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SOME CHEMICALS PRESENT IN INDUSTRIAL AND CONSUMER PRODUCTS, FOOD AND DRINKING-WATER

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International Agency for Research on Cancer

World Health Organization

DIBROMOACETIC ACID

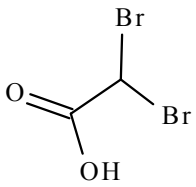
1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 631-64-1
Chem. Abstr. Name: Acetic acid, 2,2-dibromo-
IUPAC Systematic Name: 2,2-Dibromoacetic acid
Synonyms: Acetic acid, dibromo; dibromoacetate; dibromoethanoic acid

1.1.2 Structural and molecular formulae and relative molecular mass



$C_2H_2Br_2O_2$
Relative molecular mass: 217.8

1.1.3 Chemical and physical properties of the pure substance

Description: White deliquescent crystals (NTP, 2007)
Boiling-point: 232–234 °C (decomposition) (Kirk-Othmer, 1985); 195 °C at 250 mm Hg (Lide, 2005)
Melting-point: 49 °C (Lide, 2005)
Density: 2.3899 at 25 °C (Yaws & Chen, 2009)
Spectroscopy data: Infrared and magnetic resonance spectra (proton and C-13) have been reported (NTP, 2007).
Solubility: Very soluble in water, ethanol and ether (Lide, 2005)
Octanol/water partition coefficient (P): log P, 1.22 (Schultz *et al.*, 1999)
Conversion factor in air: 1 ppm = 8.91 mg/m^3 (WHO, 2004)

1.1.4 Technical products and impurities

Monobromoacetic acid was found to be an impurity at a concentration of < 1% in a lot of dibromoacetic acid used in toxicology studies in rodents (NTP, 2007).

1.1.5 Analysis

Dibromoacetic acid can be determined in drinking-water by gas chromatography with electron capture detection following extraction by an anion exchange column and conversion to its methyl ester at a limit of detection of 0.012 µg/L (EPA, 2003). It can also be determined in drinking-water following ion chromatography by electrospray ionization tandem mass spectrometry, for which the detection limit is 0.015 µg/L (EPA, 2009).

1.2 Production and use

1.2.1 Production

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

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

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

1.2.2 Use

Dibromoacetic acid is used only in research.

1.3 Occurrence

1.3.1 Natural occurrence

Dibromoacetic 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 of the 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 produced 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 for lowering 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 (IPCS, 2000; WHO, 2008).

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 source water quality and bromide levels and used the major disinfectants (chlorine, chloramines, ozone and chlorine dioxide). Concentrations of dibromoacetate in the finished water ready for distribution ranged from 2.1 to 18 µg/L.

The occurrence of disinfection by-products in drinking-water in the USA was evaluated at 35 water-treatment facilities in 1988–89 that used a broad range of source water qualities and treatment processes (Krasner *et al.*, 1989). Median total concentrations of haloacetic acids ranged from 13 to 21 µg/L, with those of dibromoacetic acid ranging from 0.9 to 1.5 µg/L. At a drinking-water utility with high levels of bromide, clearwell effluent contained dibromoacetic acid at concentrations ranging from 7.8 to 19 µg/L. At a utility where levels of bromide varied according to the season, levels of dibromoacetic acid ranged from 13 to 17 µg/L.

Data for drinking-water supplies in the USA (EPA, 2005) indicated that dibromoacetic acid is present in groundwater and surface water distribution systems at mean concentrations of 0.91 µg/L (range, < 1.0–12.85 µg/L; 90th percentile, 3.03 µg/L) and 0.96 µg/L (range, < 1.0–11.77 µg/L; 90th percentile, 2.80 µg/L), respectively. For all types of distribution system (groundwater and surface), the mean concentration of dibromoacetic acid was 0.97 µg/L (range, < 1.0–12.85 µg/L; 90th percentile, 2.96 µg/L). The minimum level reported for dibromoacetic acid was 1.0 µg/L. All observations below this level for individual species were considered to be zero for the purposes of calculations.

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 those prepared from surface water, whereas they could not be detected in those prepared from groundwater. Total haloacetic acids concentrations were in the range of 0.5–14.7 µg/L (surface water only), with levels of dibromoacetic acid ranging from not detected to 6.5 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.

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 chlorine 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 bromide

content in the source water had a major impact on the speciation of the disinfection by-products. The concentration of dibromoacetic acid was 12.5 µg/L (for chloramine plus chlorine dioxide disinfection), between 12 and 38.7 µg/L (for chlorination) and between 14.1 and 23.3 µg/L (for chlorination plus chlorine dioxide disinfection).

Water collected from 53 Canadian drinking-water treatment facilities in the winter of 1993 contained dibromoacetic acid (Williams *et al.*, 1997). When bromide concentrations were very low (< 0.01 mg/L), the water contained < 0.01 µg/L dibromoacetic acid; when they were low (0.06 mg/L), the water contained 0.9 µg/L dibromoacetic acid; and when they were moderate (0.5 mg/L), the water contained 0.8 µg/L dibromoacetic acid.

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), levels of organohalogenated compounds were evaluated in surface and groundwaters after chlorination. A mean concentration of 6.95 µg/L dibromoacetic acid was measured in post-treatment surface water (range, not detected–29.6 µg/L), whereas a mean concentration of 3.0 µg/L dibromoacetic acid was measured in post-treatment groundwater (range, not detected–7 µg/L) [limit of detection not reported].

Dibromoacetic 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 ozonation. At these two stages, the concentration of total haloacetic acids represented 60% of the level of total trihalomethanes. A significant decrease in total haloacetic acids concentration was observed when ozonated water was passed through granular activated carbon filters, but the acids were formed again during post-chlorination, although at lower concentrations than during the previous stages. The average concentration of total haloacetic acids was around 22 µg/L in tap-water (range, 11–32 µg/L). Dibromoacetic acid was detected in pre-chlorinated water (mean, 5.6 µg/L; range, 3.1–10 µg/L), sand-filtered water (mean, 6.7 µg/L; range, 5–8.4 µg/L), ozonated water (mean, 7.7 µg/L; range, 5.2–10 µg/L), granulated activated carbon-filtered water (mean, 0.6 µg/L; range, not detected–3.1 µg/L) and post-chlorinated water (mean, 3.7 µg/L; range, 2.1–5.7 µg/L).

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). Dibromoacetic acid was detected in six of the 35 Finnish waterworks between January and October 1994 with concentrations between 1.3 and 27 µg/L. Levels at the other facilities were below the limit of quantitation (0.8 µg/L). The concentration of six haloacetic acids, including dibromoacetic 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 (20 µg/L) were measured in ozonated and/or activated carbon-filtered and chloraminated drinking-waters. Higher concentrations were measured in summer than in winter [data not reported].

Between October 1994 and April 1996, a mean concentration of 0.4 µg/L dibromoacetic acid was measured in the Santa Ana River (USA) downstream from a discharge point for highly treated municipal wastewater effluent (Ding *et al.*, 1999).

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) concentrations of bromide. Several of the utilities (Houston, Southern California, Corpus Christi) were reported to add ammonia to their waters after chlorination to control the formation of disinfection by-products. Dibromoacetic acid was found at levels below the limit of detection [not reported] in the Philadelphia and Houston utilities where bromide ion concentration ranged from 50.6 to 134 µg/L. For the others utilities, where bromide ion levels ranged from 220 to 412 µg/L, the concentration of dibromoacetic acid was 8.39–9.18 µg/L.

(c) Dietary exposure from drinking-water

To assess exposure to disinfection by-products through drinking-water, a default consumption value of 2 L drinking-water per capita per day and a typical body weight (bw) of 60 kg is generally used (WHO, 2008). The underlying assumption is that of a total water consumption of 3 L per capita per day, including food consumption, which usually represents a conservative value (WHO, 2003).

The mean concentrations and ranges of dibromoacetic 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 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 concentrations of dibromoacetic acid reported in the literature, average dietary exposure through drinking-water in a standard 60-kg adult ranges from 0.013 to 0.42 µg/kg bw per day; high observed concentration values would lead to a dietary exposure of 0.05–1.29 µg/kg bw per day. Similarly, average dietary exposure through drinking-water in a 5-kg infant ranges from 0.06 to 1.88 µg/kg bw per day; and high observed concentration values would lead to a dietary exposure of 0.16–5.81 µg/kg bw per day (Table 1.1).

An estimate of dietary exposure to dibromoacetic acid arising from the consumption of drinking-water was performed by the Joint FAO/WHO expert meeting for Europe, the USA and Australia (FAO/WHO, 2009). The mean concentration of dibromoacetic acid from the 12 drinking-water utilities in the USA and Canada (3.4 µg/L) reported by FAO/WHO (2009) was used to estimate of dietary exposure. For Europe, the estimate was based on the mean consumption of 'tap-water' observed in adults in the 15 countries for which these data were available in the Concise European Food Consumption Database developed by the European Food Safety Authority (EFSA, 2008). The highest observed mean consumption of tap-water was 11 mL/kg bw per day (average consumption of 0.84 and 0.886 L per day for an average body weight of 74 and 77 kg, respectively, in Denmark and Finland). Estimated mean dietary exposure to dibromoacetic acid in Europe was therefore up to 0.039 µg/kg bw per day.

For the USA and Australia, mean dietary exposure to dibromoacetic acid was estimated to be 0.048 µg/kg bw per day (assuming a mean body weight of 65 and 68 kg and a mean consumption of drinking-water of 0.926 and 0.969 L per day, respectively, in the USA and Australia).

(d) Other dietary sources

No data on the levels of haloacetic acids in foods (other than drinking-water) were identified. Extrapolations from concentrations of disinfection by-products in drinking-water to those in food are difficult to achieve because the conditions of the chemical interactions, dosages,

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

Reference (country) *Source*	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)		2.1	18		0.08	0.603		0.32	2.7
Krasner *et al.* (1989); IPCS (2000) (USA)									
Distribution systems		0.9	1.5		0.03	0.05		0.14	0.23
Clearwell effluent with high bromide levels		7.8	19		0.26	0.63		1.17	2.85
Utility with seasonally variable bromide levels		13	17		0.43	0.57		1.95	2.55
EPA (2005) (USA)									
Distribution systems	0.97	0.00	12.85	0.03	–	0.43	0.15	–	1.93
Groundwater[b]	0.91	0.00	12.85	0.03	–	0.43	0.14	–	1.93
Surface water[b]	0.96	0.00	11.77	0.03	–	0.39	0.14	–	1.77
Peters *et al.* (1991) (Netherlands)		0.1	6.5		0.00	0.22		0.02	0.98
Palacios *et al.* (2000) (European Union)									
Post-treatment surface water	6.95	ND[d]	29.6	0.32	–	0.99	1.04	–	4.44
Post-treatment groundwater	3.0	ND[d]	7	0.10	–	0.23	0.45	–	1.05
Cancho *et al.* (1999) (Spain)[c]									
Post-chlorinated water (considered as finished water)	3.7	2.1	5.7	0.12	0.07	0.19	0.56	0.32	0.86
Williams *et al.* (1997) (Canada)									
Distribution systems		< 0.01	1.9			0.04			0.16
Very low bromide concentrations (< 0.01 mg/L)	< 0.01								
Low bromide concentrations (0.06 mg/L)	0.9			0.03			0.14		
Moderate bromide concentrations (0.5 mg/L)	0.8			0.03			0.12		
Richardson *et al.* (2003) (Israel)									
Chloramine plus chlorine dioxide disinfection	12.5			0.42			1.88		
Chlorine disinfection		12	38.7		0.40	1.29		1.80	5.81
Chlorine plus chlorine dioxide disinfection		14.1	23.3		0.47	0.78		2.12	3.50
Nissinen *et al.* (2002) (Finland)		< 0.8	27		–	0.90		0.20	4.05
Ding *et al.* (1999) (USA)	0.4			0.01			0.06		
Cowman & Singer, (1996) (USA)		ND[d]	9.18		–	0.31		1.26	1.38

[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] [From the paper, it is not clear if it is considered as water that is ready to drink.]

[c] The study reported the levels of dibromoacetic 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 this was considered as finished water.

[d] [Limit of detection not reported]

ND, not detected

temperatures, contact times and especially the precursors differ considerably (FAO/WHO, 2009).

1.3.3 Exposure through inhalation or dermal contact

Dibromoacetic acid occurs in water used for showering and bathing due to its presence in household water distribution systems (see Section 1.3.2). Dibromoacetic 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 dibromoacetic acid through dermal contact and inhalation has not been measured. Based on low dermal absorption observed for other haloacetic acids (Kim & Weisel, 1998), dermal exposure to dibromoacetic 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 in lakes and groundwater (Guo *et al.*, 2006). Dibromoacetic acid has been identified in the environment only as a by-product of the treatment of ground- and surface waters with chlorine-containing oxidizing compounds in the presence of bromide. The formation of dibromoacetic acid as a chemical by-product of chlorination and chloramination of drinking-water (Cowman & Singer, 1996) may result in its release into the environment through various waste streams.

Dibromoacetic acid is not expected to volatilize from dry or moist soil surfaces. In the atmosphere, it is expected to exist solely as a vapour (HSDB, 2010). Vapour-phase dibromoacetic acid is degraded by reaction with photochemically produced hydroxyl radicals, with a half-life of 25.3 days.

1.3.5 Occupational exposure

No data were available to the Working Group.

1.4 Regulations and guidelines

No occupational exposure limits have been established for dibromoacetic acid. Levels of haloacetic acids in drinking-water are regulated in the USA by the Environmental Protection Agency (EPA, 2010). Under the disinfection by-products rule, the sum of the concentrations of monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, monobromoacetic acid and dibromoacetic acid is limited to 60 µg/L (60 ppb).

2. Cancer in Humans

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

3. Cancer in Experimental Animals

Carcinogenicity studies of dibromoacetic acid in mice and rats are limited to those of oral administration in the drinking-water conducted by the NTP (2007), which are summarized in Table 3.1 (see also Melnick *et al.*, 2007).

3.1 Oral administration

3.1.1 Mouse

In a 2-year study, groups of 50 male and 50 female B6C3F$_1$ mice were administered dibromoacetic acid in the drinking-water at doses of 0 (controls), 50, 500 or 1000 mg/L (corresponding to average daily doses of approximately 0, 4, 45 or 87 and 0, 4, 35 or 65 mg/kg bw in male and female mice, respectively). Significant increases in the incidence of hepatocellular adenoma and

Table 3.1 Carcinogenicity studies of exposure to dibromoacetic 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) 105–106 wk Melnick *et al.* (2007); NTP (2007)	0 (control), 50, 500, 1000 mg/L (daily dose of 0, 4, 45, 87 mg/kg bw) 50/group	Liver (hepatocellular adenoma): 18/49, 37/50, 37/50, 42/50 Liver (hepatocellular carcinoma): 14/49, 9/50, 19/50, 26/50 Liver (hepatocellular adenoma or carcinoma, combined): 28/49, 41/50, 42/50, 47/50 Liver (hepatoblastoma)[a]: 0/49, 4/50, 6/50, 18/50 Lung (alveolar/bronchiolar adenoma): 7/49, 5/50, 17/50, 12/50 Lung (alveolar/bronchiolar adenoma or carcinoma, combined): 12/49, 12/50, 22/50, 17/50	$P < 0.001$ (all doses), $P < 0.001$ (trend) $P = 0.016$ (high dose), $P < 0.001$ (trend) $P < 0.001$ (high dose), $P < 0.001$ (mid-dose), $P = 0.004$ (low dose), $P < 0.001$ (trend) $P < 0.001$ (high dose), $P = 0.019$ (mid-dose), $P < 0.001$ (trend) $P = 0.016$ (mid-dose), $P = 0.019$ (trend) $P = 0.027$ (mid-dose)	> 99% pure
Mouse, B6C3F$_1$ (F) 105–106 wk Melnick *et al.* (2007); NTP (2007)	0 (control), 50, 500, 1000 mg/L (daily dose of 0, 4, 35, 65 mg/kg bw) 50/group	Liver (hepatocellular adenoma): 19/49, 26/50, 32/50, 35/49 Liver (hepatocellular carcinoma): 3/49, 3/50, 12/50, 8/49 Liver (hepatocellular adenoma or carcinoma, combined): 22/49, 28/50, 37/50, 37/49 Lung (alveolar/bronchiolar adenoma): 1/50, 3/50, 3/50, 6/50	$P < 0.001$ (high dose), $P = 0.004$ (mid-dose), $P < 0.001$ (trend) $P = 0.009$ (mid-dose), $P = 0.019$ (trend) $P < 0.001$ (high dose), $P < 0.001$ (mid-dose), $P < 0.001$ (trend) $P = 0.044$ (trend)	> 99% pure
Rat, F344/N (M) 105–106 wk Melnick *et al.* (2007); NTP (2007)	0 (control), 50, 500, 1 000 mg/L (daily dose of 0, 2, 20, 40 mg/kg bw) 50/group	All organs (malignant mesothelioma)[b]: 3/50, 1/50, 0/50, 10/50 Blood (mononuclear-cell leukaemia)[c]: 17/50, 31/50, 24/50, 13/50	$P = 0.035$ (high dose), $P < 0.001$ (trend) $P = 0.003$ (low dose), $P = 0.026$ (negative trend)	> 99% pure
Rat, F344/N (F) 105–106 wk Melnick *et al.* (2007); NTP (2007)	0 (control), 50, 500, 1 000 mg/L (daily dose of 0, 2, 25, 45 mg/kg bw) 50/group	Blood (mononuclear-cell leukaemia)[d]: 11/50, 13/50, 16/50, 22/50	$P = 0.016$ (high dose), $P = 0.006$ (trend)	> 99% pure

[a] Historical control incidence for 2-year drinking-water studies (mean ± standard deviation): 11/197 (4.5 ± 6.2%); range, 0–13%
[b] Historical control incidence for 2-year drinking-water studies (mean ± standard deviation): 15/250 (6.0 ± 4.2%); range, 0–12%
[c] Historical control incidence for 2-year drinking-water studies (mean ± standard deviation): 79/250 (31.6 ± 3.3%); range, 26–34%
[d] Historical control incidence for 2-year drinking-water studies (mean ± standard deviation): 47/200 (23.5 ± 4.4%); range, 20–30%
bw, body weight; F, female; M, male; wk, week or weeks

hepatocellular carcinoma in both males and females and of hepatoblastoma in males were observed. A significant increase in the incidence of alveolar/bronchiolar adenoma also occurred in males and females (NTP, 2007). [The Working Group noted that hepatoblastomas are rare spontaneous tumours in experimental animals.]

3.1.2 Rat

In a 2-year study, groups of 50 male and 50 female F344/N rats were administered dibromoacetic acid in the drinking-water at doses of 0 (controls), 50, 500 or 1000 mg/L (corresponding to average daily doses of approximately 0, 2, 20 or 40 and 0, 2, 25 or 45 mg/kg bw in male and female rats, respectively). Significant increases in the incidence of malignant mesothelioma in males and of mononuclear-cell leukaemia in females were observed. A significant increase in the incidence of mononuclear-cell leukaemia in low-dose males and a non-significant increase in mid-dose males also occurred, but the trend was negative. [It was therefore unclear whether the increase in low-dose males was treatment-related] (NTP, 2007). [The Working Group noted that malignant mesotheliomas are rare spontaneous tumours in experimental animals.]

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 after oral exposure in rats. The maximum blood concentration of dibromoacetate in F344/N rats was reached one hour after gavage administration (Schultz *et al.*, 1999).

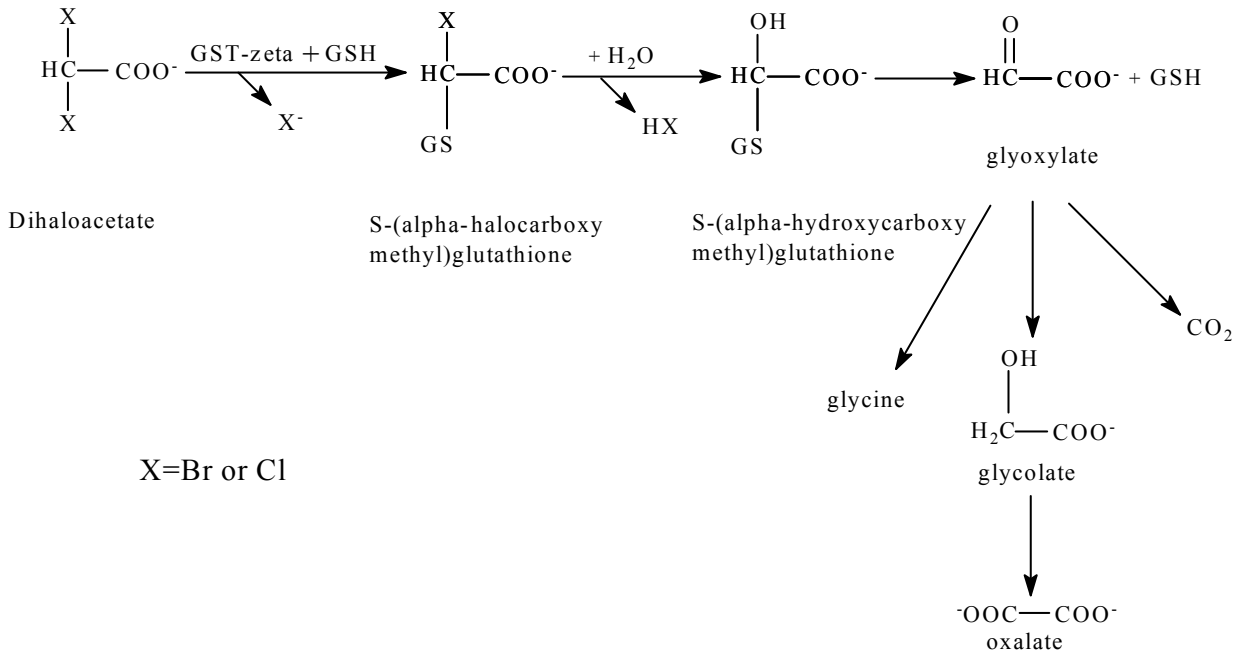
Dihaloacetates exhibit low binding to rat plasma proteins (Schultz *et al.*, 1999). Dibromoacetate was measured in the testicular interstitial fluid of male Sprague-Dawley rats after five daily gavage doses of 250 mg/kg bw. The level in testicular fluid peaked at 79 µg/mL (approximately 370 µM) 30 minutes after the last dose, and the half-life was approximately 1.5 hours (Holmes *et al.*, 2001).

After exposure of Sprague-Dawley rats to 125–1000 mg/L in the drinking-water beginning 14 days before mating and continuing throughout gestation and lactation, dibromoacetate was quantifiable in parental and fetal plasma, placental tissue, amniotic fluid and milk (Christian *et al.*, 2001), showing that dibromoacetate can cross the placenta and be absorbed by fetal tissue.

The oral bioavailability of dibromoacetate was reported to be 30% in male F344/N rats (Schultz *et al.*, 1999). The lower bioavailability compared with that of dichloroacetate is due to a greater first-pass metabolism in the liver (Bull *et al.*, 1985).

Elimination half-lives of dihaloacetates in the blood of male F344/N rats are less than 4 hours; the plasma half-life of dibromoacetate after intravenous injection is approximately 30–40 minutes (Schultz *et al.*, 1999). Elimination of dibromoacetate occurs primarily by metabolism; less than 3% of an intravenous dose of 500 µmol/kg bw (109 mg/kg bw) was excreted as the parent compound in urine and less than 0.1% was eliminated in the faeces. Bromine substitution of dihaloacetates increases the rate of metabolic clearance (Xu *et al.*, 1995), because

Fig. 4.1 Biotransformation of dihaloacetates



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

dichloroacetate is cleared at half the rate of dibromoacetate (Lin *et al.*, 1993; Narayanan *et al.*, 1999).

(b) Metabolism

The metabolism of dibromoacetic acid has been reviewed (NTP, 2007). Biotransformation of dihaloacetates to glyoxylate occurs primarily in the liver cytosol of rats, by a glutathione-dependent process (James *et al.*, 1997) that is catalysed by glutathione *S*-transferase zeta (GST-zeta) (Tong *et al.*, 1998a). This enzyme also catalyses the penultimate step in the tyrosine degradation pathway.

GST-zeta-mediated biotransformation of dihaloacetates (Fig. 4.1) involves the displacement of a halide by glutathione to form S-(α-halocarboxymethyl)glutathione, hydrolysis of this intermediate to form *S*-(α-hydroxycarboxymethyl)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 carbon dioxide and oxidation to oxalate.

Dibromoacetate is a suicide substrate for GST-zeta; 12 hours after a single injection of 0.30 mmol/kg bw, GST-zeta activity in the rat liver was reduced to 17% of that in controls (Anderson *et al.*, 1999). Hydrolysis of *S*-(α-halocarboxymethyl) glutathione forms a hemi-thioacetal that eliminates glutathione and yields glyoxylate. Because this intermediate may inactivate GST-zeta by covalently binding to a nucleophilic site on the enzyme (Wempe *et al.*, 1999), its hydrolysis and GST-zeta inactivation are competing reactions.

4.1.3 Toxicokinetic models

In a recent study, Matthews *et al.* (2010) developed a novel physiologically-based pharmacokinetic model, which included submodels for the common metabolites glyoxylate and oxalate that may be involved in the toxicity or carcinogenicity of dibromoacetic acid, and took into account hepatic metabolism as the primary mechanism of elimination (see Fig. 4.2 and Fig. 4.3).

Suicide inhibition induced by dibromoacetic acid was modelled by the irreversible covalent binding of the intermediate metabolite, α-halocarboxymethylglutathione, to the GST-zeta enzyme. Moreover, Matthews *et al.* (2010) introduced a secondary non-GST-zeta-mediated metabolic pathway for dibromoacetate. The model was calibrated using data on plasma and urine concentrations from studies of female F344 rats exposed to dibromoacetate by intravenous injection, oral gavage and administration in the drinking-water and was validated. The authors hypothesized that the model presented for dibromoacetic acid can be extended to structurally similar dihaloacetic acids.

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

Studies on the genotoxicity of dibromoacetic acid are summarized in Table 4.1.

(a) DNA adducts

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

(b) DNA damage

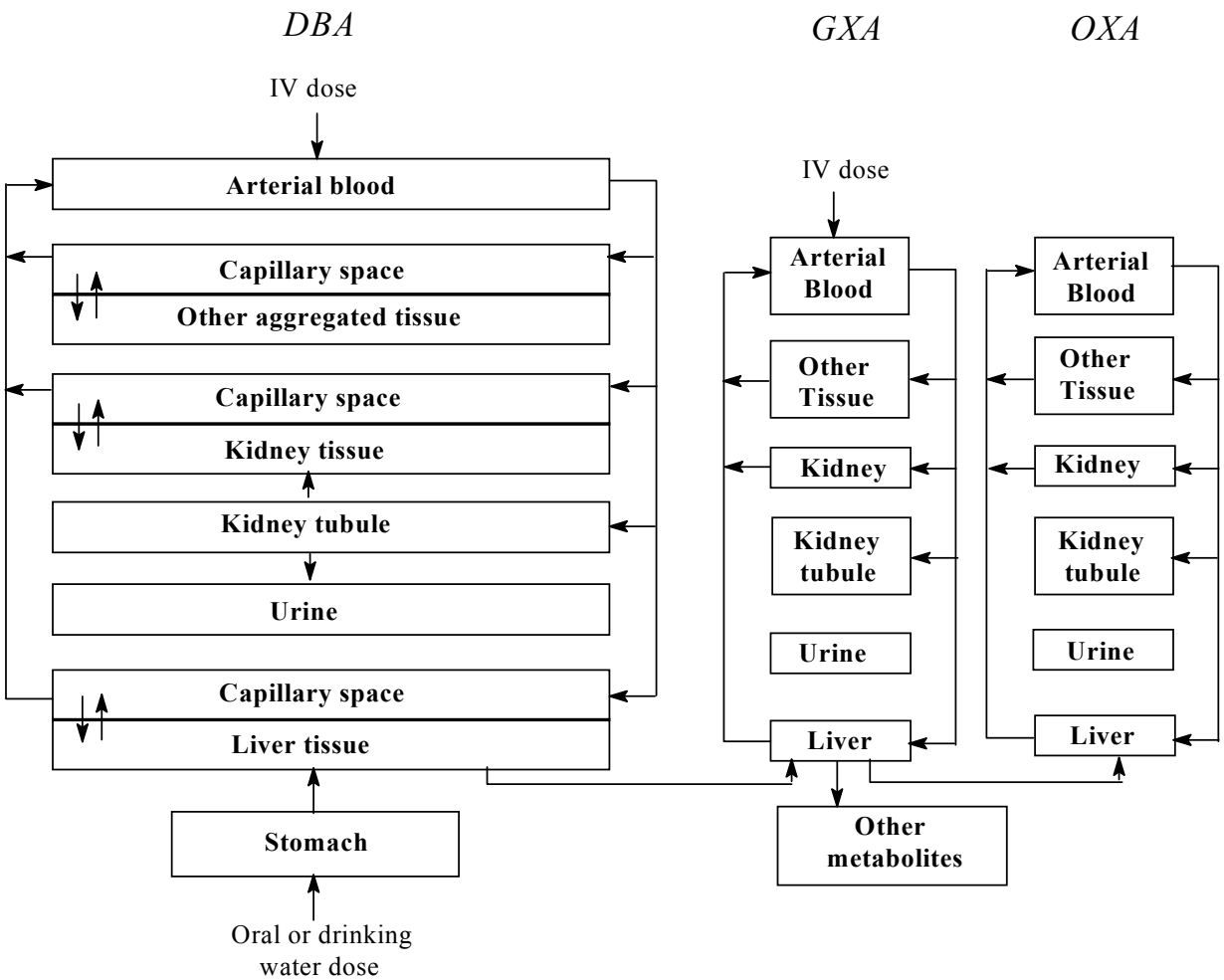
Dibromoacetate induced DNA damage in Chinese hamster ovary cells, as measured in the Comet assay (Plewa *et al.*, 2002, 2010), and DNA strand breaks in human lymphoblast cell lines (Daniel *et al.*, 1986). DNA damage was also induced in *Escherichia coli* in the SOS repair assay (Giller *et al.*, 1997) and in primary rat hepatocytes in the unscheduled DNA synthesis assay (Fang *et al.*, 2001).

(c) Mutations

Dibromoacetate was mutagenic in *Salmonella typhimurium* strain TA100 in the Ames fluctuation test (Giller *et al.*, 1997), in TA98 (Kargalioglu *et al.*, 2002) and in TA100 in the presence and absence of metabolic activation (Fang *et al.*, 2001; Kargalioglu *et al.*, 2002). It was not mutagenic in strain RSJ100, a derivative of TA1535 that contains a rat *GSTT1*–1 gene. In another series of tests, Dibromoacetic acid was mutagenic in TA100, but not TA98, in the presence or absence of metabolic activation (NTP, 2007). Glyoxylate was mutagenic in *S. typhimurium* strains TA97, TA100 and TA104 in the absence of and in strain TA102 in the presence of metabolic activation (Sayato *et al.*, 1987).

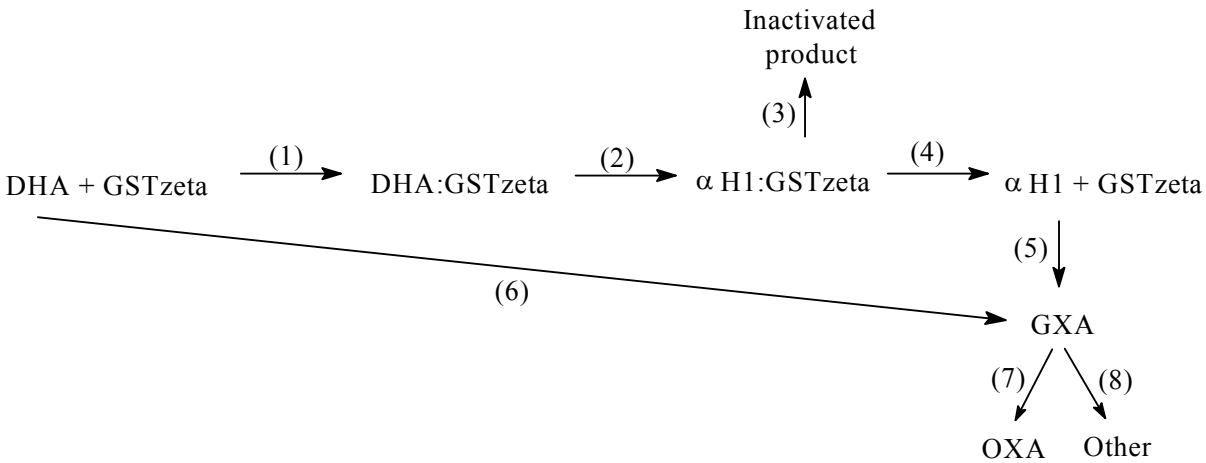
Dibromoacetate was mutagenic in the hypoxanthine-guanine phosphoribosyltransferase gene mutation assay in Chinese hamster ovary cells (Zhang *et al.*, 2010).

Fig. 4.2 Pharmacokinetic model for dibromoacetate, with glyoxylate and oxalate submodels



DBA, dibromoacetate; GXA, glyoxylate; IV, intravenous; OXA, oxalate
Reprinted from Matthews *et al.* (2010) with permission from Elsevier.

Fig. 4.3 Metabolism of dihaloacetates as implemented in the model



DHA, dihaloacetate; GST, glutathione-*S*-transferase; GXA, glyoxylate; αH1, α-halocarboxymethylglutathione; OXA, oxalate
Reprinted from Matthews *et al.* (2010) with permission from Elsevier.

(d) Chromosomal effects

Significant increases in micronucleated normochromatic erythrocytes were observed in the peripheral blood of male, but not female, B6C3F$_1$ mice treated with dibromoacetate in the drinking-water for 3 months (NTP, 2007). Moreover, dibromoacetic acid induced chromosomal damage *in vivo* in the mouse bone-marrow micronucleus assay and increased the number of micronuclei in NIH3T3 cells *in vitro* (Fang *et al.*, 2001). It failed to induce micronuclei in the erythrocytes of newt (*Pleurodeles waltl*) larvae (Giller *et al.*, 1997).

(e) Alterations in oncogenes and suppressor genes in tumours

Dibromoacetic acid (1 or 2 g/L in the drinking-water) induced liver hypomethylation of the proto-oncogene c-*myc* and of the growth factor gene *IGF-II* and increased both mRNA expressions in female B6C3F$_1$ mice and male F344 rats (Tao *et al.*, 2004).

(f) Changes in DNA methylation pattern

Dibromoacetic acid (1 or 2 g/L in the drinking-water for 28 days) induced liver hypomethylation of c-*myc* in both female B6C3F$_1$ mice and male F344 rats (Tao *et al.*, 2004) and renal hypomethylation of DNA and of c-*myc* in both male B6C3F$_1$ mice and F344 rats (Tao *et al.*, 2005).

Table 4.1 Genetic and related effects of dibromoacetic acid (dibromoacetate) and glyoxylate

Test system	Results		Dose[a] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, reverse mutation, Ames-fluctuation	+	+	10	Giller *et al.* (1997)
Salmonella typhimurium TA100, reverse mutation	+	+	500 µg/plate	Fang *et al.* (2001)
Salmonella typhimurium TA100, reverse mutation	+	+	218 µg/plate	Kargalioglu *et al.* (2002)
Salmonella typhimurium TA100, reverse mutation	+		1000 µg/plate	NTP (2007)
Salmonella typhimurium TA100, reverse mutation		+	333 µg/plate	NTP (2007)
Salmonella typhimurium TA98, reverse mutation	–	–	5000 µg/plate	Fang *et al.* (2001)
Salmonella typhimurium TA98, reverse mutation	+	+	610 µg/plate	Kargalioglu *et al.* (2002)
Salmonella typhimurium TA98, reverse mutation	–	–	10 000 µg/plate	NTP (2007)
Salmonella typhimurium RSJ100, reverse mutation	–	–	0.015	Kargalioglu *et al.* (2002)
Primary DNA damage, *Escherichia coli* strain PQ37 (SOS chromotest)	+	+	100	Giller *et al.* (1997)
Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	+	NT	50	Fang *et al.* (2001)
DNA strand break (Comet assay), Chinese hamster ovary cells *in vitro*	+	NT	163.3	Plewa *et al.* (2002)
Gene mutation, *Hprt* locus, 6-thioguanine resistance, Chinese hamster ovary K1 cells *in vitro*	+	–	21.8	Zhang *et al.* (2010)
Micronucleus formation, NIH3T3 cell *in vitro*	+	NT	100 µg/plate	Fang *et al.* (2001)
DNA adducts (8-OHdG), liver nuclear DNA, male $B6C3F_1$ mice *in vivo*	+		30 po × 1	Austin *et al.* (1996)
DNA adducts (8-OHdG), liver nuclear DNA, male $B6C3F_1$ mice *in vivo*	+		100, dw, 3 wk	Parrish *et al.* (1996)
Micronucleus formation, mouse bone marrow *in vivo*	+		50 µg/plate	Fang *et al.* (2001)
Micronucleus formation, male $B6C3F_1$ mouse peripheral erythrocytes *in vivo*	+		250, dw, 3 mo	NTP (2007)
Micronucleus formation, female $B6C3F_1$ mouse peripheral erythrocytes *in vivo*	–		2000, dw, 3 mo	NTP (2007)
Micronucleus formation, *Pleurodeles waltl in vivo*	–		160	Giller *et al.* (1997)
Glyoxylate (metabolite of dibromoacetic acid)				
Salmonella typhimurium TA100, TA104, TA97, reverse mutation	+	–	400 µg/plate	Sayato *et al.* (1987)
Salmonella typhimurium TA100, TA102, TA97, reverse mutation	–	+	1000 µg/plate	Sayato *et al.* (1987)

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

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

4.3 Mechanistic data

4.3.1 Effects on cell physiology

Dibromoacetic acid induced alveolar epithelial hyperplasia in female rats exposed for 2 years via the drinking-water (Melnick *et al.*, 2007).

Dibromoacetic acid (1 or 2 g/L in the drinking-water for 3 months) caused cytoplasmic vacuolization in hepatocytes and marginal increases in DNA hepatocyte replication in male rats (NTP, 2007).

4.3.2 Effects on cell function

Treatment of cultured hepatocytes isolated from male Long Evans rats with 1 mM (217 mg/L) dibromoacetate for 72 hours induced peroxisome proliferation (Walgren *et al.*, 2004). Dibromoacetic acid in the drinking-water caused liver peroxisome proliferation in both female $B6C3F_1$ mice (4 days at 2 g/L and 7 days at 1 g/L) and male F344 rats (2 days at 2 g/L) (Tao *et al.*, 2004). [The Working Group noted that it is not known whether peroxisome proliferation occurs at doses of dibromoacetic acid below 1000 mg/L.]

4.3.3 Other relevant data

Several comparative genotoxicity and mutagenicity studies (Giller *et al.*, 1997; Kargalioglu *et al.*, 2002; Plewa *et al.*, 2010; Zhang *et al.*, 2010) have demonstrated that dibromoacetic acid is more potent than its chlorinated analogue, dichloroacetic acid, and that they have several molecular and biochemical activities in common (Tao *et al.*, 2004). Dichloroacetic acid is considered as a possible (Group 2B) human carcinogen (IARC, 2004).

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 dibromoacetic acid causes tumours is not known.

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

DNA hypomethylation and increased expression of *c-myc* and *IGF-II* genes were suggested to be possible early events in the hepatocarcinogenicity of dihaloacetic acids in mice. An early increase in hepatocyte proliferation is probably not involved in the mechanism because no increases in the DNA labelling index were observed in mice exposed for 26 days, and the slight increase that occurred in male F344/N rats was not accompanied by an increase in liver tumour response (Tao *et al.*, 2004).

DNA damage due to oxidative stress in the livers of mice exposed to dibromoacetic acid may contribute to the hepatocarcinogenicity of this chemical (Austin *et al.*, 1996; Parrish *et al.*, 1996).

The carcinogenicity of dibromoacetic acid may also involve a genotoxic mechanism because it induces DNA damage in bacteria, and rodent and human cell lines, as well as mutations in bacteria and a rodent cell line (Daniel *et al.*, 1986; Giller *et al.*, 1997; Fang *et al.*, 2001; Kargalioglu *et al.*, 2002; Plewa *et al.*, 2002; NTP, 2007; Plewa *et al.*, 2010; Zhang *et al.*, 2010). In addition, glyoxylate, a metabolite of dihaloacetates biotransformation, is mutagenic in bacteria (Sayato *et al.*, 1987).

5. Summary of Data Reported

5.1 Exposure data

Dibromoacetic 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 dibromoacetic acid measured in drinking-water was up to 39 μg/L. The highest concentrations are observed in waters with the highest bromide content. The maximum daily human exposure to dibromoacetic acid through drinking-water, estimated from such measurements, is at the low microgram per kilogram of body weight level.

5.2 Human carcinogenicity data

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

5.3 Animal carcinogenicity data

Dibromoacetic acid was tested for carcinogenicity by administration in the drinking-water in one study in mice and one study in rats. In mice, dibromoacetic acid increased the incidence of hepatocellular adenoma and hepatocellular carcinoma in males and females, of hepatoblastoma in males, and of alveolar/bronchiolar adenoma in males and females. In rats, dibromoacetic acid increased the incidence of mesothelioma in males and of mononuclear-cell leukaemia in females. 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 dibromoacetic acid in humans. In rats, dibromoacetate is rapidly absorbed from the gastrointestinal tract after oral exposure.

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

Dibromoacetic acid induces DNA adducts in mouse liver (after acute oral administration or administration in the drinking-water for three weeks) and causes DNA damage in bacteria, and rodent and human cell lines. In addition, it caused mutations in bacteria and a rodent cell line, and micronucleus formation in male mice *in vivo*. Glyoxylate, a metabolite of dibromoacetate, is also mutagenic in bacteria.

The mechanism of tumour induction by dibromoacetic acid has not been clearly identified. The reduction of glutathione *S*-transferase-zeta activity may be involved. DNA hypomethylation and increased expression of a proto-oncogene and a growth factor gene were also suggested as possible early events. There is moderate evidence that the carcinogenicity of dibromoacetic acid involves a genotoxic mechanism. Moreover, glyoxylate, a metabolite of dibromoacetic acid, is mutagenic in bacteria.

The mechanistic data provide some additional support for the relevance of 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 dibromoacetic acid.

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

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

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