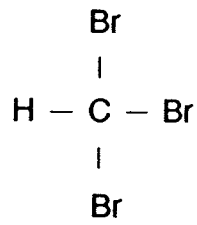
BROMOFORM

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 75-25-2
Chem. Abstr. Name: Tribromomethane
IUPAC Systematic Name: Tribromomethane
Synonyms: Methenyl tribromide; methyl tribromide

1.2 Structural and molecular formulae and molecular weight



$CHBr_3$ Mol. wt: 252.75

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Colourless liquid with chloroform-like odour (Verschueren, 1983; Budavari, 1989; Weast, 1989)
(*b*) *Boiling-point*: 149.5°C (Weast, 1989)
(*c*) *Melting-point*: 8.3°C (Weast, 1989)
(*d*) *Density*: 2.9035 at 15/4°C (Budavari, 1989)
(*e*) *Spectroscopy data*[1]: Infrared (Sadtler Research Laboratories, 1980, prism [10], grating [8]; Pouchert, 1981, 1985), nuclear magnetic resonance (Sadtler Research Laboratories, 1980, proton [6375], C-13 [1603];

[1]In square brackets, spectrum number in compilation

Pouchert, 1974) and mass spectral data [1744] (Bunn *et al.*, 1975; Coleman *et al.*, 1984) have been reported.

(*f*) *Solubility*: Soluble in water (3.0 g/l at 20°C, 3.19 g/l at 30°C), ethanol, benzene, chloroform, diethyl ether and ligroin (Mabey *et al.*, 1982; Verschueren, 1983; Weast, 1989)

(*g*) *Volatility*: Vapour pressure, 5 mm at 20°C, 5.6 mm Hg at 25°C, 10 mm Hg at 34.0°C; relative vapour density (air = 1), 8.7 (Mabey *et al.*, 1982; Verschueren, 1983; Weast, 1989)

(*h*) *Octanol/water partition coefficient (P)*: log P, 2.38 (Mabey *et al.*, 1982)

(*i*) *Stability*: Gradually decomposes in air, acquiring a yellow colour; light accelerates this decomposition (Budavari, 1989)

(*j*) *Reactivity*: Reacts rapidly with strong caustics and metals such as sodium, potassium, calcium, powdered aluminium, zinc and magnesium (Sittig, 1985); hydrolysis rate at neutral pH and 25°C is 2.5×10^{-9} per hour (Mabey *et al.*, 1982).

(*k*) *Conversion factor*[2]: $mg/m^3 = 10.34 \times ppm$

1.4 Technical products and impurities

Bromoform is available in various grades from > 95% to > 99% purity; it may be stabilized with ethanol (e.g., 1-3%) or diphenylamine. It is also available in grades specifically for coal flotation and the separation of mineral compounds (Riedel-de Häen, 1986; American Tokyo Kasei, 1988; Aldrich Chemical Co., 1990).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Bromoform can be prepared by reacting chloroform (see IARC, 1987) with aluminium tribromide at less than or equal to 60°C; by reacting ethanol with sodium hypobromite; or by the redistribution reaction between chloroform and ethyl bromide (Harlow & Ross, 1932; Soroos & Hinkamp, 1945; Sherman & Kavasmaneck, 1980).

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[2]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming standard temperature (25°C) and pressure (760 mm Hg)

(*b*) *Use*

Bromoform has been used as an intermediate in organic synthesis, as an ingredient in fire-resistant chemicals, as a gauge fluid in geological assaying, as a solvent for waxes, greases and oils, and as a sedative (Sittig, 1985; Sax & Lewis, 1987).

(*c*) *Regulatory status and guidelines*

Standards have been established for trihalomethanes (including bromoform) in drinking-water (see monograph on chlorinated drinking-water, p. 59) in several countries. Occupational exposure limits and guidelines for bromoform are presented in Table 1.

Table 1. Occupational exposure limits and guidelines for bromoform[a]

Country	Year	Concentration (mg/m^3)	Interpretation[b]
Belgium	1987	5 (skin)	TWA
Brazil	1987	4 (skin)	TWA
Canada (Saskatchewan)	1980	10	STEL
Denmark	1987	5 (skin)	TWA
Finland	1987	5 (skin)	TWA
		15	STEL
Indonesia	1987	5 (skin)	TWA
Mexico	1987	5	TWA
Netherlands	1987	5 (skin)	TWA
Norway	1984	5 (skin)	TWA
Switzerland	1987	5 (skin)	TWA
UK	1987	5 (skin)	TWA
USA			
ACGIH	1989	5 (skin)	TWA
OSHA	1989	5 (skin)	TWA
USSR	1987	5	MAC
Venezuela	1987	5	TWA and ceiling
Yugoslavia	1987	5 (skin)	TWA

[a]From Cook (1987); American Conference of Governmental Industrial Hygienists (ACGIH) (1989); US Occupational Safety and Health Administration (OSHA) (1989)
[b]TWA, time-weighted average; STEL, short-term exposure limit; MAC, maximum allowable concentration

2.2 Occurrence

(*a*) *Natural occurrence*

Mean levels of bromoform in the tissues of temperate marine macroalgae (*Ascophyllum nodosum, Fucus vesiculosis, Enteromorpha linza, Ulva lacta, Gigartina stellata*) ranged from 8 to 120 ng/g dry weight. Bromoform was released to seawater at a rate of 0.14-14 μg/g of dry algae per day (Gschwend *et al.*, 1985).

Macroalgae collected near the Bermuda Islands (*Fucales sargassum*) and at the Cape of Good Hope (*Laminariales laminaria*) showed a specific pattern of emissions of volatile organohalides into the air. The main components were bromoform, bromodichloromethane and chlorodibromomethane (Class *et al.*, 1986).

(*b*) *Air*

The volatilization half-time of bromoform from rivers and streams has been estimated to range from 63 min to 24 days, depending on turbulence and temperature. A typical half-time, based on actual data, was 66 h (Kaczmar *et al.*, 1984).

Ullrich (1982) studied the organohalogen compound concentrations in the air of four public indoor swimming pools in western Berlin. Mean bromoform concentrations ranged from 0.7 to 6 $\mu g/m^3$.

In a review of data on the presence of volatile organic chemicals in the atmosphere of the USA in 1970-80, a median concentration of 0.64 $\mu g/m^3$ bromoform was reported for the four urban/suburban data points examined and below the limit of detection for industrial areas (74 data points) (Brodzinsky & Singh, 1983).

Bromoform levels in air samples collected in 1985 over the Atlantic Ocean were 0.6-460 ppt (6.2-4.8 $\mu g/m^3$); baseline levels of biogenic bromoform in air were 0.6-6.6 ppt (6.2-68.2 ng/m^3). The highest levels were found in samples taken at beaches with intense algal populations. Air samples collected in 1985 from a forest area in southern Germany contained 1.2 ppt (12.4 ng/m^3) bromoform (Class *et al.*, 1986).

In the USA, air samples collected 2 cm above the surface of five outdoor pools contained < 0.1 $\mu g/m^3$ bromoform; those above four indoor pools contained < 0.1-20 $\mu g/m^3$ and those above four spas (whirlpools or hot tubs) contained < 0.1-62 $\mu g/m^3$. Samples collected 2 m above the surface contained < 0.1 $\mu g/m^3$, < 0.1-14 $\mu g/m^3$ and < 0.1-14 $\mu g/m^3$, respectively (Armstrong & Golden, 1986).

Air samples collected in the USA between 1984 and 1987 showed that the atmospheric concentrations of bromoform averaged 6.3 ng/l at Point Barrow, Alaska, and 3.1 ng/l at Cape Kumukahi, Hawaii. Large pulses of organic bromine

(mainly bromoform) enter the atmosphere during the three-month Arctic spring (Fogelqvist, 1985; Cicerone *et al.*, 1988).

(c) *Water and sediments*

The formation of trihalomethanes in drinking-water (see also the monograph on Chlorinated drinking-water, p. 56 *et seq.*) and the effects of temperature and pH have been discussed extensively (Williams, 1985). The formation of bromoform during drinking-water chlorination depends on the presence of bromide in untreated water.

Bromoform was detected (but not quantified) in headspace analysis of nine of ten Pacific seawater samples collected in 1983 (Hoyt & Rasmussen, 1985).

Bromoform has been measured or detected in many drinking-water systems, both in samples collected at treatment facilities or along the distribution system (Table 2) and in samples collected from natural and untreated water sources (Table 3). Concentrations in treated drinking-water typically ranged from < 1 to 10 µg/l (with higher values in some locations), compared with concentrations in untreated (natural) waters which are typically less than 1 µg/l.

Table 2. Bromoform concentrations in treated[a] drinking-water, 1973-89

Location, date[b]	Sample site/raw water source (treatment)[c]	Concentration (µg/l)[d]	Reference
80 US cities (NORS), 1975	T and D/ground and surface (75% of raw water chlorinated)	ND-92	Symons *et al.* (1975)
113 Public water supplies, 1976	Water supplies/NS	Mean, 12; median, < 0.3	Brass *et al.* (1977)
945 US sites, 1981-82	T/ground	2.4-5.1[e] (max., 110)	Westrick *et al.* (1984)
13 US community systems, 1984-85	T and D/NS	< 0.2-3.1	Reding *et al.* (1989)
10 US utilities, 1985	T/ground and surface (chlorinated)	< 10 (6 sites) ND (4 sites)	Stevens *et al.* (1989)
35 US sites	T/ground and surface	Median	Krasner *et al.* (1989)
Spring 1988		0.33	
Summer 1988		0.57	
Autumn 1988		0.88	
Winter 1989		0.51	
Southwestern US city, 1975	NS/ground (treated)	43.1-74.2	Henderson *et al.* (1976)

Table 2 (contd)

Location, date[b]	Sample site/raw water source (treatment)[c]	Concentration (μg/l)[d]	Reference
East Texas, 1977	NS/surface (14 sites) NS/ground (11 sites) (chlorinated)	ND-85.0 ND-258	Glaze & Rawley (1979)
Houston, Texas, summer 1978 to winter 1980	D/surface D/ground (chlorinated and unchlorinated)	max., 2 max., 28 (mean, 5)	Cech *et al.* (1982)
Miami, Florida January 1975 July 1975	NS/ground (finished water)	 1.5 4.0	Loy *et al.* (1976)
19 Tennessee sites Autumn 1980 Winter 1980 Spring 1981 Summer 1981	T/ground and surface (13 samples) (2 of 20 samples) (3 of 20 samples) (5 of 20 samples)	 ND ND-0.17 ND-0.012 ND-0.20	Minear & Morrow (1983)
Old Love Canal, NY, 1978	D/NS (5 of 8 sites)	0.02-0.08	Barkley *et al.* (1980)
New Jersey, 1977-79	NS/surface (197 of 604 samples) NS/ground (235 of 1072 samples)	max., 3.7 max., 34.3	Page (1981)
40 Michigan utilities, NS	T/surface (22 sites) T/ground (18 sites) (chlorinated)	ND ND-1.6	Furlong & D'Itri (1986)
3 Puerto Rican cities, NS	D/ground and surface	ND-0.1	Rodriguez-Flores (1983)
70 Canadian cities, 1976-77	D and T/ground and surface (chlorinated)	0-0.2 (median, < 0.01)	Health & Welfare Canada (1977)
30 Canadian sites, 1979	T/ground and surface	mean, < 1; max., 1-2	Otson *et al.* (1982)
10 Canadian Great Lakes sites Summer 1982 Winter 1983 Spring 1983	T/ground and surface	 ND-< 0.1 ND-< 0.1 mean, 0.1	Otson (1987)
Burlington, Ontario, Canada, 1981 Niagara Falls, Ontario 1981 Port Robinson, Ontario 1981	D/surface, ground and treated	0.150 0.84 0.3	Comba & Kaiser (1983)

Table 2 (contd)

Location, date[b]	Sample site/raw water source (treatment)[c]	Concentration (μg/l)[d]	Reference
Chippawa, Ontario, 1981	D/surface	0.01	Kaiser & Comba (1983)
Lancashire-Cheshire, UK, 1974	D/NS (chlorination)	< 0.01-2.5	McConnell (1976)
Southeastern England/NS	D/ground and surface (chlorinated)	ND	Trussell *et al.* (1980)
5 Belgian utilities, 1977-78	T/surface	0-3.6	Quaghebeur & De Wulf (1980)
9 Belgian utilities, 1977-78	D/surface (10/14 chlorinated)	0-0.7	
	T/ground	0-4.4	
	D/ground	0-2.7	
12 German cities, 1977	NS/NS	ND-4.9 (mean, 0.9)	Eklund *et al.* (1978a,b,c)
18 German cities, 1978-80	D/surface (river) (43 samples)	0.3-14 (mean, 4.3)	Gabel *et al.* (1981)
50 German cities, 1978-80	D/surface (river) (100 samples) (chlorinated)	0.1-14 (mean, 2.7)	
9 German cities, 1978-79	D/NS	0.4-40.4	Lahl *et al.* (1982)
Bremen and Leverkusen, Germany, 1976-78	NS/NS	ND-28	Bauer (1981)
Tübingen, Germany, 1981	D/NS	0.35-1.15 (mean, 0.77)	Hagenmaier *et al.* (1982)
	D/surface	0.01-0.05 (mean, 0.04)	
Gothenberg, Sweden, 1977	D/surface (treated)	0.016	Eklund *et al.* (1978a,b,c)
Southern China, NS	D/local catchments (Cl_2)	6.3	Trussell *et al.* (1980)
Southern Philippines/NS	D/ground and surface (Cl_2)	ND	Trussell *et al.* (1980)
Northern Philippines/NS	D/surface (Cl_2)	ND	Trussell *et al.* (1980)
Northern Egypt/NS	D/surface (Cl_2)	ND	Trussell *et al.* (1980)
Southern Indonesia/NS	D/surface (Cl_2)	ND	Trussell *et al.* (1980)
Southeastern Australia/ NS	D/surface (Cl_2)	ND	Trussell *et al.* (1980)
Southern Brazil/NS	D/surface (Cl_2)	ND	Trussell *et al.* (1980)
Eastern Nicaragua/NS	D/surface (Cl_2)	ND	Trussell *et al.* (1980)

Table 2 (contd)

Location, date[b]	Sample site/raw water source (treatment)[c]	Concentration (μg/l)[d]	Reference
Northern Venezuela/NS	D/surface (Cl_2)	ND	Trussell *et al.* (1980)
Eastern Peru/NS	D/ground and surface (Cl_2)	ND	Trussell *et al.* (1980)

[a]Treatment not always specified

[b]NORS, National Organics Reconnaissance Survey; NS, not specified

[c]D, distribution system; T, treatment plant; treatment given as and when described by the author(s)

[d]ND, not detected

[e]Range of median values for randomly and nonrandomly selected water supplies serving fewer than and more than 10 000 people

Table 3. Bromoform concentrations in untreated (natural) water, 1973-79

Location, date[a]	Sample source	Concentration (ng/l)[b]	Reference
Gothenberg, Sweden, 1977	Seawater	27	Eklund *et al.* (1978b,c)
Northern Taiwan, NS	Well	ND	Trussell *et al.* (1980)
Lake Ontario, Canada, 1981	Lake (82 sites)	ND-7	Kaiser *et al.* (1983)
Niagara River, Ontario, Canada, 1981	River (17 sites)	ND-6	
Welland River, Ontario, Canada, watershed,	Surface (river)		Kaiser & Comba (1983)
Summer, 1980		ND-60	
Spring 1981		ND-1100	
North and South Atlantic, 1985	Seawater	0.8->6	Class *et al.* (1986)
Ulm, Germany, NS	Rainwater	5	Class *et al.* (1986)

[a]NS, not specified

[b]ND, not detected

Rook (1974) demonstrated that bromoform, observed at concentrations ranging from 0.5 to 10 μg/l following chlorination of stored surface waters, was a product of chlorination of the humic substances in natural waters.

In the 1975 US National Organics Reconnaissance Survey of water supplies in 80 US cities, bromoform was not found in any of the raw water samples (minimum quantifiable concentration, 1-4 µg/l) (Symons *et al.*, 1975).

According to the US Environmental Protection Agency STORET system, concentrations of bromoform in 131 samples of surface water in 1970-79 ranged from 0.1 to 1 µg/l in 1% of the samples, 1-10 µg/l in 97% of the samples, and 10-100 µg/l in 2% of the samples (Perwak *et al.*, 1980).

In the 1982 US Nationwide Urban Runoff Program, bromoform was detected in samples from one of the 15 reporting cities at a concentration of 1 µg/l (Cole *et al.*, 1984).

The US Environmental Protection Agency estimated that 17 tonnes of bromoform were generated in the US in 1978 by water chlorination. On the basis of the 1976 National Organic Monitoring Survey, the general population was estimated to be exposed to 7 µg bromoform per day from drinking-water, assuming a maximal concentration of 280 µg/l and an intake of 2.18 l per day, the daily exposure increased to 600 µg per day (Perwak *et al.*, 1980).

Bromoform levels in tap water collected at four locations in a Swedish community ranged from 0.24 to 0.34 µg/l; when the treatment facility briefly changed the disinfectant from chlorine to chlorine dioxide, bromoform was not detected (detection limit, 0.01 µg/l) (Norin *et al.*, 1981).

Samples of water were collected between August and October 1980 from one supply system in São Paulo State, Brazil. Mean levels of bromoform were 0.1 µg/l in treated water (after chlorination) and 0.06 µg/l in treated water from the reservoir (II) (de Fernicola & de Azevedo, 1984).

Bromoform has been identified as the major halogenated organic compound produced as a result of chlorinating seawater. Potential daily bromoform production by a pilot plant for conversion of ocean thermal energy was estimated to be 1300 g/day; the bromoform concentration contained in the diluted discharge water was estimated to be 0.93 µg/l (Hartwig & Valentine, 1983).

Bromoform concentrations in samples of chlorinated seawater at a desalination test facility on Wrightsville Beach, NC, USA, were 23-209 µg/l. In general, bromoform concentrations increased through the various pretreatment processes; in effluents from activated carbon columns, however, levels ranged from not detected to 36 µg/l (Singer, 1982).

Pretreatment of seawater with chlorine at a pilot desalination facility in the USA produced average concentrations of bromoform ranging from 13 to 110 µg/l during the different steps of the two pretreatment processes (Chang & Singer, 1984).

Samples of chlorinated intake and discharge seawater collected in 1980 from a power plant in Port Everglades, FL, contained bromoform at levels ranging from 75 to 78 μg/l and from 32 to 86 μg/l, respectively. The concentration of bromoform in the unchlorinated intake water was 1 μg/l. Chlorination of the seawater in the laboratory with 1, 2, and 4 mg/l chlorine resulted in corresponding bromoform concentrations of 6.5, 107 and 272 μg/l (Carpenter *et al.*, 1981).

In 1980, the mean concentrations of bromoform in Arctic seawater were 9.8 ng/l in open surface water and 58 ng/l in surface water close to the Svalbard shore (Fogelqvist, 1985).

Water samples were collected from five outdoor pools, four indoor pools, and four spas (whirlpools or hot tubs) in Lubbock, TX, USA. The concentrations of bromoform in the outdoor pools, which used chlorine-based chemicals for chlorination, were < 0.1-1 μg/l. Two of the indoor pools in which only chlorination was used had levels of < 0.1-1 μg/l; one indoor pool in which only bromination (sodium hypobromite) was used had levels of 8-60 μg/l; and the fourth indoor pool, in which chlorination and bromination were alternated had levels of 11-49 μg/l. The spa in which only chlorination was used had levels of < 0.1-1 μg/l; the two spas in which only bromination was used had levels of 3-183 μg/l; and the spa in which the combination was used had levels of 50-89 μg/l. The average concentration of bromoform in Lubbock, TX, tap water was < 0.1 μg/l (Armstrong & Golden, 1986).

Bromination (3 mg bromine/l) of the water in a Swedish public swimming pool resulted in the formation of bromoform at 400 μg/l (Norin & Renberg, 1980).

Water samples were collected in 1978-79 from eight covered swimming pools in Bremen, Germany, to determine the concentration of bromoform. The source of fresh water was mixed river and groundwater for four pools and groundwater for four pools. The level of bromoform in the pools with mixed sources was 45 μg/l, and that for the pools with groundwater, not detectable (ND). The range of means of bromoform in the four pools with a mixed water source was 0.5-12 μg/l (total range, ND-88 μg/l); that in the four pools with a groundwater source was ND-0.1 μg/l (total range, ND-0.2 μg/l) (Lahl *et al.*, 1981).

The concentrations of bromoform in three thermal spas in western Germany in which the initial bromide concentration was 0.5-0.7 mg/l were 2.3-9.6 μg/l (Weil *et al.*, 1980).

Scotte (1984) studied the concentrations of organohalogen compounds in the water of 10 covered swimming pools in France. The mean concentrations of bromoform were 0.1 μg/l in the four pools treated with Surchlor GR 60 (anhydrous sodium dichloroisocyanurate), none in the two treated with gaseous chlorine, 1.0 μg/l in two treated with sodium hypochlorite and 481.2 μg/l in two treated with bromine.

Effluents from a wastewater treatment plant on Boston Harbor, MA, USA, sampled in 1984 and 1985, contained a mean bromoform level of 1.65 µg/l (range, not detected to 6.9 µg/l) and had an estimated mass input rate of 1.39 kg per day (Kossik *et al.*, 1986).

Heating water to prepare food has been shown to eliminate a large part of trihalomethanes in the water, particularly as a function of temperature and heating time. Bromoform levels were reduced from 35.9 µg/l in tap water to 21.3 µg/l after heating at 80°C for 1 min, to 13.9 µg/l after heating to 100°C, to 13.5 µg/l after boiling for 1 min, and to 6.8 µg/l after boiling for 5 min (Lahl *et al.*, 1982).

(*d*) *Animals*

Bioaccumulation of bromoform has been studied in five marine species. The uptake and depuration is rapid (equilibrium is reached in 24-48 h), and the concentration factors are relatively low (< 1-10 times the water concentration) (Gibson *et al.*, 1980).

(*e*) *Human tissues and secretions*

Analysis of whole blood samples collected from a population of 250 patients with no known exposure to volatile organic compounds revealed a mean bromoform level of 0.6 ng/ml (range, ND-3.4 ng/ml); the number of individuals with detected levels of bromoform was not specified, but 11 had significantly elevated levels (greater than two standard deviations above the mean) (Antoine *et al.*, 1986).

2.3 Analysis

Selected methods for the analysis of bromoform in air, water and other matrices are presented in Table 4. The US Environmental Protection Agency methods for analysing water (Methods 8010 and 8240) have also been used for liquid and solid wastes. Volatile components of solid waste samples are first extracted with methanol, prior to purge-and-trap concentration and analysis by gas chromatography-electrolytic conductivity detection (Method 8010) or gas chromatography-mass spectrometry (Method 8240). The detection limit for bromoform using Method 8010 is 0.20 µg/l, and the practical quantification limit using Method 8240 is 5 µg/l for groundwater and for soil/sediment samples (US Environmental Protection Agency, 1986a,b).

US Environmental Protection Agency Method 624 has also been adapted to the analysis of bromoform in fish, with an estimated detection limit of 10 µg/kg (Easley *et al.*, 1981).

Table 4. Methods for the analysis of bromoform

Sample matrix	Sample preparation[a]	Assay procedure[b]	Limit of detection	Reference
Air	Adsorb on activated charcoal; desorb (carbon disulfide); inject aliquot	GC/FID	0.01 mg per sample	Eller (1987)
	Draw air through Tenax sample tube; heat; desorb into cold trap	GC/MS	20 ng	US Environmental Protection Agency (1988a) [Method TO-1)
	Collect cryogenically into stainless-steel bottle; inject sample	GC/EC-FI-FPD/GC/MS	0.7 ppt	Hoyt & Rasmussen (1985)
Seawater	Collect in vacuum extraction flask; pressurize with zero air; inject headspace sample	GC/EC-FI-FPD/GC/MS	1 ppt	Hoyt & Rasmussen (1985)
Water	Purge (inert gas); trap (OV-1 on Chromosorb-W/Tenax/silica gel); desorb as vapour (heat to 180°C, backflush with inert gas) onto packed GC column	GC/ECD	0.20 µg/l	US Environmental Protection Agency (1988b) [Method 601]
		GC/MS	4.7 µg/l	US Environmental Protection Agency (1988c) [Method 624]
	Purge (inert gas); trap (OV-1 on Chromosorb-W/Tenax/silica gel); desorb as vapour (heat to 180°C, backflush with inert gas) onto capillary GC column	GC/ECD	1.6 µg/l	US Environmental Protection Agency (1988d) [Method 502.2]
		GC/MS	0.12 µg/l	US Environmental Protection Agency (1988e) [Method 524.2]
	Add internal standard (isotope-labelled bromoform); purge; trap and desorb as above	GC/MS	1.0 µg/l	US Environmental Protection Agency (1988f) [Method 1624]
	Extract in pentane; inject onto GC	GC/EC (>50 µg/l) GC/MS (<50 µg/l)	0.5 µg/l	US Environmental Protection Agency (1988g) [Method 501.2]
Adipose tissue	Purge from liquefied fat at 115°C; trap on silica gel; desorb thermally	GC/HSD	2.3 µg/l	Peoples *et al.* (1979)

Table 4 (contd)

Sample matrix	Sample preparation[a]	Assay procedure[b]	Limit of detection	Reference
Blood serum	Purge from water-serum mixture containing anti-foam reagent at 115°C; trap on Tenax/silica gel; desorb thermally	GC/HSD	2.3 µg/l	Peoples *et al.* (1979)

[a]GC, gas chromatograph

[b]GC/FID, gas chromatography/flame ionization detection; GC/MS, gas chromatography/mass spectrometry; GC/EC-FI-FPD, gas chromatography/electron capture-flame ionization-flame photometric detection; GC/ECD, gas chromatography/electrolytic conductivity detection; GC/HSD, gas chromatography/halide selective detection

Sorbent tube sampling is the approved method of the National Institute for Occupational Health/Occupational Safety and Health Administration (USA) for collecting the most hazardous gases and vapours from the air—in this case bromoform. A sample is collected by drawing air through a tube, where the airborne chemical is trapped in the sorbent. The trapped chemical is solvent-extracted from the tube and analysed using gas chromatography with a flame ionization detector to determine the amount of chemical present. A direct-reading system is available with colour detector tubes to monitor and detect bromoform in air (SKC Inc., 1990).

Bromoform can be determined in water by glass capillary column gas chromatography and electron capture detection, with a detection limit of 1 ng/l (Eklund *et al.*, 1978b,c).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals (Table 5)

(*a*) *Oral administration*

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, eight weeks old, were given bromoform (> 95% pure) in corn oil by gavage at 50 or 100 mg/kg bw (males) and 100 or 200 mg/kg bw (females) on five days per week for 103 weeks. Survival at 105 weeks was: males—vehicle control, 41/50; low-dose, 37/50; high-dose, 36/50; females—control, 25/50; low-dose, 13/50; high-dose, 20/50. Decreased survival in

female mice was associated in part with utero-ovarian abscesses. No tumour occurred in a significantly larger proportion of treated than of control mice. The proportion of high-dose male mice with alveolar/bronchiolar neoplasms of the lung was significantly lower than that of controls ($p < 0.015$, incidental tumour test) (National Toxicology Program, 1989).

Rat: Groups of 50 male and 50 female Fischer 344 rats, seven to eight weeks old, were given bromoform (> 95% pure) in corn oil by gavage at 100 or 200 mg/kg bw on five days per week for 103 weeks. Survival at 105 weeks was: males—vehicle control, 34/50; low-dose, 30/50; high-dose, 11/50; females—control, 33/50; low-dose, 28/50; high-dose, 28/50. Adenomatous polyps of the large intestine occurred in 0/50 control, 0/50 low-dose and 2/50 high-dose male rats, and adenocarcinoma of the large intestine occurred in one additional high-dose male rat. Adenomatous polyps occurred in 0/50 control, 1/50 low-dose and 6/50 high-dose female rats, and adenocarcinomas occurred in two additional high-dose animals. The proportion of high-dose female rats with neoplasms of the large intestine was significantly larger than in controls ($p = 0.004$, pairwise comparison; $p < 0.001$, trend test, logistic regression). Neoplasms of the large intestine are uncommon in controls of this strain (males—study laboratory, 0/285; all National Toxicology Program laboratories, 3/1873 (0.2%); females—all National Toxicology Program laboratories, 0/1888). The incidence of preputial gland neoplasms was significantly decreased in high-dose male rats (control, 10/41; low-dose, 5/38; high-dose, 1/34; $p = 0.014$, pairwise comparison, logistic regression). In female rats, the incidences of stromal polyps of the uterus, fibroadenomas of the mammary gland and adenomas of the anterior pituitary gland were significantly decreased in the high-dose group (stromal polyps—vehicle control, 10/49; low-dose, 9/50; high-dose, 2/50; $p = 0.019$, logistic regression; fibroadenomas—vehicle control, 22/50; low-dose, 17/50; high-dose, 6/50; $p < 0.001$, logistic regression; pituitary adenomas—vehicle control, 29/48; low-dose, 12/46; high-dose, 16/48; $p = 0.011$, logistic regression) (National Toxicology Program, 1989).

(*b*) *Intraperitoneal administration*

Mouse: In a screening assay based on the enhanced induction of lung tumours, groups of 20 male strain A/St mice, six to eight weeks old, were injected intraperitoneally three times per week with bromoform (> 95% pure) in tricaprylin at 4, 48 or 100 mg/kg bw for a total of 18, 23 or 24 injections (total doses, 72, 1100 or 2400 mg/kg bw). Twenty males given tricaprylin only served as controls. All surviving mice were killed 24 weeks after the first injection, at which time survival was 15/20 of controls, 17/20 in the low-dose, 15/20 in the mid-dose and 15/20 in the high-dose group. The average numbers of lung tumours per mouse were 0.27 ± 0.15 (SE) in controls, 0.53 ± 0.21 at the low dose, 1.13 ± 0.36 at the mid-dose and

0.67 ± 0.21 at the high dose [proportion of mice with tumours not given]; the average number of lung tumours in the mid-dose group was significantly higher than that in controls ($p < 0.05$, Student's t test). In a positive control group given a single intraperitoneal injection of urethane at 1000 mg/kg bw, the average number of lung tumours per mouse was 19.6 ± 2.4 (Theiss *et al.*, 1977).

3.2 Other relevant data

(*a*) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

Bromoform at 0.008-0.04 mmol/kg bw (2-10 mg/kg bw) given by gavage as an aqueous solution to rats was rapidly absorbed and distributed to liver, brain, kidney, blood and fat; the highest concentrations were found in fat 30 min after administration (Parra *et al.*, 1986). ^{14}C-Bromoform at 0.39 mmol/kg bw (16 µCi/kg bw; 100 mg/kg bw) administered orally in corn oil to rats by gavage was absorbed and eliminated in the expired air as unchanged bromoform (67% of dose) or as ^{14}C-carbon dioxide (4% of dose) in 8 h; radiolabel amounting to about 2% of the dose was eliminated in the urine, and about 2% of the dose was retained in body tissues. ^{14}C-Bromoform administered similarly to mice (0.59 mmol/kg bw; 32 µCi/kg bw; 150 mg/kg bw) was absorbed and eliminated in the expired air as unchanged bromoform (6% of dose) or as ^{14}C-carbon dioxide (40% of dose) in 8 h; about 5% of the administered radiolabel was eliminated in the urine, and 12% was retained in body tissues (Mink *et al.*, 1986). Bromoform is metabolized to carbon monoxide *in vivo* (Anders *et al.*, 1978; Stevens & Anders, 1981) and *in vitro*; the latter reaction requires NADPH and oxygen and is stimulated eight fold by glutathione (Ahmed *et al.*, 1977). Bromoform was metabolized to dibromocarbonyl, the bromine analogue of phosgene, by rat hepatic microsomal fractions (Stevens & Anders, 1979; Pohl *et al.*, 1980).

(ii) *Toxic effects*

The LD_{50} of a single subcutaneous injection of bromoform in olive oil was estimated to be 7.2 mmol/kg (1.82 g/kg) bw in male Swiss mice (Kutob & Plaa, 1962); the single intraperitoneal 48-h LD_{50} in corn oil was 414 µl/kg bw in male Sprague-Dawley rats (CR-1 strain; Agarwal & Mehendale, 1983). The single-dose oral LD_{50}s (Emulphor:ethanol:saline 1:1:8 administered by gavage) were 1400 mg/kg bw in male and 1500 mg/kg bw in female ICR Swiss mice (Bowman *et al.*, 1978). Oral LD_{50} values (in corn oil) were 1388 and 1147 mg/kg bw in male and female Sprague-Dawley rats (Chu *et al.*, 1980, 1982a) and 933 mg/kg bw in male and female Fischer 344/N rats (National Toxicology Program, 1989); the values for male

Table 5. Summary of carcinogenicity studies of bromoform in experimental animals

Reference	Species/ strain	Sex	Dose schedule	Experimental parameter/ observation	Group				Significance	Comments
					0	1	2	3		
National Toxicology Program (1989)	Mouse $B6C3F_1$	M	5 d/week, gavage, corn oil, 103 weeks	Dose (mg/kg)	0	50	100	-		
				Survival (105 weeks)	41/50	37/50	36/50			
				Alveolar/bronchiolar neoplasm	11/50	7/50	2/49		$p < 0.015$	Decrease
		F		Dose (mg/kg)	0	100	200	-		Utero-ovarian abscesses
				Survival (105 weeks)	25/50	13/50	20/50			
				Lymphoma	11/49	5/50	3/50			
Theiss *et al.* (1977)	Mouse strain A/St	M	3 d/week, i.p. inject., tricaprylin, 18, 23 or 24 doses	Dose (mg/kg)	0	4	48	100		Screening test in strain in which lung adenomas are common; ± SE
				Total dose (mg/kg)	0	72	1100	2400		
				Survival (24 weeks)	15/20	17/20	15/20	15/20		
				Lung adenomas per mouse	0.27 ± 0.15	0.53 ± 0.21	1.13 ± 0.36	0.67 ± 0.21		
National Toxicology Program (1989)	Rat F344	M	5 d/week, gavage, corn oil, 103 weeks	Dose (mg/kg)	0	100	200	-		
				Survival (105 weeks)	34/50	30/50	11/50			
				Large intestine						
				Adenomatous polyp	0/50	0/50	2/50			
				Adenocarcinoma	0/50	0/50	1/50			
				Preputial gland neoplasm	10/41	5/38	1/34		$p = 0.014$	Decrease
		F		Dose (mg/kg)	0	100	200	-		
				Survival (105 weeks)	33/50	28/50	28/50			
				Large intestine						
				Adenomatous polyp	0/50	1/50	6/50		$p = 0.004$	Increase
				Adenocarcinoma	0/50	0.50	2/50			
				Uterine stromal polyp	10/49	9/50	2/50		$p = 0.019$	Decrease
				Mammary fibroadenoma	22/50	17/50	6/50		$p < 0.001$	Decrease
				Pituary adenomas	29/48	12/46	16/48		$p = 0.011$	Decrease

and female $B6C3F_1$ mice were 707 and 1072 mg/kg bw bromoform, respectively. Signs of acute toxicity included sedation, prostration, lachrymation, lethargy, shallow breathing, reduction in peripheral lymphocyte count and liver damage (Agarwal & Mehendale, 1983; Bowman *et al.*, 1978; Chu *et al.*, 1982a; National Toxicology Program, 1989).

Daily oral treatment of male and female CD-1 mice with 50-250 mg/kg bw bromoform (in 10% Emulphor in water) for 14 days resulted in decreased fibrinogen levels in blood, liver damage (increased ASAT), decreased serum glucose and blood urea nitrogen and decreased cellular and humoral immunity at 250 mg/kg bw (Munson *et al.*, 1982). Similarly, administration of 145 and 289 mg/kg bw bromoform in corn oil per day for 14 days to male CD-1 mice resulted in centrilobular pallor, focal inflammation and increased mitosis in the liver. Tubular hyperplasia and glomerular degeneration and reduced uptake of organic acids were observed in the kidney after administration of the high dose (Condie *et al.*, 1983).

Daily oral administration of 600 and 800 mg/kg bw bromoform by gavage for 14 days induced lethargy, shallow breathing and ataxia and was lethal to all male and female Fischer 344/N rats. Body weight reduction was observed at 400 mg/kg bw; enlargement of the thyroid gland was observed at 400 and 800 mg/kg bw. $B6C3F_1$ mice receiving similar treatment were less sensitive. In a 13-week study, male and female Fischer 344/N rats were administered 12-200 mg/kg bw bromoform and male and female $B6C3F_1$ mice were administered 25-400 mg/kg bw bromoform by gavage on five days per week. Body weight reduction was observed in male mice treated with the high dose. Hepatocellular vacuolization was observed in male rats at all doses and in male mice at 200 and 400 mg/kg bw (National Toxicology Program, 1989).

Male and female Sprague-Dawley rats received 5-2500 mg/l bromoform in drinking-water for 90 days. The highest dose, which corresponded to an approximate daily intake of 29-55 mg/rat, resulted in liver lesions, reduced lymphocyte counts (after a 90-day recovery period) and a reduction in serum lactic dehydrogenase activity (Chu *et al.*, 1982b).

Administration of bromoform for two years (see section 3.1) resulted in hepatic fatty changes, including vacuolization, in male and female rats and in female but not male mice in all treated groups (National Toxicology Program, 1989).

In a screening assay based on the production of γ-glutamyltranspeptidase-positive foci in the liver, nine male rats were given a single dose of bromoform at 1 mmol/kg (250 mg/kg) bw [route of administration unspecified] following a two-thirds hepatectomy. Bromoform did not have a significant effect (Herren-Freund & Pereira, 1986).

(iii) *Effects on reproduction and prenatal toxicity*

Swiss CD-1 mice were given bromoform by gavage in corn oil at daily doses of 0, 50, 100 or 200 mg/kg bw in a reproductive study using a continuous breeding protocol. Treatment was continued for 18 weeks: one week prior to cohabitation, 14 weeks of cohabitation and three weeks thereafter. Toxicity was observed at the two higher levels, as decreased body weight and kidney weight and increased liver weight, but there was no adverse effect on fertility in either the parental or F_1 generation. A decrease in neonatal (F_1) survival was noted in the high-dose group. The body weights of treated F_1 males were significantly lower than the corresponding control values (Gulati *et al.*, 1989).

Sprague-Dawley rats were administered bromoform in corn oil by gavage at daily doses of 0, 50, 100 or 200 mg/kg bw on gestation days 6-15. No maternal toxicity was observed, and bromoform did not alter the incidence of resorptions, litter size or fetal weight. There was a dose-related increase in the incidence of skeletal variations, primarily involving the sternum, the interparietal bones and ribs (Ruddick *et al.*, 1983). [The Working Group noted that too few fetuses (12-16 per dose level) were examined for visceral malformations for a conclusion about lack of malformations in soft tissues to be drawn.]

(iv) *Genetic and related effects* (Table 6)

Bromoform was mutagenic to *Salmonella typhimurium* occasionally, especially when tested in closed containers. In single studies, bromoform caused mitotic arrest (c-mitosis) in *Allium cepa*, mutation in *Drosophila melanogaster* and mouse lymphoma L5178Y cells, and sister chromatid exchange in human lymphocytes and (weakly) in Chinese hamster CHO cells. In two of three studies with cultured Chinese hamster cells, chromosomal aberrations were reported. Sister chromatid exchange was induced in mice *in vivo* in two reports, and induction of micronuclei was seen in one but not in a second study. In one study, chromosomal aberrations were not induced in bone-marrow cells of mice treated *in vivo*. No DNA binding was observed in livers of bromoform-treated rats.

(*b*) *Humans*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

A single correlation study (Isacson *et al.*, 1983), described in the monograph on chlorinated drinking-water (p. 113), mentioned bromoform, but the information could not be used to evaluate the carcinogenicity of this chemical individually.

Table 6. Genetic and related effects of bromoform

Test system	Result		Dose LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	0.0000	Simmon *et al.* (1977)[a]
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	0	500.0000	Rapson *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	-	300.0000	Haworth *et al.* (1983)[b]
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	-	250.0000	Varma *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mtuation	-	-	1667.0000	National Toxicology Program (1989)[c]
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	0.0000	Mersch-Sunderman (1989)
SA2, *Salmonella typhimurium* TA102, reverse mutation	-	-	0.0000	Mersch-Sunderman (1989)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	0	0.0000	Simmon *et al.* (1977)[a]
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	1667.0000	National Toxicology Program (1989)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	300.0000	Haworth *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	0.0000	Varma *et al.* (1988)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	300.0000	Haworth *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mtuation	-	-	1667.0000	National Toxicology Program (1989)[c]
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	0.0000	Varma *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	300.0000	Haworth *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	500.0000	National Toxicology Program (1989)[c]
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	0.0000	Varma *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	-	0.0000	Mersch-Sunderman (1989)
SAS, *Salmonella typhimurium* TA97, reverse mutation	-	-	1667.0000	National Toxicology Program (1989)[c]
SAS, *Salmonella typhimurium* TA97, reverse mutation	+	-	0.0000	Mersch-Sunderman (1989)[d]
ACC, *Allium cepa*, C-mitosis	+	0	0.0000	Östergren (1944)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+	0	3000.0000	Woodruff *et al.* (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	-	0	1000.0000	Woodruff *et al.* (1985)
DMH, *Drosophila melanogaster*, reciprocal translocations	-	0	3000.0000	Woodruff *et al.* (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	+	+	70.0000	National Toxicology Program (1989)
SIC, Sister chromatid exchange, Chinese hamster CHO cells	(+)	-	290.0000	National Toxicology Program (1989)[b]
CIC, Chromosomal aberrations, Chinese hamster CHO cells	+	-	1070.0000	National Toxicology Program (1989)[b]

Table 6 (contd)

Test system	Result		Dose LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CIC, Chromosomal aberrations, Chinese hamster CHL cells	(+)	+	116.0000	Ishidate (1987)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	20.0000	Morimoto & Koizumi (1983)
SVA, Sister chromatid exchange, mouse bone-marrow cells *in vivo*	+	0	25.0000	Morimoto & Koizumi (1983)
SVA, Sister chromatid exchange, mouse bone-marrow cells *in vivo*	+	0	800.0000	National Toxicology Program (1989)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	-	0	800.0000	National Toxicology Program (1989)
MVM, Micronucleus test, ddy mice *in vivo*	-	0	1400.0000	Hayashi *et al.* (1988)
MVM, Micronucleus test, B6C3F$_1$ mice *in vivo*	+	0	800.0000	National Toxicology Program (1989)
BVD, DNA binding to rat liver *in vivo*	-	0	380.0000	Pereira *et al.* (1982)

[a]Closed container
[b]One of two participating laboratories obtained positive results.
[c]Results from SRI laboratories
[d]Spot test +, standard -

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Bromoform has a limited number of industrial uses. It is also found in chlorinated drinking-water as a consequence of the reaction between chlorine, added during water treatment, and natural organic substances in the presence of bromide ion. Bromoform has been detected in chlorinated drinking-water in many parts of the world; it has also been detected in untreated water, but at lower levels. Bromoform is the major organohalide produced by chlorination of seawater during desalination. It is a major component of the organohalides produced by marine algae.

The major route of human exposure to bromoform is from drinking-water, although ambient air is also an important source of exposure in some areas.

4.2 Experimental carcinogenicity data

Bromoform was tested for carcinogenicity in a two-year study by oral gavage in male and female B6C3F$_1$ mice and Fischer 344 rats. It induced adenomatous polyps and adenocarcinomas of the large intestine in male and female rats. Bromoform did not increase the proportion of mice with tumours. In a screening test by intraperitoneal injection, there was a slight increase in the average number of lung tumours in strain A mice given the middle dose of bromoform.

4.3 Human carcinogenicity data

No relevant data were available to the Working Group.

4.4 Other relevant data

In experimental animals, bromoform induced liver and kidney damage and decreased the immune response.

There is some evidence of developmental toxicity in the absence of maternal toxicity in rats.

Mutagenic effects of bromoform were observed occasionally in bacteria. In single studies, bromoform induced mitotic arrest in plants, mutations in insects and in cultured mammalian cells and sister chromatid exchange in human lymphocytes.

Chromosomal aberrations were induced in cultured mammalian cells. In single studies in rodents *in vivo*, bromoform did not bind to DNA or cause chromosomal aberrations. Sister chromatid exchange was induced in rodents *in vivo*.

4.5 Evaluation[1]

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

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

Overall evaluation

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

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[1]For definition of the italicized terms, see Preamble, pp. 30-33.

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