interim killings at weeks 14, 53 and 105. Survival in males at week 114 of the experiment was 25/50, 34/50, 29/50 and 14/50 and at week 128 was 15/50, 25/50, 16/50 and 8/50 in control, low-, mid- and high-dose animals. Survival in females at week 114 was 27/50, 32/50, 25/50 and 21/50 and that at week 129 was 14/50, 23/50, 17/50 and 7/50, respectively. By week 114, mortality in males in the high-dose group was significantly higher than that in controls ($p < 0.05$, Fisher's exact test, one-sided). No increased incidence of tumours was observed (Reuzel *et al*., 1991).

Groups of 50 male and 50 female Fischer 344/DuCrj rats, six weeks of age, were administered methyl bromide (purity, > 99.9%) by whole-body inhalation at concentrations of 0 (controls), 4, 20 or 100 ppm [0, 16, 78 or 389 mg/m^3] for 6 h per day on five days per week for 104 weeks. At week 105, all surviving animals were killed. Necropsy was performed on all animals and all organs were examined histologically. Survival at week 104 was 34/50, 34/50, 31/50 and 33/50 in control, low-, mid- and high-dose males and 42/49, 38/50, 39/50 and 41/50 in control, low-, mid- and high-dose females, respectively. The incidence of adenomas of the pituitary gland was significantly increased in high-dose males compared with controls (16/50, 23/50, 19/50 and 30/50 in control, low-, mid- and high-dose, respectively; $p < 0.01$, chi-square test). In females, no increase in the incidence of tumours related to treatment was observed (Gotoh *et al*., 1994).

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

4.1 Absorption, distribution, metabolism and excretion

The metabolism of methyl bromide has been reviewed (International Programme on Chemical Safety (WHO), 1995).

4.1.1 *Humans*

No study describing toxicokinetics of methyl bromide in humans *in vivo* was available for evaluation.

In human erythrocytes *in vitro*, methyl bromide is consumed, probably with formation of a glutathione conjugate. The reaction involves a glutathione *S*-transferase enzyme that metabolizes methyl halides. This enzyme has not been found in erythrocytes of mouse, rat, cattle, sheep, pig or rhesus monkey. The enzyme is present only in part of the human population: among 45 people investigated, only 27 conjugated glutathione with methyl bromide. The enzyme in erythrocytes of conjugators is different from other glutathione *S*-transferases with respect to substrate specificity, affinity chromatography, and inhibition characteristics; it has been designated as glutathione *S*-transferase θ (Hallier *et al.*, 1990; Schröder *et al.*, 1992; Hallier *et al.*, 1993; Pemble *et al.*, 1994; Schröder *et al.*, 1996).

The interindividual differences in the ability of humans to conjugate methyl bromide suggest that the polymorphic human glutathione *S*-transferase enzyme present in erythrocytes is relevant for the disposition of methyl bromide in humans. Iwasaki *et al.* (1989) described a field study of methyl bromide workers in Japan, whose levels of the methyl bromide-derived haemoglobin adduct (*S*-methylcysteine in haemoglobin) were measured. In a subgroup of seven workers with the highest exposure levels (filling of spray cans and gas cylinders), three had high adduct levels (the highest levels in the whole study), whereas the four other workers of the same exposure subgroup had levels that were close to the background in nonexposed persons (Iwasaki, 1988a,b; Iwasaki *et al.*, 1989).

4.1.2 *Experimental animals*

Studies on rats and dogs have shown that inhaled methyl bromide is rapidly absorbed through the lungs. In rats, it is also rapidly absorbed following oral exposure.

After absorption, methyl bromide or metabolites are rapidly distributed to many tissues including the lung, adrenal gland, kidney, liver, nasal turbinates, brain, testis and adipose tissue. In an inhalation study in rats, the methyl bromide concentrations in tissues reached a maximum after 1 h of exposure, but decreased rapidly. Methyl bromide is probably metabolized by glutathione conjugation, the formed *S*-methylglutathione being sequentially catabolized to *S*-methyl-L-cysteine and then to carbon dioxide.

Methylation of proteins and lipids has been observed in the tissues of several species, including humans, after exposure via inhalation. Methylated DNA bases have also been detected following exposure of rodents *in vivo* or rodent cells *in vitro* to methyl bromide.

In inhalation studies using ^{14}C-labelled methyl bromide, exhalation of $^{14}CO_2$ was the major route of elimination of ^{14}C. A smaller amount of ^{14}C was excreted in the urine. Following oral administration, urinary excretion was the major route of elimination of ^{14}C (IARC, 1986).

After exposure of male CD rats (nose only) to 55 ppm [213 mg/m^3] [^{14}C]methyl bromide for 3 min, 43% of the radioactivity was exhaled during an observation period of 32 h (Jaskot *et al.*, 1988).

4.2 Toxic effects

The toxicity of methyl bromide has been reviewed (WHO, 1995; Yang *et al*., 1995).

4.2.1 *Humans*

More than 950 methyl bromide poisonings have been reported, involving fatalities, systemic poisoning, irritation to skin, eyes and respiratory tract, and damage to the central nervous system, liver and kidney (IARC, 1986). Several reports on poisonings after short- and long-term exposure to methyl bromide, some of them fatal, have also been published (Behrens & Dukes, 1986; Goldman *et al*., 1987; O'Neal, 1987; Zwaveling *et al*., 1987; Herzstein & Cullen, 1990; Polkowski *et al*., 1990; Kishi *et al*., 1991; Hustinx *et al*., 1993; Deschamps & Turpin, 1996; Garnier *et al*., 1996; Langård *et al*., 1996; De Haro *et al*., 1997).

4.2.2 *Experimental systems*

Signs of methyl bromide toxicity following acute exposure include irritation of the eyes and respiratory tract, tremor, incoordination, depression of the central nervous system and convulsions. Long-term exposure induces pulmonary congestion, central nervous system effects, and renal and hepatic lesions. After oral administration to rats, hyperplasia and hyperkeratosis (and squamous-cell carcinomas) of the forestomach were observed (IARC, 1986).

Methyl bromide, given by gavage (50 mg/kg on five days per week) for 13 weeks to Wistar rats induced inflammation, acanthosis, fibrosis and a high incidence of pseudo-epitheliomatous hyperplasia in the forestomach; these changes were aggravated upon continued administration for a total of 25 weeks, by which time all of the 11 rats examined showed hyperplastic changes (Boorman *et al*., 1986). In groups in which the treatment was discontinued after 13 weeks, the changes regressed, but adhesions, fibrosis and mild acanthosis persisted for 12 weeks (week 25 of the experiment).

Following inhalation exposure of male Sprague-Dawley rats for 4 h per day on five days per week to either 150 ppm [580 mg/m^3] for 11 weeks or 200, 300 or 400 ppm [780, 1160 or 1550 mg/m^3] for six weeks, mortality occurred at exposure levels ≥ 300 ppm. Observed effects included necrotic areas in the brain and heart, fatty degeneration in the liver, isolated acinar cell necroses in the pancreas, and, at the highest concentration, atrophic changes in the testis. Olfactory epithelium was not studied (Kato *et al*., 1986).

Following short-term inhalation exposure to 160 ppm [620 mg/m^3] methyl bromide (6 h per day on five days per week for up to six weeks), B6C3F$_1$ mice were found to be more sensitive than Fischer 344/N rats: 50% of male mice died after eight exposures and 50% of female mice after six exposures, while similar mortality was observed in male rats only after 14 exposures. Neuronal necrosis and testicular degeneration were observed in both species; nephrosis was observed in nearly all mice, while necrosis of the olfactory epithelium was more marked in rats. Myocardial degeneration occurred in rats and to a lesser degree in male mice. In the adrenal cortex, there was cytoplasmic vacuolation in rats and inner zone atrophy in female mice (Eustis *et al*., 1988).

In a carcinogenicity study of methyl bromide (see Section 3.2.1), survival of $B6C3F_1$ mice was decreased in males exposed to 100 ppm [390 mg/m^3], the highest concentration. Olfactory necrosis and metaplasia, cardiac degeneration and chronic cardiomyopathy, cerebral and cerebellar degeneration and sternal dysplasia were observed in both males and females at the highest concentration and were more frequent in males (United States National Toxicology Program, 1992).

In an inhalation study in which Wistar rats were exposed to 3, 30 or 90 ppm [12, 120 or 350 mg/m^3] for 6 h per day on five days per week for 29 months, a dose-dependent increase in basal-cell hyperplasia of the olfactory epithelium was observed in both sexes; this could be observed after 12 months and did not appreciably increase in frequency or severity by 24 or 29 months. In the highest-dose group, there was an increased incidence of heart thrombi in both females and males; myocardial degeneration was observed in females and cartilaginous metaplasia in both sexes. The incidence of oesophageal hyperkeratosis was elevated in treated males and females, but reached significance only in males at the highest dose group. Hyperkeratosis of the stomach was more frequent in the highest-dose group, but was not in significant excess (Reuzel *et al.*, 1991).

Extensive destruction of the olfactory epithelium was observed in male Fischer 344 rats exposed to 200 ppm [780 mg/m^3] methyl bromide for 6 h per day for five days. By day 3, despite continued exposure, there was replacement of the olfactory epithelium by a squamous-cell layer, followed by progressive reorganization toward the normal architecture, and by week 10, 75–80% of the epithelium appeared histologically normal. Olfactory epithelial-cell replication was maximal on day 3 of exposure, with a labelling index of 14.7% compared with 0.7% in the controls (Hurtt *et al.*, 1988). Degeneration and subsequent regeneration were also observed in an inhalation experiment with Fischer 344 rats exposed to 175 ppm [680 mg/m^3] 6 h twice, separated by a 28-day interval (Bolon *et al.*, 1991).

Nasal olfactory cell degeneration was observed at exposure levels ≥ 175 ppm [680 mg/m^3], when Fischer 344 rats were exposed to methyl bromide for 6 h per day for five days. A dose-dependent vacuolar degeneration of the zona fasciculata of the adrenal glands and cerebellar granule cell degeneration were also observed, while hepatocellular degeneration was confined to dose levels ≥ 250 ppm [970 mg/m^3]; cerebral cortical degeneration and (minor) testicular damage were observed only at the highest dose level, 325 ppm [1260 mg/m^3] (Hurtt *et al.*, 1987).

When food fumigated with methyl bromide (total bromine content 80, 200 or 500 ppm; methyl bromide < 20 ppm) was administered to male and female Fischer 344 rats for two years, no toxicologically important changes in clinical, chemical, haematological or histological parameters were observed. There was, however, a minor (3–6%) decrement in the weight gain among the males after 60 weeks (Mitsumori *et al.*, 1990).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

The developmental toxicity of methyl bromide was studied in rats and rabbits. Male and female Wistar rats were exposed by inhalation to methyl bromide for 7 h per day on five days per week for three weeks before mating, and the females were also exposed through 19 days of gestation. New Zealand white rabbits were inseminated and exposed for 7 h daily on days 1–24 of gestation. The target concentrations were 20 and 70 ppm [80 and 270 mg/m^3] for both species. None of the rats died during the experiment, while 24/25 rabbits inhaling the high dose died. There were minor variations in the weight development of the rats during gestation, which were, however, inconsequential by the end of gestation. Methyl bromide had no effect on the pregnancy rate, embryonic viability, or weight or length development of the fetuses; neither did it induce terata in either species (Sikov *et al.*, 1981).

Inhalation exposure of rats to 160 ppm [620 mg/m^3] or 400 ppm [1550 mg/m^3] methyl bromide for ≥ 6 weeks caused testicular degeneration (Kato *et al*., 1986; Eustis *et al*., 1988). However, when male Fischer 344 rats were exposed to 200 ppm [780 mg/m^3] methyl bromide for 6 h per day for five days and followed for two months, no effect was observed at any time during or after the exposure on testis weight, daily sperm production, cauda epididymal sperm count, sperm morphology, percentage motile sperm, linear sperm velocity, or epididymal or testicular histology (Hurtt & Working, 1988).

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)

Methyl bromide induced SOS repair in *Salmonella typhimurium* and gene mutation in *Salmonella typhimurium* TA100 and TA1535; it was also mutagenic to *Escherichia coli* WP2 *uvrA*, plants and *Drosophila*. It did not induce unscheduled DNA synthesis in cultured rat hepatocytes. It induced sister chromatid exchanges *in vitro* in lymphocytes from human donors who were classified as non-conjugators of methyl bromide with glutathione.

Methyl bromide induced micronuclei in bone-marrow and peripheral blood cells of rats and mice.

Methyl bromide binds covalently to DNA *in vitro* and *in vivo* in various organs in rats and mice.

Table 1. Genetic and related effects of methyl bromide

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS repair *umu*-test, *Salmonella typhimurium* TA1535/pSK1002	+	+	116	Ong *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	0.4	Simmon *et al*. (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	0.5	Moriya *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	1.9	Kramers *et al*. (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	0.1% atm	JETOC (1997)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	NG	Moriya *et al*. (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	0.1% atm	JETOC (1997)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Moriya *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.5% in air	JETOC (1997)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	NG	Moriya *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Moriya *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Kramers *et al*. (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	0.5% in air	JETOC (1997)
ECF, *Escherichia coli* SD-4, forward mutation	+	NT	570	Djalali-Behzad *et al*. (1981)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	+	+	0.2% atm	JETOC (1997)
EC2, *Escherichia coli* WP2, reverse mutation	+	+	NG	Moriya *et al*. (1983)
KPF, *Klebsiella pneumoniae*, forward mutation	+	NT	4.75	Kramers *et al*. (1985)
HSM, *Hordeum* species, mutation	(+)	NT	130	Ehrenberg *et al*. (1974)
DMM, *Drosophila melanogaster*, somatic wing-spot assay, mitotic recombination	+		8 inh	Katz (1987)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		0.38 inh	Kramers *et al*. (1985)
URP, Unscheduled DNA synthesis, male Wistar rat primary hepatocytes *in vitro*	–	NT	30	Kramers *et al*. (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	0.1	Kramers *et al*. (1985)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
G51, Gene mutation, mouse lymphoma L5178Y cells, all other loci *in vitro*	+	NT	0.1	Kramers *et al*. (1985)
T7S, Cell transformation, SA7/Syrian hamster embryo cells	–	NT	30 µg/mL	Hatch *et al*. (1983)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	(+)	NT	167 µg/mL 10 sec	Tucker *et al*. (1986)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	+	5	Garry *et al*. (1990)
SHL, Sister chromatid exchange, human lymphocytes from glutathione conjugators *in vitro*	–	NT	19.5 µg/mL 1 h	Hallier *et al*. (1993)
SHL, Sister chromatid exchange, human lymphocytes from glutathione non-conjugators *in vitro*	+	NT	19.5 µg/mL 1 h	Hallier *et al*. (1993)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	(+)	95	Garry *et al*. (1990)
MVM, Micronucleus test, BDF_1 mouse bone marrow and peripheral blood *in vivo*	+		600 mg/m^3 inh 6 h × 14	Ikawa *et al*. (1986)
MVR, Micronucleus test, Fischer 344 rat bone marrow *in vivo*	+		1300 mg/m^3 inh 6 h × 14	Ikawa *et al*. (1986)
BID, Binding (covalent) to calf thymus DNA *in vitro*	+	NT	48	Starratt & Bond (1988)
BVD, Binding (covalent) to DNA, CBA mouse liver and spleen *in vivo*	+		6.5 inh 1 h × 1	Djalali-Behzad *et al*. (1981)
BVD, Binding (covalent) to DNA, Fischer 344 rat liver, lung, stomach and forestomach *in vivo*	+		ca. 3.3 po × 1	Gansewendt *et al*. (1991)
BVD, Binding (covalent) to DNA, Fischer 344 rat liver, lung, stomach and forestomach *in vivo*	+		3.8 inh 6 h × 1	Gansewendt *et al*. (1991)

[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; atm, atmosphere; NG, not given; inh, inhalation; po, oral

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to methyl bromide may occur in its production, in pest control and in fumigation of soil. Methyl bromide is naturally produced in oceans. It is commonly detected in ambient air and at low levels in water.

5.2 Human carcinogenicity data

One cohort study of workers at three chemical manufacturing plants included a subgroup with potential exposure to methyl bromide, among whom there were two deaths from testicular cancer (0.11 expected).

5.3 Animal carcinogenicity data

Methyl bromide was tested by oral administration in rats and by inhalation in mice and rats. In one 90-day study by oral administration in rats, methyl bromide was reported to produce squamous-cell carcinomas of the forestomach. In a second, 25-week study designed to investigate further the findings of the previous study, early hyperplastic lesions of the forestomach developed after 25 weeks of continuous treatment by gavage. In two inhalation studies in mice, no significant increase in the incidence of tumours was observed. In one inhalation study in rats, an increase in the incidence of adenomas of the pituitary gland was observed in high-dose male rats. In another study in rats, no increase in tumour incidence was observed.

5.4 Other relevant data

Methyl bromide is metabolized by glutathione conjugation and excreted as carbon dioxide. In animal studies, it caused toxicity and irritation and organ toxicity in many organs. It binds covalently to DNA *in vitro* and also in various organs in the rat *in vivo*. Methyl bromide is mutagenic in bacteria; it induces gene mutations and sister chromatid exchanges *in vitro* in mammalian cells. Methyl bromide gave positive results for several genetic activity end-points in *Drosophila*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of methyl bromide.

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

Overall evaluation

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

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