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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

BROMOCHLOROACETIC ACID

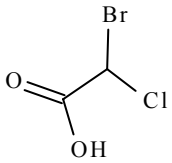
1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 5589-96-8
Chem. Abstr. Name: Acetic acid, 2-bromo-2-chloro-
IUPAC Systematic Name: 2-Bromo-2-chloroacetic acid
Synonyms: Acetic acid, bromochloro- (7CI, 8CI, 9CI); bromochloroacetate; bromochloroacetic acid; chlorobromoacetic acid

1.1.2 Structural and molecular formulae and relative molecular mass



$C_2H_2BrClO_2$
Relative molecular mass: 173.39

1.1.3 Chemical and physical properties of the pure substance

Description: Crystalline compound (NTP, 2009)
Boiling-point: bp_{760} 215 °C (Weast, 1983)
Melting-point: 27.5–31.5 °C (WHO, 2004)
Density: 1.98 at 20 °C (WHO, 2004)
Spectroscopy data: Infrared and magnetic resonance spectra (proton and C-13) have been reported (NTP, 2009).
Solubility: Soluble in water and methanol (Xie *et al.*, 1993); in dilute solutions at pH > 6, more than 99.99% of the chemical exists as the dissociated carboxylate anion, bromochloroacetate. Bromochloroacetate contains an asymmetric carbon atom and, therefore, can exist in two non-superimposable forms, the (+)- and (–)-bromochloroacetate stereoisomers (NTP, 2009).
Octanol/water partition coefficient (P): log P, 1.08 (WHO, 2004)
Conversion factor in air:
1 ppm = 7.09 mg/m^3 (WHO, 2004)

1.1.4 Technical products and impurities

Dibromoacetic acid was found to be the major impurity at concentrations of 2.35% and 0.83% in two lots of bromochloroacetic acid used in toxicology studies in rodents (NTP, 2009).

1.1.5 Analysis

Bromochloroacetic acid can be determined in the drinking-water by gas chromatography with electron capture detection following extraction by anion exchange column and conversion to its methyl ester. The limit of detection is 0.016 µg/L (EPA, 2003). It can also be determined in drinking-water following ion chromatography by electrospray ionization tandem mass

spectrometry, for which the limit of detection is 0.11 µg/L (EPA, 2009).

1.2 Production and use

1.2.1 Production

Bromochloroacetic acid can be produced by bromination of chloroacetic acid with a 2:1 bromide/bromate mixture under acidic conditions (Adimurthy *et al.*, 2006).

Bromochloroacetic acid is produced commercially only in small quantities for research purposes.

Information available in 2010 indicated that bromochloroacetic acid was manufactured by five companies in the USA and one company each in Germany and Switzerland (Chemical Sources International, 2010).

1.2.2 Use

Bromochloroacetic acid is used only in research.

1.3 Occurrence and exposure

1.3.1 Natural occurrence

Bromochloroacetic acid is not known to occur naturally.

1.3.2 Occurrence and exposure in drinking-water

(a) Formation of halogenated disinfection by-products in drinking-water

The drinking-water disinfectant chlorine reacts with natural organic matter to produce halogenated disinfection by-products, and trihalomethanes and haloacetic acids are the two most prevalent groups of known specific by-products formed during disinfection of natural waters with chlorine-containing oxidizing compounds (Hua & Reckhow, 2007). These compounds are formed when drinking-water supplies containing natural organic matter (e.g. humic or fulvic acids) are disinfected with compounds such as chlorine gas, hypochlorous acid and hypochlorite (Huang *et al.*, 2004). When bromide is present in the source water, it may be oxidized to hypobromous acid–hypobromite ion, which can react with organic matter to form brominated organic compounds. The reaction of brominated and/or chlorinated oxidizing agents with natural organic matter produces mixed brominated and chlorinated compounds. The relative amount of brominated haloacetates produced in chlorinated drinking-water is a function of the concentration of bromide in the source water and of the initial bromine/chlorine ratio. The relative amounts of disinfection by-products produced in drinking-water supplies are affected by the nature and concentration of the organic precursor materials, water temperature, pH, the type of disinfectant, the disinfectant dose and contact time (Liang & Singer, 2003; Huang *et al.*, 2004). Treatment of natural waters with chloramine or chlorine dioxide produces haloacetic acids, but at levels substantially lower than those formed by free chlorine (Richardson *et al.*, 2000; Hua & Reckhow, 2007). Because commonly used alternative disinfectants (ozone, chloramines and chlorine dioxide) produce lower levels of most haloacetic acids, many water utilities have switched from chlorination to these alternatives to meet the regulation limits in terms of disinfection by-products (Krasner *et al.*, 2006; Richardson *et al.*, 2007).

Data from the USA revealed that water-treatment systems that used chlorine dioxide had higher levels of nine haloacetic acids than those that used chlorine or chloramine only (McGuire *et al.*, 2002). This is because the water-treatment systems that used chlorine dioxide also used chlorine or chloramines (mostly as post-disinfectants). Similarly to chloramines and chlorine dioxide, ozone used in water treatment is well known to lower the levels of haloacetic acids

formed relative to chlorination (Richardson *et al.*, 2007). However, when source waters contain elevated levels of natural bromide, the levels of brominated compounds were shown to increase when pre-ozone treatment was performed before chlorination (IPCS, 2000; Richardson *et al.*, 2007).

According to IPCS (2000) and WHO (2008), the optimized use of combinations of disinfectants that function as primary and secondary disinfectants should allow further control of disinfection by-products. There is a trend towards combination/sequential use of disinfectants: ozone is used exclusively as a primary disinfectant; chloramines are used exclusively as a secondary disinfectant; and both chlorine and chlorine dioxide are used in either role.

According to WHO (2004), bromide ions occur naturally in surface water and groundwater; their levels exhibit seasonal fluctuations, and can also increase due to saltwater intrusion resulting from drought conditions or pollution (IPCS, 2000).

(b) Concentrations in drinking-water

A nationwide study of the occurrence of disinfection by-products in different geographical regions of the USA was conducted between October 2000 and April 2002 (Weinberg *et al.*, 2002), in which samples were taken from 12 water-treatment plants that had different levels of source water quality and bromide and used the major disinfectants (chlorine, chloramines, ozone and chlorine dioxide). Concentrations of bromochloroacetic acid in finished water samples ranged from 1.3 to 18 µg/L.

Data from drinking-water supplies in the USA (EPA, 2000 cited in WHO 2004) indicated that bromochloroacetic acid was detected in groundwater and surface water distribution systems at mean concentrations of 1.47 and 3.61 µg/L, respectively.

In a survey of 20 drinking-waters prepared from different source waters in the Netherlands (Peters *et al.*, 1991), haloacetic acids were found in all drinking-waters prepared from surface water, whereas they could not be detected in drinking-waters prepared from groundwater. The total concentrations of haloacetic acids were in the range of 0.5–14.7 µg/L (surface water only) with levels of bromochloroacetic acid ranging from 0.2 to 2.5 µg/L. The limit of detection of this study was 0.1 µg/L, and brominated acetic acids accounted for 65% of the total haloacetic acid concentration.

Bromochloroacetic acid was measured in water samples taken from a water-treatment plant in Barcelona (Spain) between November 1997 and March 1998 (Cancho *et al.*, 1999). Haloacetic acids were rapidly formed during the pre-chlorination step, but their concentration did not increase during either sand filtration or the ozonation step. At these two stages, the concentration of total haloacetic acids represented 60% of the total trihalomethane levels. A significant decrease in total concentration of haloacetic acids was observed when ozonated water was passed through granular activated carbon filters, but the acids were formed again during post-chlorination, although at concentrations lower than those during the previous stages. The average total level of haloacetic acids was around 22 µg/L in tap-water (range, 11–32 µg/L). Bromochloroacetic acid was not detected in raw water, but was detected in pre-chlorinated water (mean, 8.8 µg/L; range, 6.4–15 µg/L), sand-filtered water (mean, 8.2 µg/L; range, 7.1–11 µg/L), ozonated water (mean, 9.1 µg/L; range, 8–11.4 µg/L), granulated activated carbon-filtered water (mean, 0.8 µg/L; range, not detected–3.2 µg/L) and post-chlorinated water (mean, 2.5 µg/L; range, 1–3.9 µg/L), i.e. water that was ready for consumption. [The limit of detection was not reported.]

Water samples were collected from 35 Finnish waterworks between January and October in 1994 and from three waterworks and distribution systems during different seasons in 1995 (Nissinen *et al.*, 2002). Bromochloroacetic acid

was detected at 32 of the 35 Finnish waterworks sampled in 1995 with concentrations between 0.3 and 19 µg/L. Levels at the other facilities were below the limit of quantitation of 0.2 µg/L. The concentration of six haloacetic acids, including bromochloracetic acid, exceeded that of trihalomethanes. Chlorinated drinking-waters originating from surface waters contained the highest concentration of haloacetic acids (108 µg/L). The lowest concentrations of disinfection by-products were measured from ozonated and/or activated carbon-filtered and chloraminated drinking-waters (20 µg/L). Higher concentrations of the six haloacetic acids were measured in summer than in winter [data not reported].

In the USA, finished waters from the Philadelphia (PA) Suburban Water Co., the Metropolitan Water District of Southern California, and utilities at the cities of Houston (TX) and Corpus Christi (TX) were collected at the point of entry to the water distribution system and analysed for the nine haloacetic acids (Cowman & Singer, 1996). These samples included waters with relatively low (Philadelphia), moderate (Houston), and high (Southern California, Corpus Christi) bromide concentrations. Several of the utilities (Houston, Southern California, Corpus Christi) added ammonia to their waters after chlorination to control disinfection by-product formation. Levels of bromochloroacetic acid were below the limit of detection [not reported] in the Philadelphia utility, where the bromide ion concentration was 50.6 µg/L. For the others utilities, where levels of bromide ion ranged from 72 to 412 µg/L, those of bromochloroacetic acid ranged from 4.68 to 10.8 µg/L.

Drinking-water was studied in Israel because its source water (the Sea of Galilee, a freshwater lake, also called Lake Kinereth) has among the highest natural levels of bromide in the world for surface water (2000 µg/L) and chlorine dioxide is used for disinfection at full-scale treatment plants (Richardson *et al.*, 2003). Chlorine-containing disinfection by-products that are usually dominant under conditions of low levels of bromide (for chlorination and chloramine disinfection) — chloroform and dichloroacetic acid — were found at very low concentrations or not at all in these samples, with a shift to bromoform and dibromoacetic acid occurring under these conditions of high levels of bromide. Thus, the high bromide content in the source water had a major impact on the speciation of the disinfection by-products. Bromochloroacetic acid was detected at levels between 1 and 3.9 µg/L.

Between October 1994 and April 1996, a mean concentration of 0.6 µg/L bromochloroacetic acid was measured in the Santa Ana River (USA) downstream of a discharge point for highly treated municipal wastewater effluent (Ding *et al.*, 1999).

A study was conducted in nine distribution systems of the greater area of Québec City (Province of Québec, Canada) (Legay *et al.*, 2010). Nine individual haloacetic acids, including bromochloroacetic acid, were analysed during 2006–08, and concentrations were: mean, 25.3–115.2 µg/L; 25th percentile, 16.7–73.5 µg/L; 50th percentile, 23.0–113.5 µg/L; and 75th percentile, 31.6–145.1 µg/L.

In a study based on data from several European countries (Belgium, France, Germany, Italy, the Netherlands and Spain) and covering two decades (from 1980 to 2000; Palacios *et al.*, 2000), the levels of organohalogenated compounds in surface and groundwaters after chlorination were evaluated. A mean concentration of 3.53 µg/L bromochloroacetic acid was measured in post-treatment surface water (range, not detected–13.7 µg/L), but was not detected in post-treatment groundwater from disinfection utilities [limit of detection not reported].

(c) Dietary exposure from drinking-water

To assess exposure to disinfection by-products through drinking-water, WHO uses a default consumption value of 2 L drinking-water

per capita per day and a typical body weight (bw) of 60 kg (WHO, 2008). The underlying assumption is that of a total water consumption of 3 L per capita per day, including water present in food (WHO, 2003).

The mean concentrations and ranges of bromochloroacetic acid from all references available were used by the Working Group to assess dietary exposure in adults and infants (weighing 60 kg and 5 kg, respectively), assuming a consumption of 2 L and 0.75 L drinking-water, respectively, i.e. 33 mL/kg bw and 150 mL/kg bw, respectively (Table 1.1). The infant scenario (expressed in mL/kg bw) would correspond to the consumption of 9 L drinking-water per day in a 60-kg adult and therefore cover any possible scenario of physically active persons and increased temperature.

Based on the available data on average concentrations of bromochloroacetic acid, dietary exposure through drinking-water in a standard 60-kg adult ranges from 0.02 to 0.08 µg/kg bw per day, and high observed concentration values would lead to a dietary exposure of 0.1–0.6 µg/kg bw per day. Similarly, dietary exposure through drinking-water in a 5-kg infant ranges from 0.1 to 0.4 µg/kg bw per day, and high observed concentration values would lead to a dietary exposure of 0.4–2.8 µg/kg bw per day (Table 1.1).

(d) Other dietary sources

No data on the levels of haloacetic acids in foods (other than drinking-water) could be identified. Extrapolations from values in drinking-water to values in food are difficult to achieve because the conditions of the chemical interactions, dosages, temperatures, contact times and especially the precursors differ considerably (FAO/WHO, 2009).

1.3.3 Exposure through inhalation or dermal contact

Bromochloroacetic acid occurs in water used for showering and bathing due to its presence in household water distribution systems (see Section 1.3.2). Bromochloroacetic acid was also detected in the water of two large public swimming pools disinfected with either chlorine or bromine in Barcelona (Spain) (Richardson *et al.*, 2010).

Exposure to bromochloroacetic acid through dermal contact and inhalation was not measured. Based on the low dermal absorption observed for other haloacetic acids (Kim & Weisel, 1998), dermal exposure to bromochloroacetic acid is not liable to be significant. In contrast, inhalation of the substance in vapour/mist might occur during showering, bathing or swimming, as is anticipated for other disinfection by-products (Richardson *et al.*, 2007).

1.3.4 Environmental occurrence

Many haloacetates are distributed ubiquitously in the biosphere, including lakes and groundwater. The formation of bromochloroacetic acid as a chemical by-product of chlorination and chloramination of drinking-water may result in its release into the environment through various waste streams (Cowman & Singer, 1996).

When released into the air, an estimated vapour pressure of 0.14 mm Hg at 25 °C indicates that bromochloroacetic acid exists solely as a vapour in the atmosphere. Vapour-phase bromochloroacetic acid is degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals. Bromochloroacetic acid does not contain chromophores that absorb at wavelengths > 290 nm and is therefore not expected to be susceptible to direct photolysis by sunlight (HSDB, 2010).

When released into water, bromochloroacetic acid is not expected to adsorb to suspended solids or sediment based upon the estimated soil

Table 1.1 Dietary exposure to bromochloroacetic acid from drinking-water[a]

Reference	Country	Concentration (µg/L)			Estimated exposure in adults (µg/kg bw per day)			Estimated exposure in children (µg/kg bw per day)		
		Mean	Min.	Max.	Mean	Min.	Max.	Mean	Min.	Max.
Weinberg *et al.* (2002)	USA		1.3	18		0.05	0.60		0.21	2.70
Cancho *et al.* (1999)	Spain[b]	2.5	1.0	3.9	0.08	0.03	0.13	0.38	0.15	0.59
Nissinen *et al.* (2002)	Finland		0.3	19		0.01	0.63		0.05	2.85
Richardson *et al.* (2003)	Israel		1.0	3.9		0.03	0.13		0.15	0.59
Ding *et al.* (1999)	USA	0.6			0.02			0.09		
Peters *et al.* (1991)	Netherlands		0.2	2.5		0.006	0.08		0.03	0.38
Palacios *et al.* (2000)	European Union[c]	3.53	ND	13.7	0.12		0.46	0.53		2.06
Cowman & Singer (1996)	USA		4.68	10.8		0.16	0.36		0.70	1.62

[a] Calculated by the Working Group, assuming a daily intake and a body weight for adults of 2 L and 60 kg, and for children of 0.75 L and 5 kg, respectively.

[b] The study reported concentrations of bromochloroacetic acid according to different water treatments (e.g. chlorinated water, sand-filtered water, ozonated water, granulated activated carbon-filtered water); for the dietary exposure assessment, the chlorinated water values were used because it was considered as finished water.

[c] [Limit of detection not reported]

bw, body weight; max., maximum; min., minimum; ND, not detected

organic carbon–water partitioning coefficient of 1.9 (Swann *et al.*, 1983).

Data on biodegradation were not available to the Working Group, but the dissociation constant of 1.40 indicates that bromochloroacetic acid exists almost entirely in the anion form at pH values of 5–9 and therefore volatilization from water surfaces is not expected to be an important fate process (HSDB, 2010). An estimated bioconcentration factor of 3.2 suggests that the potential for bioconcentration in aquatic organisms is low. Hydrolysis is not expected to be an important environmental fate process because this compound lacks functional groups that hydrolyse under environmental conditions (HSDB, 2010).

1.3.5 Occupational exposure

No data were available to the Working Group.

1.4 Regulations and guidelines

No occupational exposure limits or recommended guidelines for maximum safe levels in drinking-water have been established for bromochloroacetic acid.

Levels of haloacetic acids in drinking-water in the USA are regulated by the Environmental Protection Agency (EPA, 2010). Under the disinfection by-products rule, the sum of the concentrations of monochloroacetic, dichloroacetic, trichloroacetic, monobromoacetic and dibromoacetic acids is limited to 60 µg/L (60 ppb). Bromochloroacetic acid is not included among the five haloacetic acids regulated by the Environmental Protection Agency under this current rule.

2. Cancer in Humans

See Introduction to the *Monographs* on Bromochloroacetic Acid, Dibromoacetic Acid and Dibromoacetonitrile.

3. Cancer in Experimental Animals

3.1 Oral administration

See Table 3.1

3.1.1 Mouse

In a 2-year carcinogenicity study, groups of 50 male and 50 female B6C3F$_1$ mice were given drinking-water containing 0 (controls), 250, 500 or 1000 mg/L bromochloroacetic acid (equivalent to average daily doses of approximately 0, 25, 50 or 90 and 0, 15, 30 or 60 mg/kg bw in males and females, respectively). Bromochloroacetic acid caused a significantly increased incidence of benign and malignant liver tumours: hepatocellular adenoma in males of the low- and mid-dose groups and in all exposed groups of females; hepatocellular carcinoma in males of the mid- and high-dose groups and females of the mid-dose group; hepatocellular adenoma or carcinoma (combined) in all exposed groups of males and females; and hepatoblastoma in all exposed groups of males (NTP, 2009).

3.1.2 Rat

In a 2-year carcinogenicity study, groups of 50 male and 50 female F344/N rats were given drinking-water containing 0 (controls), 250, 500 or 1000 mg/L bromochloroacetic acid (equivalent to average daily doses of approximately 0, 10, 20 or 40 and 0, 13, 25 or 50 mg/kg bw in males and females, respectively). Bromochloroacetic acid caused an increased incidence of rare adenomas of the large intestine (colon and rectum) in

Table 3.1 Carcinogenicity studies of exposure to bromochloroacetic acid in the drinking-water in experimental animals

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 105 wk NTP (2009)	0 (control), 250, 500 or 1000 mg/L 50/group	Liver (hepatocellular adenoma, multiple): M–13/50, 27/50, 25/50, 19/50 (M) F–16/50, 37/50, 34/50, 43/50 (F)	$P \leq 0.01$ (low- and mid-dose, M; all doses, F)	> 95% pure; the incidence of multiple hepatocellular adenoma and multiple hepatocellular carcinoma in exposed males and females and of multiple hepatoblastoma in exposed males was significantly ($P \leq 0.01$) increased.
		Liver (hepatocellular adenoma, including multiple): M[a]–27/50, 40/50, 40/50, 31/50 F[b]–27/50, 48/50, 44/50, 46/50	$P = 0.005$ (low- and mid-dose M) $P < 0.001$ (all doses, F) $P < 0.001$ (trend, F)	
		Liver (hepatocellular carcinoma): M[c]–19/50, 25/50, 36/50, 45/50 F[d]–14/50, 23/50, 26/50, 20/50	$P < 0.001$ (mid- and high-dose M) $P = 0.011$ (mid-dose F) $P < 0.001$ (trend, M)	
		Liver (hepatocellular adenoma or carcinoma, combined): M[e]–34/50, 44/50, 49/50, 49/50 (M) F[f]–31/50, 49/50, 46/50, 46/50 (F)	$P = 0.013$ (low-dose M) $P \leq 0.001$ (mid- and high-dose M) $P < 0.001$ (all doses, F) $P < 0.001$ (trend; M, F)	
		Liver (hepatoblastoma, multiple): M–0/50, 2/50, 12/50, 14/50	$P < 0.01$ (mid- and high-dose M)	
		Liver (hepatoblastoma, including multiple): M[g]–4/50, 11/50, 28/50, 34/50	$P = 0.047$ (low-dose M) $P < 0.001$ (mid- and high-dose M, trend M)	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 105 wk NTP (2009)	0 (control), 250, 500 or 1000 mg/L 50/group	All organs (malignant mesothelioma): M[h]–1/50, 5/50, 10/50, 6/50	$P = 0.003$ (mid-dose M)	> 95% pure; the number of fibroadenomas/ fibroadenoma-bearing rat was significantly ($P \leq 0.01$) increased in the 500-mg/L and 1000-mg/L females.
		Large intestine, colon and rectum (adenoma): M[i]– 0/50, 2/50, 0/50, 4/50 F[j]– 0/50, 0/50, 3/50, 7/50	$P = 0.009$ (high-dose F) $P < 0.001$ (trend, F)	
		Mammary gland (fibroadenoma, multiple): F–22/50, 24/50, 43/50, 38/50 Mammary gland (fibroadenoma, including multiple): F[k]–43/50, 43/50, 47/50, 46/50	$P \leq 0.01$ (mid- and high-dose)	
		Pancreatic islets (adenoma): M[l]–3/50, 4/50, 9/50, 3/50	$P = 0.049$ (mid-dose)	
		Liver (hepatocellular adenoma): F[m]–0/50, 0/50, 0/50, 3/50	$P = 0.012$ (trend, F)	

[a] Historical incidence for 2-year drinking-water studies in mice: 140/247 (56.7% ± 13.0%); range, 37–72%
[b] Historical incidence for 2-year drinking-water studies in mice: 133/297 (44.8 ± 11.9%); range, 29–61%
[c] Historical incidence for 2-year drinking-water studies in mice: 91/247 (36.9 ± 8.6%); range, 28–48%
[d] Historical incidence for 2-year drinking-water studies in mice: 51/297 (17.1 ± 9.5%); range, 6–28%
[e] Historical incidence for 2-year drinking-water studies in mice: 182/247 (73.7 ± 11.7%); range, 57–85%
[f] Historical incidence for 2-year drinking-water studies in mice: 158/297 (53.1 ± 11.3%); range, 35–63%
[g] Historical incidence for 2-year drinking-water studies in mice: 28/247 (11.3 ± 13.6%); range, 0–34%
[h] Historical incidences for 2-year drinking-water studies in rats: 9/300 (3.0 ± 2.8%); range, 0–6%
[i] Historical incidences for 2-year drinking-water studies in rats: 0/300
[j] Historical incidences for 2-year drinking-water studies in rats: 0/250
[k] Historical incidences for 2-year drinking-water studies in rats: 176/250 (70.4 ± 9.8%); range, 62–86%
[l] Historical incidences for 2-year drinking-water studies in rats: 23/296 (8 ± 2%); range, 6–10%
[m] Historical incidences for 2-year drinking-water studies in rats: 3/250 (1.2 ± 1.8%); range, 0–4%
bw, body weight; d, day or days; F, female; M, male; wk, week or weeks

male and female rats, with a significant increase in high-dose females. The incidence of rare malignant mesotheliomas at multiple sites was increased in all exposed groups of males and was significantly increased in the mid-dose group. Although the incidence of fibroadenoma of the mammary gland in females was not statistically significantly increased, the number of animals with multiple mammary gland fibroadenomas was increased in the mid-dose and high-dose groups. The incidence of pancreatic islet-cell adenoma was significantly increased in mid-dose males. The incidence of hepatocellular adenoma in high-dose females exceeded the historical control range (NTP, 2009).

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

No data were available to the Working Group.

4.1.2 Experimental systems

(a) Absorption, distribution and excretion

Dihaloacetates are rapidly absorbed from the gastrointestinal tract of rats after oral exposure (James *et al.*, 1998; Schultz *et al.*, 1999). The maximum blood concentration of bromochloroacetate in F344/N rats was reached 1.5 h after administration by gavage (Schultz *et al.*, 1999).

Dihaloacetates exhibit low binding to rat plasma proteins: in the plasma of treated F344 rats, 93% of the measured bromochloroacetate was in the unbound fraction (Schultz *et al.*, 1999).

The oral bioavailability of bromochloroacetate was reported to be 47% in male F344/N rats (Schultz *et al.*, 1999). The lower bioavailability of bromochloroacetate compared with other dihaloacetates is due to a greater first-pass metabolism in the liver.

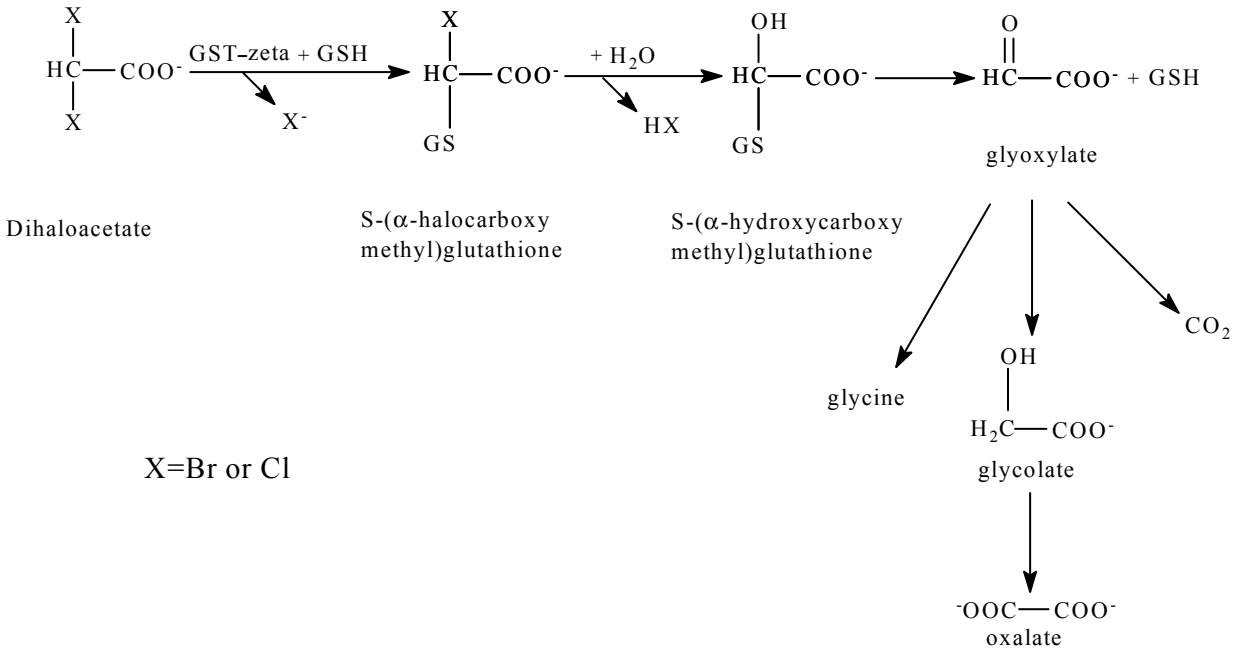
Elimination half-lives of dihaloacetates in the blood of male F344/N rats are less than 4 hours; the plasma half-life of bromochloroacetate after intravenous injection is approximately 45 minutes. Elimination of dihaloacetates occurs primarily by metabolism; after an intravenous dose of 500 μmol/kg bw [86.7 mg/kg bw] bromochloroacetate, excretion as the parent compound was less than 3% in the urine and less than 0.1% in the faeces. Bromine substitution of dihaloacetates increases the rate of metabolic clearance (Schultz *et al.*, 1999).

(b) Metabolism

The metabolism of bromochloroacetic acid has been reviewed (NTP, 2009). Biotransformation of dihaloacetates to glyoxylate occurs primarily in the liver cytosol of rats and humans by a glutathione-dependent process (James *et al.*, 1997) catalysed by glutathione *S*-transferase-zeta (GST-zeta) (Tong *et al.*, 1998a).

During GST-zeta-mediated oxygenation of dihaloacetates to glyoxylate, glutathione is required but not consumed. GST-zeta-mediated biotransformation of dihaloacetates (Fig. 4.1) involves displacement of a halide by glutathione to form *S*-(α-halo-carboxymethyl)glutathione, hydrolysis of this intermediate to form *S*-(α-hydroxy-carboxymethyl)glutathione and elimination of glutathione to produce glyoxylate (Tong *et al.*, 1998b). Among the brominated/chlorinated dihaloacetates, the relative rates of glyoxylate formation catalysed by purified GST-zeta are: bromochloroacetate > dichloroacetate > dibromoacetate (Austin *et al.*, 1996). Glyoxylate can undergo transamination to glycine, decarboxylation to form carbon dioxide and oxidation to oxalate. Glyoxylate may induce toxicity by reacting covalently with proteins, e.g. *N*-terminal amino groups or lysine ε-amino groups (Anderson *et al.*, 2004).

Fig. 4.1 Biotransformation of dihaloacetates



Adapted from Tong *et al.* (1998a)

Bromochloroacetic acid is a suicide substrate for GST-zeta; 12 hours after a single injection (0.30 mmol/kg bw), GST-zeta activity in the rat liver is reduced to 19% of that in controls (Anderson *et al.*, 1999). Hydrolysis of *S*-(α-halocarboxymethyl)glutathione forms a hemithioacetal that eliminates glutathione and yields glyoxylate. Because this intermediate may inactivate GST-zeta by covalently binding to a nucleophilic site on the enzyme (Anderson *et al.*, 1999; Wempe *et al.*, 1999), its hydrolysis and GST-zeta inactivation are competing reactions. Recovery of GST-zeta activity occurs via de-novo synthesis of the protein. Because GST-zeta is identical to maleylacetoacetate isomerase, the enzyme that catalyses the penultimate step of the tyrosine degradation pathway, its loss by exposure to dihaloacetates leads to the accumulation of maleylacetoacetate and maleylacetone which may cause tissue damage by reacting with cellular nucleophiles (Ammini *et al.*, 2003).

The elimination half-life of (–)-bromochloroacetic acid in male F344 rats is approximately sixfold shorter than that of (+)-bromochloroacetic acid, indicating that the rate of GST-zeta-catalysed metabolism of bromochloroacetic acid is much faster for the (–)-stereoisomer (Schultz & Sylvester, 2001). [The Working Group noted that the carcinogenicity studies in animals were performed using a racemic mixture of bromochloroacetic acid.] Because the metabolism of bromochloroacetic acid stereoisomers in naive and GST-zeta-depleted cytosol of rats is dependent on the presence of glutathione, Schultz and Sylvester (2001) suggested that an additional GST isoenzyme that is not inactivated by dihaloacetates might provide a minor contribution to the formation of glyoxylate in non-pretreated animals.

(c) Toxicokinetic models

No data were available to the Working Group.

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

Several studies have demonstrated the genotoxicity of bromochloroacetic acid (see Table 4.1).

(a) DNA adducts

Oxidative stress can result in oxidative damage to DNA, most commonly measured as increases in 8-hydroxydeoxyguanosine (8-OHdG) adducts. After acute oral administration of bromochloroacetic acid to male B6C3F$_1$ mice, a significant increase in 8-OHdG/deoxyguanosine ratios in liver nuclear DNA was observed (Austin *et al.*, 1996). After administration of bromochloroacetic acid in the drinking-water to male B6C3F$_1$ mice at concentrations of 0.1, 0.5 or 2.0 g/L for 3–10 weeks, the 8-OHdG content in liver nuclear DNA was increased (Parrish *et al.*, 1996). These findings demonstrate that bromochloroacetic acid causes oxidative stress/damage.

(b) DNA damage

Bromochloroacetic acid induced DNA damage in Chinese hamster ovary cells, as measured in the Comet assay (Plewa *et al.*, 2010).

(c) Mutations

In two bacterial mutagenicity assays, bromochloroacetic acid gave positive results in *Salmonella typhimurium* strain TA100 regardless of the presence of a metabolic activation system. It was not mutagenic in strain TA98 or in *Escherichia coli* WP2 *uvrA*/pKM101 regardless of the presence of a metabolic activation system (NTP, 2009). Glyoxylate (a metabolite of dihaloacetate biotransformation) was mutagenic in *S. typhimurium* strains TA97, TA100 and TA104 in the absence of a metabolic activation system and in strain TA102 in the presence of a metabolic activation system (Sayato *et al.*, 1987).

(d) Chromosomal effects

No increase in chromosomal damage (micronucleus formation in blood lymphocytes) was reported after administration of bromochloroacetic acid in the drinking-water to mice for 3 months (NTP, 2009).

4.3 Mechanistic data

4.3.1 Effects on cell physiology

No data were available to the Working Group.

4.3.2 Effects on cell function

After daily administration of 0, 8, 24, 72 or 216 mg/kg bw bromochloroacetic acid by gavage for 14 days, male mice showed altered expression of the genes involved in cell communication and adhesion, cell cycle control, proliferation, metabolism, signal transduction, stress response, spermatogenesis and male fertility (Tully *et al.*, 2005).

4.4 Susceptibility

No data were available to the Working Group. [However, the Working Group noted that disruption of GST-zeta in type-I hereditary tyrosinaemia has been linked to liver cancer in humans.]

4.5 Mechanisms of carcinogenesis

The mechanism by which bromochloroacetic acid induces neoplasms is not known.

It has been suggested that the reduction of GST-zeta activity by dihaloacetic acids may cause accumulation of toxic intermediates because this enzyme is involved in the tyrosine degradation pathway (Ammini *et al.*, 2003).

Table 4.1 Genetic and related effects of bromochloroacetic acid and glyoxylate

Test system	Results		Dose[a] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, reverse mutation	+	+	33	NTP (2009)
Salmonella typhimurium TA98, reverse mutation	–	–	33	NTP (2009)
Escherichia coli WP2 *uvrA*/pKM101, mutant colonies	–	–	1000	NTP (2009)
DNA strand breaks (Comet assay), Chinese hamster ovary cells *in vitro*	+	NT	520	Plewa *et al.* (2010)
DNA adducts (8-OHdG) in liver nuclear DNA, male B6C3F1 mice *in vivo*	+		30 po × 1	Austin *et al.* (1996)
DNA adducts (8-OHdG) in liver nuclear DNA, male B6C3F1 mice *in vivo*	+		125, dw, 3 wk	Parrish *et al.* (1996)
Micronucleus formation, B6C3F1 mouse blood lymphocytes *in vivo*	–		62.5, dw, 3 mo	NTP (2009)
Glyoxylate (metabolite of bromochloroacetic acid)				
Salmonella typhimurium TA100, TA104, TA97, reverse mutation	+	–	400 µg/plate	Sayato *et al.* (1987)
Salmonella typhimurium TA102, reverse mutation	–	+	1000	Sayato *et al.* (1987)

[a] *in vitro* test, µg/mL; *in vivo* test, mg/kg bw/d

+, positive; –, negative; bw, body weight; d, day or days; dw, drinking-water; HID, highest ineffective dose; LED, lowest effective dose; mo, month or months; NT, not tested; 8-OHdG, 8-hydroxydeoxyguanosine; po, oral; wk, week or weeks

DNA damage due to oxidative stress in the livers of mice exposed to halogenated acetic acids, including bromochloroacetic acid, may contribute to the hepatocarcinogenicity of these chemicals (NTP, 2009).

The carcinogenicity of bromochloroacetic acid may also involve a genotoxic mechanism because it induces DNA damage (Austin *et al.*, 1996; Parrish *et al.*, 1996; Plewa *et al.*, 2010). Glyoxylate, a metabolite of dihaloacetates biotransformation, is mutagenic in *S. typhimurium* (Sayato *et al.*, 1987; NTP, 2009).

5. Summary of Data Reported

5.1 Exposure Data

Bromochloroacetic acid is formed as a by-product during the disinfection of water by chlorination in the presence of organic matter and bromide. The concentration of bromochloroacetic acid measured in drinking-water was up to 19 µg/L. The highest concentrations of bromochloroacetic acid were observed in waters with the highest bromide content. The maximum daily human exposure to bromochloroacetic acid through drinking-water, estimated from such measurements, is at the low microgram per kilogram body weight level.

5.2 Human carcinogenicity data

No epidemiological studies were identified that evaluated exposure specifically to bromochloroacetic acid. This chemical occurs in mixtures in disinfected water, studies on which are reviewed in the Introduction to the *Monographs* on Bromochloroacetic Acid, Dibromoacetic Acid and Dibromoacetonitrile.

5.3 Animal carcinogenicity data

Bromochloroacetic acid was tested for carcinogenicity by administration in the drinking-water in one study in mice and one study in rats. In mice, bromochloroacetic acid caused a significantly increased incidence of hepatocellular adenoma and hepatocellular carcinoma in males and females, and of hepatoblastoma in males. In rats, bromochloroacetic acid caused a significantly increased incidence of mesothelioma in males, of large intestine adenoma in males and females, and of pancreatic islet cell adenoma in males. It also increased the multiplicity of fibroadenomas of the mammary gland in females. Tumours of the large intestine, mesotheliomas and hepatoblastomas are rare spontaneous neoplasms in experimental animals.

5.4 Other relevant data

No data were available to the Working Group on the toxicokinetics of bromochloroacetic acid in humans. In rats, dihaloacetates are rapidly absorbed from the gastrointestinal tract after oral administration.

Bromochloroacetic acid is primarily biotransformed to glyoxylate in the liver cytosol of rats and humans by a glutathione-dependent process catalysed by glutathione *S*-transferase-zeta. Glyoxylate can further undergo transamination to glycine, decarboxylation to carbon dioxide and oxidation to oxalate.

The mechanism by which bromochloroacetic acid induces tumours is not known, but a reduction in glutathione *S*-transferase-zeta activity may be involved. There is moderate evidence that the carcinogenicity of bromochloroacetic acid may involve a genotoxic mechanism because this chemical is a bacterial mutagen, produces 8-hydroxydeoxyguanosine in mouse liver (after acute oral administration or administration for three weeks in the drinking-water) and induces DNA damage in Chinese hamster ovary cells.

Glyoxylate, a metabolite of bromochloroacetic acid, is also mutagenic in bacteria.

The mechanistic data provide some additional support for the relevance of the data on cancer in experimental animals to humans.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of bromochloroacetic acid.

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

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

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