HALOGENATED ACETONITRILES

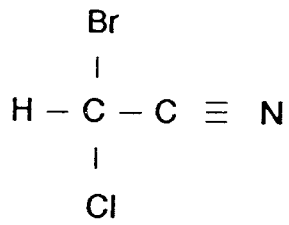
1. Chemical and Physical Data

Bromochloroacetonitrile

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 83463-62-1
Chem. Abstr. Name: Bromochloroacetonitrile
IUPAC Systematic Name: Bromochloroacetonitrile

1.2 Structural and molecular formulae and molecular weight



$C_2HBrClN$ Mol. wt: 154.39

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Liquid
(*b*) *Boiling-point*: 138-140°C (Oliver, 1983)
(*c*) *Density*: 1.68 (Trehy & Bieber, 1981)
(*d*) *Spectroscopy data*: Mass spectroscopy data have been reported (Coleman *et al.*, 1984).
(*e*) *Octanol/water partition coefficient (P)*: log P, 0.28 (calculated by the method of Leo *et al.*, 1971)
(*f*) *Half-time in water at 25°C*: 55 h at pH 8.32 (Trehy & Bieber, 1981)
(*g*) *Conversion factor*[1]: $mg/m^3 = 6.32 \times ppm$

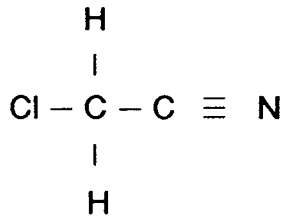
[1]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming standard temperature (25°C) and pressure (760 mm Hg)

Chloroacetonitrile

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 107-14-2
Chem. Abstr. Name: Chloroacetonitrile
IUPAC Systematic Name: Chloroacetonitrile
Synonyms: Chloracetonitrile; 2-chloroacetonitrile; alpha-chloroacetonitrile; chloromethyl cyanide; monochloroacetonitrile; monochloromethyl cyanide

1.2 Structural and molecular formulae and molecular weight



C_2H_2ClN Mol. wt: 75.50

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Colourless liquid (Eastman Kodak Co., 1987; Sax & Lewis, 1987)
(*b*) *Boiling-point*: 126-127°C (Weast, 1989)
(*c*) *Density*: 1.193 at 20°C (Weast, 1989)
(*d*) *Spectroscopy data*[1]: Infrared, raman [7886]; Pouchert, 1981, 1985a,b), nuclear magnetic resonance (Sadtler Research Laboratories, 1980, proton [6783]; Pouchert, 1974, 1983) and mass spectral data [23] have been reported (STN International, 1989a).
(*e*) *Solubility*: Very soluble in ethanol and diethyl ether (STN International, 1989a; Weast, 1989)
(*f*) *Octanol/water partition coefficient (P)*: log P, 0.23 (Chemical Information Systems, 1990)
(*g*) *Conversion factor*[2]: $mg/m^3 = 3.09 \times ppm$

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[1]In square brackets, spectrum number in compilation

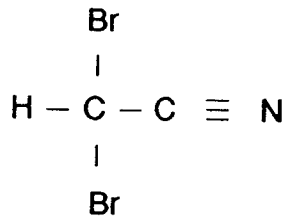
[2]Calculated from: mg/m^3 = (molecular weight/24.45) x ppm, assuming standard temperature (25°C) and pressure (760 mm Hg)

Dibromoacetonitrile

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 3252-43-5
Chem. Abstr. Name: Dibromoacetonitrile
IUPAC Systematic Name: Dibromoacetonitrile

1.2 Structural and molecular formulae and molecular weight



C_2HBr_2N Mol. wt: 198.84

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Liquid
(*b*) *Boiling-point*: 169-170°C (Oliver, 1983)
(*c*) *Density*: 2.369 (Trehy & Bieber, 1981)
(*d*) *Spectroscopy data*[1]: Infrared, raman [6434]; Pouchert, 1981, 1985a,b), nuclear magnetic resonance (Sadtler Research Laboratories, 1980, proton [2567], grating [883]; Pouchert, 1974, 1983) and mass spectral data (STN International, 1989a [162C]) have been reported.
(*e*) *Octanol/water partition coefficient (P)*: log P, 0.42 (calculated by the method of Leo *et al.*, 1971)
(*f*) *Half-time in water at 25°C*: 500 h at pH 7.4; 85 h at pH 8.3; 19 h at pH 9.0 (Bieber & Trehy, 1983)
(*g*) *Conversion factor*[2]: $mg/m^3 = 8.13 \times ppm$

Dichloroacetonitrile

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 3018-12-0
Chem. Abstr. Name: Dichloroacetonitrile

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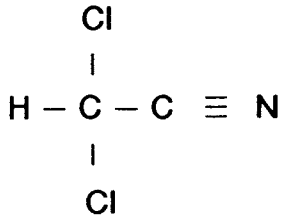
[1]In square brackets, spectrum number in compilation

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

IUPAC Systematic Name: Dichloroacetonitrile
Synonyms: Dichloromethyl cyanide

1.2 Structural and molecular formulae and molecular weight



C_2HCl_2N Mol. wt: 109.94

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Liquid
(*b*) *Boiling-point*: 112-113°C (Weast, 1989)
(*c*) *Density*: 1.369 at 20°C (Weast, 1989)
(*d*) *Spectroscopy data*[1]: Infrared, raman [4637, 4639]), nuclear magnetic resonance (Sadtler Research Laboratories, 1980, proton [23934]) and mass spectral data (Coleman *et al.*, 1984) have been reported.
(*e*) *Solubility*: Soluble in ethanol (Weast, 1989) and methanol (STN International, 1989a)
(*f*) *Octanol/water partition coefficient (P)*: log P, 0.14 (Chemical Information Systems, 1990)
(*g*) *Half-time in water at 25°C*: 30 h at pH 8.3; 0.75 h at pH 9.77 (Bieber & Trehy, 1983)
(*h*) *Conversion factor*[2]: $mg/m^3 = 4.50 \times ppm$

Trichloroacetonitrile

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 545-06-2
Chem. Abstr. Name: Trichloroacetonitrile
IUPAC Systematic Name: Trichloroacetonitrile

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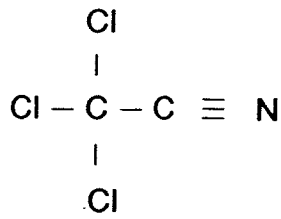
[1]In square brackets, spectrum number in compilation

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

Synonyms: Cyanotrichloromethane; 2,2,2-trichloroacetonitrile; trichloromethyl cyanide; trichloromethylnitrile

1.2 Structural and molecular formulae and molecular weight



C_2Cl_3N Mol. wt: 144.39

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Colourless liquid (Budavari, 1989; Sax & Lewis, 1987)
(*b*) *Boiling-point*: 85.7°C (Budavari, 1989)
(*c*) *Melting-point*: –42°C (Weast, 1989)
(*d*) *Density*: 1.4403 at 25/4°C (Weast, 1989)
(*e*) *Spectroscopy data*[1]: Infrared (Sadtler Research Laboratories, 1980, prism [38232, 42996]; grating [17218, 23996]; Pouchert, 1981, 1985a,b) and mass spectral data [383]; Coleman *et al.*, 1984) have been reported.
(*f*) *Solubility*: Insoluble in water (STN International, 1989a)
(*g*) *Conversion factor*[2]: $mg/m^3 = 5.91 \times ppm$

1.4 Technical products and impurities

Chloroacetonitrile is available at 98-> 99% purity, dibromoacetonitrile at 95-97% purity, dichloroacetonitrile at 95-98% purity and trichloroacetonitrile at ≥ 98% purity (Riedel-de Haën, 1986; Eastman Kodak Co., 1987; American Tokyo Kasei, 1988; Fairfield Chemical Co., 1988; Pfaltz & Bauer, 1988; Aldrich Chemical Co., 1990).

The trade name for trichloroacetonitrile is Tritox.

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[1]In square brackets, spectrum number in compilation

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

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Chloroacetonitrile was synthesized by Bisschopinck in 1873 by the reaction of chloroacetamide with phosphoric anhydride (STN International, 1989b). It has been produced commercially by the high-temperature chlorination of acetonitrile (Movsum-Zade *et al.*, 1977).

Dibromoacetonitrile and dichloroacetonitrile have been synthesized by the reaction of *N*-bromosuccinimide (or *N*-chlorosuccinimide) with cyanoacetic acid (Trehy & Bieber, 1981). Bromochloroacetonitrile has been synthesized by the reaction of a mixture of *N*-chlorosuccinimide and *N*-bromosuccinimide with cyanoacetic acid, and fractional distillation of the resulting mixture of haloacetonitriles (Pereira *et al.*, 1984a; Bull *et al.*, 1985). Bromochloroacetonitrile has also been synthesized by the bromination of chloroacetonitrile with bromine (Trehy & Bieber, 1981).

Trichloroacetonitrile was synthesized by Bisschopinck in 1873 by the reaction of trichloroacetamide with phosphoric anhydride (STN International, 1989b). It has been produced commercially by reaction of acetonitrile with chlorine or sulfonyl chloride in the presence of a catalyst at elevated temperatures (Dow Chemical Co., 1975). Trichloroacetonitrile has also been synthesized from ethyl trichloroacetate and aqueous ammonia and by reaction of methylnitrile, hydrochloric acid and chlorine gas (Budavari, 1989).

(*b*) *Use*

Chloroacetonitrile has reportedly been used as a fumigant and as a chemical intermediate; trichloroacetonitrile has reportedly been used as an insecticide (Sax & Lewis, 1987).

(*c*) *Regulatory status and guidelines*

No regulatory standards or guidelines have been published for exposures to halogenated acetonitriles.

2.2 Occurrence

Halogenated acetonitriles have been identified in the environment only as by-products of the chlorination of ground- and surface waters for disinfection of

drinking-water supplies. Therefore, the only known route of environmental release of halogenated acetonitriles is as a constituent of potable water supplies. Potential precursors for the formation of these compounds during chlorination are algae, humic substances and proteinaceous material—all naturally occurring water components. The brominated acetonitriles are formed when bromide is present in the water during chlorination. Halogenated acetonitriles have not been detected in raw (untreated) water sources (Trehy & Bieber, 1981; Keith *et al.*, 1982; Oliver, 1983).

(*a*) *Natural occurrence*

None of the halogenated acetonitriles is known to occur as a natural product.

(*b*) *Water and sediments*

Dichloroacetonitrile was detected in tap-water samples taken from two buildings in Durham, NC, USA (McKinney *et al.*, 1976).

In a two-year study of trace organic compounds in drinking-water in Philadelphia, PA, Suffet *et al.* (1980) tested samples collected at three treatment plants and one hotel, which originated from two surface water (river) sources. Dichloroacetonitrile was identified in four of nine samples originating from the Delaware River but in neither of the two samples originating from the Schuylkill River. No quantitative analysis was performed.

Three dihaloacetonitriles (bromochloroacetonitrile, dibromoacetonitrile and dichloroacetonitrile) were identified in chlorinated ground- and surface water supplies in southern Florida (USA). Although individual concentrations were not determined, the highest total concentration of dihaloacetonitriles found was 42 µg/l in a chlorinated well-water supply. The relative concentrations of the three dihaloacetonitriles varied considerably from supply to supply, and none was found in water supplies that had been lime-softened. Experimental chlorination of lakewater samples confirmed that dihaloacetonitriles were formed in the chlorination process (Trehy & Bieber, 1980, 1981).

Bromochloroacetonitrile and dibromoacetonitrile were identified in stored, chlorinated Rhine water in The Netherlands. The concentrations of bromochloroacetonitrile before and after chlorination were < 0.1 and 3 µg/l, respectively, and those of dibromoacetonitrile, < 0.1 and 1 µg/l (Zoeteman *et al.*, 1982).

Analysis of chlorinated drinking-water samples from ten cities in Ontario, Canada, showed dichloroacetonitrile at 0.3-8.1 µg/l and bromochloroacetonitrile at not detected (< 0.1 µg/l) to 1.8 µg/l. Neither was detected in any of the raw water samples tested; dibromoacetonitrile was not detected in either the raw-water or drinking-water samples. When chlorine was reacted with fulvic acid (a major component of humic substances found in natural waters) for 4-120 h,

dichloroacetonitrile was produced in concentrations of 3.5-6.5 μg/l, and bromochloroacetonitrile was not detected (< 0.1 μg/l); when chlorine was reacted with a blue-green alga, dichloroacetonitrile occurred at 0.5-3.5 μg/l and bromochloroacetonitrile at not detected to 0.6 μg/l; after reaction with a green alga, dichloroacetonitrile occurred at 0.3-1.0 μg/l and the bromine compound at not detected to 1.1 μg, indicating that dihaloacetonitriles can be produced by chlorinating aquatic humic substances and algae under conditions used for water treatment (Oliver, 1983).

Samples collected following prechlorination of raw water in 1984 from a drinking-water treatment plant at Cholet, France, contained dichloroacetonitrile at 0.14 μg/l and trichloroacetonitrile at 0.11 μg/l (Bruchet *et al.*, 1985).

Samples of chlorinated wastewater from an extended aeration treatment plant in the USA contained 7-14 μg/l dichloroacetonitrile. Chlorinated lakewater samples from West Palm Beach, FL, contained 5-19 μg/l dichloroacetonitrile and those from Gainsville, FL, 10-17 μg/l (chlorine contact time, 5-70 min). Experimental studies confirmed that dichloroacetonitrile is formed when amino acids, such as aspartic acid, tyrosine and tryptophan, are chlorinated (Trehy *et al.*, 1986, 1987).

Treated water at 10 Canadian sites along the Great Lakes in the spring contained dichloroacetonitrile at a mean concentration of 0.3 μg/l. It was not detected (detection limit, 0.1 μg/l) in treated water samples during the summer or winter or in any of the raw-water samples (Otson, 1987).

Treatment plant samples collected from 29 US community water systems (using free chlorine disinfection) in 1984 and 1985 contained bromochloroacetonitrile at 0.2-9.4 μg/l (25 of 29 sites), dibromoacetonitrile at 0.3-11 μg/l (14 of 29 sites) and dichloroacetonitrile at 0.2-21 μg/l (27 of 29 sites). Distribution samples from the system contained bromochloroacetonitrile at 0.4-10 μg/l (21 of 26 sites), dibromoacetonitrile at 0.2-2.5 μg/l (11 of 26 sites) and dichloroacetonitrile at 0.3-24 μg/l (21 of 26 sites) (quantification limits, 0.2-0.3 μg/l) (Reding *et al.*, 1989).

Water samples collected from 10 US utilities in 1985 (using free chlorine disinfection, in one of which ammonia was added before distribution) contained bromochloroacetonitrile at < 10 μg/l at all of seven sites for which data were available, dibromoacetonitrile at < 10 μg/l at three of the seven sites and dichloroacetonitrile at < 10 μg/l at all of 10 sites; trichloroacetonitrile was not found at any of the eight sites for which data were available (Stevens *et al.*, 1989).

Samples of finished water were taken from 35 US utilities in spring, summer, autumn and winter, 1988-89. The median concentrations (μg/l) of halogenated acetonitriles measured were: bromochloroacetonitrile, 0.50-0.70;

dibromoacetonitrile, 0.48-0.54; dichloroacetonitrile, 1.1-1.2; and trichloroacetonitrile, not detected (detection limits, < 0.012 and < 0.029, according to season) (Krasner *et al.*, 1989).

2.3 Analysis

Difficulties in analysising halogenated acetonitriles in environmental samples have been attributed to their instability under the analytical conditions used (Oliver, 1983). Halogenated acetonitriles hydrolyse in water to haloacetamides and then to haloacetic acids (Bieber & Trehy, 1983). Destruction by hydrolysis is appreciable at the pH (8.0-8.5) frequently found in water treatment plants. The rate of hydrolysis increases at elevated temperature and pH (Trehy & Bieber, 1981; Bieber & Trehy, 1983; Oliver, 1983).

Dichloroacetonitrile has been determined in drinking-water by concentration on an adsorption column, followed by gas chromatography-flame ionization detection or gas chromatography-electron capture detection (Chriswell *et al.*, 1983).

Dihaloacetonitriles can be measured in water by solvent (pentane) extraction, usually after salting out using sodium chloride or sodium sulfate, followed by gas chromatography-electron capture detection (Oliver, 1983; Reckhow & Singh, 1984; Krasner *et al.*, 1989; Reding *et al.*, 1989.

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

3.1 Carcinogenicity studies in animals (Tables 1 and 2)

(*a*) *Oral administration*

Mouse: In a screening assay based on the enhanced induction of lung tumours, groups of 40 female strain A/J mice, 10 weeks old, were given 10 mg/kg bw chloroacetonitrile, dichloroacetonitrile, trichloroacetonitrile, bromochloroacetonitrile or dibromoacetonitrile [purity unspecified] in 10% Emulphor by oral gavage three times per week for eight weeks. A group of 40 animals given 10% Emulphor only served as controls. Survival at the end of the study (at nine months of age) was: control, 31/40; chloroacetonitrile-treated, 28/40; dichloroacetonitrile-treated, 30/40; trichloroacetonitrile-treated, 32/40; bromochloroacetonitrile-treated, 32/40; and dibromoacetonitrile-treated, 31/40. The numbers of animals with lung tumours and

the average numbers of tumours per animal were: control, 3/31 and 0.1; chloroacetonitrile-treated, 9/28 and 0.43 ($p < 0.05$); dichloroacetonitrile-treated, 7/30 and 0.23; trichloroacetonitrile-treated, 9/32 and 0.38 ($p < 0.05$); bromochloroacetonitrile-treated, 10/32 and 0.34 ($p < 0.05$); dibromoacetonitrile-treated, 5/31 and 0.19 (Bull & Robinson, 1985).

Table 1. Results of skin application of halogenated acetonitriles to female Sencar mice[a]

Expt. no.	Treatment	Dose (mg/kg)	No. of animals			
			Effective	With tumours	With papilloma	With carcinoma
1	Chloroacetonitrile	200×6	38	11**	7	4
2		400×6	37	11**	9	4
2		800×6	38	6	1	6
1	Dichloroacetonitrile	200×6	39	4	4	0
2		400×6	35	4	2	3
2		800×6	35	1	1	0
1	Trichloroacetonitrile	200×6	34	2	1	1
2		400×6	36	11**	5	6
3		400×6	38	1	0	1
2		800×6	36	3	2	1
3		800×6	29	2	1	1
2	Bromochloroacetonitrile	200×6	35	1	0	1
2		400×6	37	7	0	7
2		800×6	37	8*	3	6
1	Dibromoacetonitrile	200×6	36	8*	6	2
2		400×6	35	17**	9	8
3		400×6	35	16**	7	9
2		800×6	37	7	5	2
3		800×6	37	3	1	2
1	Acetone	0.2 ml×6	34	1	0	1
2		0.2 ml×6	37	3	3	0
3		0.2 ml×6	34	5	1	4

[a]From Bull *et al.* (1985)

*$p < 0.05$, Fisher's exact test

**$p < 0.01$, Fisher's exact test

Table 2. Summary of carcinogenicity studies of halogenated acetonitriles in experimental animals

Reference	Species/ strain	Sex	Dose schedule	Experimental parameter/ observation	Group*						Significance	Comment
					0	1	2	3	4	5		
Bull & Robinson (1985)	Mouse A/J	F	3 d/week, orally, Emulphor, 24 doses	Dose (mg/kg) Survival (9 months) Lung adenoma Lung adenomas per mouse	0 31/40 3/31 0.10	10 28/40 9/28* 0.43	10 30/40 7/30 0.23	10 32/40 9/32* 0.38	10 32/40 10/32* 0.34	10 31/40 5/31 0.19	*$p < 0.05$	Low doses
Bull *et al.* (1985)	Mouse Sencar	F	3 d/week, skin appl., acetone, 24 weeks	Dose (mg/kg)	0	800	800	800	800	400		No tumour; few details

*Group 0, vehicle control; group 1, chloroacetonitrile; group 2, dichloroacetonitrile; group 3, trichloroacetonitrile; group 4, bromochloroacetonitrile; group 5, dibromoacetonitrile

(*b*) *Skin application*

Mouse: In a series of three initiation-promotion experiments, groups of 40 female Sencar mice [age unspecified] were given topical applications of 200, 400 or 800 mg/kg bw chloroacetonitrile (> 99% pure), dichloroacetonitrile (> 99% pure), trichloroacetonitrile (98% pure), bromochloroacetonitrile (93% pure) or dibromoacetonitrile (96% pure) in 0.2 ml acetone three times per week for two weeks. Two weeks following the last application of the halogenated acetonitrile, 1.0 μg 12-*O*-tetradecanoylphorbol 13-acetate (TPA) was applied topically three times per week for 20 weeks. Animals were observed for one year. The numbers of animals with skin tumours and the numbers of squamous-cell papillomas and carcinomas are given in Table 1 (Bull *et al.*, 1985). [The Working Group noted that the results were variable and were derived from three separate studies not conducted simultaneously.]

In another experiment, groups of 40 female Sencar mice [age unspecified] were given topical applications of 800 mg/kg bw chloroacetonitrile, dichloroacetonitrile, trichloroacetonitrile or bromochloroacetonitrile or 400 mg/kg bw dibromoacetonitrile at the same purity described above in 0.2 ml acetone three times per week for 24 weeks. A group of 40 female mice given topical applications of acetone on the same schedule served as controls. No skin tumour occured (Bull *et al.*, 1985). [The Working Group noted that the duration of the study was not specified.]

3.2 Other relevant data

(*a*) *Experimental systems*

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

Rats given 0.75 mmol/kg bw bromochloroacetonitrile (116 mg/kg bw), chloroacetonitrile (57 mg/kg bw), dibromoacetonitrile (149 mg/kg bw), dichloroacetonitrile (82.5 mg/kg bw) or trichloroacetonitrile (108 mg/kg bw) dissolved in tricaprylin by gavage excreted 12.8, 14.2, 7.7, 9.3 or 2.3%, respectively, of the dose in the urine as thiocyanate within 24 h (Pereira *et al.*, 1984b). The halonitriles are apparently metabolized to the corresponding cyanohydrins, which eliminate cyanide; the cyanide is metabolized to thiocyanate by rhodanese.

Rats given 0.002 mmol/kg bw (0.20 mg/kg bw), 0.02 (2.0 mg/kg bw) or 0.14 (15 mg/kg bw) [1-^{14}C]dichloroacetonitrile by gavage in water excreted 62-73% of the dose by six days; most of the radiolabel was excreted in the urine (42-45%) and faeces (14-20%) (Roby *et al.*, 1986). Exhalation of ^{14}C-carbon dioxide amounted to 3.2-8.1% of the administered dose of dichloroacetonitrile. After six days, 19.3% of the dose was retained in the tissues; the largest amounts were found in blood (4-8% of dose), muscle (4-8%), skin (3-6%) and liver (about 2%). In rats given

0.002 mmol/kg bw (0.21 mg/kg bw), 0.02 mmol/kg bw (2.0 mg/kg bw) or 0.14 mmol/kg bw (15 mg/kg bw) [2-^{14}C]-dichloroacetonitrile by gavage in water, a total of 82-86% of the dose was eliminated in the urine, faeces and expired air (as ^{14}C-carbon dioxide) within 48 h; urinary radiolabel accounted for 35-40% and ^{14}C-carbon dioxide for 33-34% of the dose. After two days, 12-17% of the dose was retained in the tissues; and the largest amounts were found in liver (about 5% of dose), muscle (3-5%), blood (2-5%) and skin (about 1%).

After oral administration of 0.02 mmol/kg bw (2.0 mg/kg bw) or 0.14 mmol/kg bw (15 mg/kg bw) [1-^{14}C]-dichloroacetonitrile to mice by gavage in water, 85 and 83%, respectively, of the dose was eliminated in the urine, faeces and expired air (as ^{14}C-carbon dioxide) by 24 h (Roby *et al.*, 1986). The urine contained 64-70% of the dose, the faeces contained 9-13% and about 5% was eliminated as carbon dioxide; 11-12% was retained in the tissues. The largest amount of radiolabel was found in the liver (about 4% of dose), muscle and skin (about 2%) and blood and fat (about 1%). When mice were given 0.02 mmol/kg bw (2.0 mg/kg) or 0.14 mmol/kg bw (15 mg/kg) [2-^{14}C]-dichloroacetonitrile by gavage in water, 84-88% of the dose was eliminated in the urine, faeces and expired air (as ^{14}C-carbon dioxide) within 24 h; the urine (42-43% of dose) and expired air (31-37%) contained the most radiolabel. Nine percent of the administered radiolabel was retained in the tissues after 24 h; most was found in the liver (about 5% of dose), and 0.5-1% of the dose was present in muscle, kidney and skin.

Chloroacetonitrile is metabolized to hydrogen cyanide by mouse hepatic microsomal fractions (Tanii & Hashimoto, 1984).

Except trichloroacetonitrile, the haloacetonitriles considered here were shown to be electrophiles on the basis of their reactivity with *para*-nitrobenzylpyridine and DNA, in the ranking dibromoacetonitrile > bromochloroacetonitrile > chloroacetonitrile > dichloroacetonitrile (Lin *et al.*, 1986).

(ii) *Toxic effects*

Chloroacetonitrile

The acute oral LD_{50} of chloroacetonitrile was estimated to be 1.8 mmol/kg bw [136 mg/kg] in male ddY mice (Tanii & Hashimoto, 1984). Chloroacetonitrile was inactive in a bioassay for γ-glutamyltranspeptidase-positive foci in a bioassay for rat liver (Herren-Freund & Pereira, 1986).

Dichloroacetonitrile

The acute oral (by gavage) LD_{50}s of dichloroacetonitrile were 339 and 330 mg/kg bw for male and female CD rats and 270 and 279 mg/kg bw for male and

female CD-1 ICR mice, respectively (Hayes *et al.*, 1986). Signs of toxicity included ataxia, depressed respiration and prostration but no gross pathological change.

Daily administration of 12-90 mg/kg bw dichloroacetonitrile in corn oil by gavage to male and female CD rats for 14 days induced no toxicity, as measured by mortality rates, body weights and clinical chemistry and haematological parameters, although the relative weight of some organs was slightly reduced (Hayes *et al.*, 1986).

Daily treatment of male and female CD rats by gavage with 8, 33 or 65 mg/kg bw dichloroacetonitrile in corn oil for 90 days resulted in 25-50% mortality in the 65-mg/kg bw group and 5-10% in the 8- and 33-mg/kg bw groups. Significant signs of toxicity were reduced body weights in males and females, reduced weights of most organs in males and reduced serum cholesterol levels at the highest dose; clinical chemistry and haematological parameters were generally unchanged. Livers appeared to be larger in treated females (Hayes *et al.*, 1986).

Dichloroacetonitrile was inactive in a bioassay for γ-glutamyltranspeptidase-positive foci in rat liver (Herren-Freund & Pereira, 1986).

Trichloroacetonitrile

Trichloroacetonitrile was inactive in a bioassay for γ-glutamyltranspeptidase-positive foci in rat liver (Herren-Freund & Pereira, 1986).

Dibromoacetonitrile

The acute oral LD_{50}s of dibromoacetonitrile were 245 and 361 mg/kg bw in male and female CD rats and 289 and 303 mg/kg bw in male and female CD-1 ICR mice, respectively (Hayes *et al.*, 1986). Signs of toxicity included ataxia, depressed respiration and prostration, but no gross pathological change was observed.

Daily administration of 23-180 mg/kg bw dibromoacetonitrile to male and female CD rats in corn oil by gavage for 14 days resulted in 100% mortality in the 180-mg/kg bw group and 20-40% in the 90-mg/kg bw group. Besides a dose-dependent depression in weight gain, the only significant signs of toxicity were decreases in relative spleen and thymus weights (males) and an increase in relative liver weight (females) in the 90-mg/kg bw group (Hayes *et al.*, 1986).

Daily treatment of male and female CD rats by gavage with 6, 23 or 45 mg/kg bw dibromoacetonitrile in corn oil for 90 days resulted in 5-10% mortality in the 23- and 45-mg/kg bw groups. Significant signs of toxicity were reduced body weights in males in the 45-mg/kg bw group. Relative organ weights, clinical chemistry and haematological parameters were generally unchanged (Hayes *et al.*, 1986).

Dibromoacetonitrile was inactive in a bioassay for γ-glutamyltranspeptidase-positive foci in rat liver (Herren-Freund & Pereira, 1986).

No data on acute toxicity were available for bromochloroacetonitrile or trichloroacetonitrile. No data on subacute or subchronic toxicity were available for chloroacetonitrile, bromochloroacetonitrile or trichloroacetonitrile. None of the halogenated acetonitriles has been examined for chronic toxicity.

(iii) *Effects on reproduction and prenatal toxicity*

Chloroacetonitrile

In a screening study (Smith *et al.*, 1987), Long-Evans rats were administered chloroacetonitrile in tricaprylin by gavage at 55 mg/kg bw daily on gestation days 7-21. The litters were culled on postnatal day 6 (to six to eight pups) and again at weaning, when litters were reduced to four pups, which were retained until 41 or 42 days of age. One of the 30 treated dams died. There was a significant decrease in maternal weight gain during the period of treatment. No effect on pregnancy, proportion of resorptions, pup survival or growth after birth was observed. Litter weight at the time of birth was significantly lower than in the controls.

Bromochloroacetonitrile

In the screening study described above (Smith *et al.*, 1987), one of the 20 dams treated with bromochloroacetonitrile died. Litter weight at the time of birth was slightly lower than in the controls, and weight gain to day 4 was also decreased. There was no significant effect on the percentages of pregnant females or resorptions and no effect on neonatal survival.

Dibromoacetonitrile

In the screening study described above but using a dose of 50 mg/kg bw (Smith *et al.*, 1987), four of the 26 dams treated with dibromoacetonitrile died. There was a significant decrease in maternal weight gain during the period of treatment. Litter weight at the time of birth was lower than in the controls, and weight gain to lactation day 4 was significantly decreased. There was no significant effect on the percentages of pregnant females or resorptions and no effect on neonatal survival after birth.

Dichloroacetonitrile

In two screening studies performed as described above (Smith *et al.*, 1987), no mortality was seen in a group of 20 females treated with 55 mg/kg bw/day dichloroacetonitrile in one study, but two of the 23 treated dams died in a second

study. Maternal weight gain was significantly decreased in both studies. There was a significant decrease in the percentage of dams delivering viable litters, an increase in resorption of litters and fetuses and decreased survival of neonates after birth. Litter weight at the time of birth was significantly decreased, and weight gain to lactation day 4 was lower in the treated group than in controls.

Groups of 22-24 mated Long-Evans rats were administered dichloroacetonitrile in tricaprylin by gavage at 0, 5, 15, 25 or 45 mg/kg bw daily on gestation days 6-18 (Smith *et al.*, 1989). Maternal deaths (9%) occurred at the high-dose levels, and significant increases in postimplantation losses were observed in the groups given 25 mg/kg bw (35%) and 45 mg/kg bw (80%). At the high-dose level, resorption of entire litters occurred in 60% of the survivors. Maternal weight gain and fetal body weight were decreased at the high-dose level. The frequency of malformations of the soft tissues, particularly cardiovascular and urogenital organs, was significantly increased at the high-dose level, at which there was also an increase in the percentage of skeletal malformations. Thus, dichloroacetonitrile induced malformations, but only at dose levels at which there was both severe embryolethality and maternal toxicity.

Trichloroacetonitrile

In two screening studies (Smith *et al.*, 1987), performed as described above, five of 25 females treated with 55 mg/kg bw/day trichloroacetonitrile died in one study while none of 20 died in the second. Maternal weight gain was significantly decreased in both studies. There was a significant decrease in the percentage of pregnant females, an increase in the number of litters resorbed and a decrease in neonatal survival. Litter weight was decreased at birth and postnatally.

Groups of 22-24 mated Long-Evans rats were administered trichloroacetonitrile gavage in tricaprylin by gavage at 0, 1, 7.5, 15, 35 or 55 mg/kg bw daily on gestation days 6-18 (Smith *et al.*, 1988). Maternal mortality occurred in the groups given 35 and 55 mg/kg bw, and maternal weight gain was significantly decreased at the highest dose level. Whole litters were resorbed at levels of 7.5 mg/kg bw and above, and a significant increase in the incidence of fetal resorptions was observed at 15 mg/kg bw (49%), 35 mg/kg bw (62%) and 55 mg/kg bw (78%). Fetal body weights were significantly decreased at 35 mg/kg bw, but not at other dose levels. The incidences of malformations, primarily cardiovascular and urogenital, were significantly increased in the groups given 15, 35 and 55 mg/kg bw. Thus, trichloroacetonitrile induced malformations in rats at embryolethal dose levels. Embryolethality occurred at dose levels below those which caused maternal toxicity and malformations.

(iv) *Genetic and related effects* (Table 3)

The genetic and related effects of the haloacetonitriles considered have been reviewed (Bull, 1985).

Bromochloroacetonitrile

Mutation was induced in *Salmonella typhimurium*. Sister chromatid exchange was induced in Chinese hamster ovary (CHO) cells and DNA strand breaks in human lymphoblast cell lines. In mice dosed for five days, neither micronuclei in bone marrow nor abnormal sperm morphology was induced.

Chloroacetonitrile

Chloroacetonitrile did not induce mutation in a single study with *S. typhimurium*. Sister chromatid exchange was induced in one study using Chinese hamster ovary (CHO) cells, and DNA strand breaks (weakly) were induced in another using a human lymphoblast cell line. In mice dosed for five days, neither micronuclei in bone marrow nor abnormal sperm morphology was induced.

Dibromoacetonitrile

Dibromoacetonitrile was not mutagenic in either *S. typhimurium* or *Drosophila melanogaster*. Sister chromatid exchange was induced in Chinese hamster ovary (CHO) cells and DNA strand breaks in human lymphoblast cell lines. In mice dosed for five days, neither micronuclei in bone marrow nor abnormal sperm morphology was induced.

Dichloroacetonitrile

Dichloroacetonitrile induced mutation in *S. typhimurium* and in one study in *D. melanogaster*. Mitotic recombination was not induced in yeast. Dichloroacetonitrile induced sister chromatid exchange in Chinese hamster ovary (CHO) cells and DNA strand breaks (weakly) in a human cell line. In mice dosed for five days, neither micronuclei in bone marrow nor abnormal sperm morphology was induced.

Trichloroacetonitrile

Trichloroacetonitrile did not induce mutation in *S. typhimurium*. Sister chromatid exchange was induced in Chinese hamster ovary (CHO) cells and DNA strand breaks in human cell lines. In mice dosed for five days, neither micronuclei in bone marrow nor abnormal sperm morphology was induced.

Table 3. Genetic and related effects of bromochloroacetonitrile

Test system	Result		Dose LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	+	13.0000	Bull *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	26.0000	Bull *et al.* (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	0.0000	Bull *et al.* (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	-	0.0000	Bull *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	105.0000	Bull *et al.* (1985)
SIC, Sister chromatid exchange, Chinese hamster CHO cells *in vitro*	+	+	0.6500	Bull *et al.* (1985)
DIH, DNA strand breaks, human lymphoblast cell line	+	0	0.0000	Daniel *et al.* (1986)
MVM, Micronucleus test, CD-1 mice *in vivo*	-	0	50.0000	Bull *et al.* (1985)
SPF, Sperm morphology, B6C3F$_1$ mice *in vivo*	-	0	50.0000	Meier *et al.* (1985)

Table 3 (contd). Genetic and related effects of chloroacetonitrile

Test system	Result		Dose LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1500.0000	Bull *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1500.0000	Bull *et al.* (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mtuation	–	–	0.0000	Bull *et al.* (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	0.0000	Bull *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1500.0000	Bull *et al.* (1985)
SIC, Sister chromatid exchange, Chinese hamster CHO cells *in vitro*	+	+	4.0000	Bull *et al.* (1985)
DIH, DNA strand breaks, human lymphoblast cell line	(+)	0	225.0000	Daniel *et al.* (1986)
MVM, Micronucleus test, CD-1 mice *in vivo*	–	0	50.0000	Bull *et al.* (1985)
SPF, Sperm morphology, B6C3F_1 mice *in vivo*	–	0	50.0000	Meier *et al.* (1985)

Table 3 (contd). Genetic and related effects of dibromoacetonitrile

Test system	Result		Dose LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	115.0000	Bull *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	115.0000	Bull *et al.* (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mtuation	–	–	0.0000	Bull *et al.* (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	0.0000	Bull *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	115.0000	Bull *et al.* (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	–	0	200.0000	Valencia *et al.* (1985)
SIC, Sister chromatid exchange, Chinese hamster CHO cells *in vitro*	+	+	0.0300	Bull *et al.* (1985)
DIH, DNA strand breaks, human lymphoblast cell line	+	0	0.0000	Daniel *et al.* (1986)
MVM, Micronucleus test, CD-1 mice *in vivo*	–	0	50.0000	Bull *et al.* (1985)
SPF, Sperm morphology, B6C3F_1 mice *in vivo*	–	0	50.0000	Meier *et al.* (1985)

Table 3 (contd). Genetic and related effects of dichloroacetonitrile

Test system	Result		Dose LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	250.0000	Simmon *et al.* (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	175.0000	Bull *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	22.0000	Bull *et al.* (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mtuation	-	-	0.0000	Bull *et al.* (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	-	0.0000	Bull *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	680.0000	Bull *et al.* (1985)
SCG, *Saccharomyces cerevisiae*, mitotic recombination	-	0	0.0000	Simmon *et al.* (1977)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	+	0	200.0000	Valencia *et al.* (1985)
SIC, Sister chromatid exchange, Chinese hamster CHO cells *in vitro*	(+)	+	1.0000	Bull *et al.* (1985)
DIH, DNA strand breaks, human lymphoblast cell line	(+)	0	220.0000	Daniel *et al.* (1986)
MVM, Micronucleus test, CD-1 mice *in vivo*	-	0	50.0000	Bull *et al.* (1985)
SPF, Sperm morphology, B6C3F$_1$ mice *in vivo*	-	0	50.0000	Meier *et al.* (1985)

Table 3 (contd). Genetic and related effects of trichloroacetonitrile

Test system	Result		Dose LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	840.0000	Bull *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	840.0000	Bull *et al.* (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.0000	Bull *et al.* (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	0.0000	Bull *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	840.0000	Bull *et al.* (1985)
SIC, Sister chromatid exchange, Chinese hamster CHO cells *in vitro*	+	+	2.0000	Bull *et al.* (1985)
DIH, DNA strand breaks, human lymphoblast cell line	+	0	0.0000	Daniel *et al.* (1986)
MVM, Micronucleus test, CD-1 mice *in vivo*	–	0	50.0000	Bull *et al.* (1985)
SPF, Sperm morphology, B6C3F$_1$ mice *in vivo*	–	0	50.0000	Meier *et al.* (1985)

(*b*) *Humans*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Halogenated acetonitriles are not produced on an industrial scale. Chloro- and trichloroacetonitriles have been used on a limited basis in the past as pesticides.

Several halogenated acetonitriles have been detected in chlorinated drinking-water in a number of countries as a consequence of the reaction of chlorine with natural organic substances (and bromine in the case of brominated acetonitriles) present in untreated water. The only known route of human exposure is through chlorinated drinking-water.

4.2 Experimental carcinogenicity data

Halogenated acetonitriles (chloroacetonitrile, dichloroacetonitrile, trichloroacetonitrile, bromochloroacetonitrile and dibromoacetonitrile) were tested in a limited carcinogenicity study in female Sencar mice by skin application, in an initiation/promotion study in female Sencar mice by skin application and in a screening assay for lung tumours in female strain A mice by oral administration. No skin tumour was produced by any of the haloacetonitriles after skin application in mice. In the initiation/promotion study, reproducible, significant increases in the numbers of animals with skin tumours were seen only with dibromoacetonitrile; no dose-related increase in the incidence of skin tumours was observed. Marginal increases in the proportion of mice with lung tumours occurred with all of the halogenated acetonitriles, but the increases were significant only with chloroacetonitrile, trichloroacetonitrile and bromochloroacetonitrile.

4.3 Human carcinogenicity data

No data were available to the Working Group.

4.4 Other relevant data

In short-term screening studies *in vivo*, chloroacetonitrile, bromochloroacetonitrile and dibromoacetonitrile caused minimal developmental toxicity in the presence of significant maternal toxicity. In developmental toxicity studies, dichloroacetonitrile and trichloroacetonitrile caused malformations and embryolethality in the presence of maternal toxicity; with trichloroacetonitrile, embryolethality was also observed at lower dose levels in the absence of maternal toxicity.

Mutations were induced in bacteria by bromochloroacetonitrile and dichloroacetonitrile but not by chloroacetonitrile, dibromoacetonitrile or trichloroacetonitrile. Mutations were induced in insects by dichloroacetonitrile but not by dibromoacetonitrile.

Sister chromatid exchange was induced in cultured mammalian cells by all five halogenated acetonitriles. DNA strand breaks were induced in human lymphocytes *in vitro* by bromochloroacetonitrile, dibromoacetonitrile and trichloroacetonitrile.

In orally treated mice, neither micronuclei in bone-marrow cells nor sperm-head abnormalities were induced by any of the five halogenated acetonitriles.

4.5 Evaluations[1]

There is *inadequate evidence* for the carcinogenicity of bromochloroacetonitrile in experimental animals.

There is *inadequate evidence* for the carcinogenicity of chloroacetonitrile in experimental animals.

There is *inadequate evidence* for the carcinogenicity of dibromoacetonitrile in experimental animals.

There is *inadequate evidence* for the carcinogenicity of dichloroacetonitrile in experimental animals.

There is *inadequate evidence* for the carcinogenicity of trichloroacetonitrile in experimental animals.

No data were available from studies in humans on the carcinogenicity of halogenated acetonitriles.

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

Overall evaluations

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

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

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

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

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

5. References

Aldrich Chemical Co. (1990) *1990-1991 Aldrich Handbook of Fine Chemicals*, Milwaukee, WI, pp. 275, 406, 1267

American Tokyo Kasei (1988) *TCI American Organic Chemicals 88/89 Catalog*, Portland, OR, pp. 262, 1217

Bieber, T.I. & Trehy, M.L. (1983) Dihaloacetonitriles in chlorinated natural waters. In: Jolley, R.L., Brungs, W.A., Cotruvo, J.A., Cumming, R.B., Mattice, J.S. & Jacobs, V.A., eds, *Water Chlorination: Environmental Impact and Health Effects*, Vol. 4, Book 1, *Chemistry and Water Treatment*, Ann Arbor, MI, Ann Arbor Science, pp. 85-96

Bruchet, A., Tsutsumi, Y., Duguet, J.P. & Mallevialle, J. (1985) Characterization of total halogenated compounds during water treatment processes. In: Jolley, R.L., Bull, R.J., Davis, W.P., Katz, S., Roberts, M.H., Jr & Jacobs, V.A., eds, *Water Chlorination: Chemistry, Environmental Impact and Health Effects*, Vol. 5, Chelsea, MI, Lewis Publishers, pp. 1165-1184

Budavari, S., ed. (1989) *The Merck Index*, 11th ed., Rahway, NJ, Merck & Co., p. 1515

Bull, R.J. (1985) Carcinogenic and mutagenic properties of chemicals in drinking water. *Sci. total Environ.*, 47, 385-413

Bull, R.J. & Robinson, M. (1985) Carcinogenic activity of haloacetonitrile and haloacetone derivatives in the mouse skin and lung. In: Jolley, R.L., Bull, R.J., Davis, W.P., Katz, S., Roberts, M.H., Jr & Jacobs, V.A., eds, *Water Chlorination: Chemistry, Environmental Impact and Health Effects*, Vol. 5, Chelsea, MI, Lewis Publishers, pp. 221-227

Bull, R.J., Meier, J.R., Robinson, M., Ringhand, H.P., Laurie, R.D. & Stober, J.A. (1985) Evaluation of mutagenic and carcinogenic properties of brominated and chlorinated acetonitriles: by-products of chlorination. *Fundam. appl. Toxicol.*, 5, 1065-1074

Chemical Information Systems (1990) *ISHOW Database*, Baltimore, MD

Chriswell, C.D., Gjerde, D.T., Schultz-Sibbel, G., Fritz, J.S. & Ogawa, I. (1983) *An Evaluation of the Adsorption Properties of Silicalite for Potential Application to Isolating Polar Low-molecular-weight Organics from Drinking Water* (EPA-600/1-83-001; NTIS PB83-148502), Research Triangle Park, NC, US Environmental Protection Agency

Coleman, W.E., Munch, J.W., Kaylor, W.H., Streicher, R.P., Ringhand, H.P. & Meier, J.R. (1984) Gas chromatography/mass spectroscopy analysis of mutagenic extracts of aqueous chlorinated humic acid. A comparison of the byproducts to drinking water contaminants. *Environ. Sci. Technol.*, *18*, 674-681

Daniel, F.B., Schenck, K.M., Mattox, J.K., Lin, E.L.C., Haas, D.L. & Pereira, M.A. (1986) Genotoxic properties of haloacetonitriles: drinking water by-products of chlorine disinfection. *Fundam. appl. Toxicol.*, *6*, 447-453

Dow Chemical Co. (1975) Vapor phase chlorination of acetonitrile in the presence of water. US Patent 3923860 [CA84(9): 58685c]

Eastman Kodak Co. (1987) *Kodak Laboratory and Research Products* (Catalog No. 53), Rochester, NY, pp. 88, 420

Fairfield Chemical Co. (1988) *General Catalog No. 9: Organic Research Chemicals, Custom Synthesis, Bulk Chemicals 1989-1990*, Blythewood, SC, pp. 17, 30, 48, 50

Hayes, J.R., Condie, L.W., Jr & Borzelleca, J.F. (1986) Toxicology of haloacetonitriles. *Environ. Health Perspect.*, *69*, 183-202

Herren-Freund, S.L. & Pereira, M.A. (1986) Carcinogenicity of by-products of disinfection in mouse and rat liver. *Environ. Health Perspect.*, *69*, 59-65

Keith, L.H., Hall, R.C., Hanisch, R.C., Landolt, R.G. & Henderson, J.E. (1982) New methods for analyzing water pollutants. *Water Sci. Technol.*, *14*, 59-71

Krasner, S.W., McGuire, M.J., Jacangelo, J.G., Patania, N.L., Reagan, K.M. & Aieta, E.M. (1989) The occurrence of disinfection by-products in drinking water in a nationwide study. In: *Annual Conference of the American Water Works Association, Los Angeles, CA*, Denver, CO, American Water Works Association, pp. 1-32

Leo, A., Hansch, C. & Elkins, D. (1971) Partition coefficients and their uses. *Chem. Rev.*, *71*, 525-558

Lin, E.L.C., Daniel, F.B., Herren-Freund, S.L. & Pereira, M.A. (1986) Haloacetonitriles: metabolism, genotoxicity, and tumor-initiating activity. *Environ. Health Perspect.*, *69*, 67-71

McKinney, J.D., Maurer, R.R., Hass, J.R. & Thomas, R.O. (1976) Possible factors in the drinking water of laboratory animals causing reproductive failure. In: Keith, L.H., ed., *Identification and Analysis of Organic Pollutants in Water*, Ann Arbor, MI, Ann Arbor Science, pp. 417-432

Meier, J.R., Bull, R.J., Stober, J.A. & Cimino, M.C. (1985) Evaluation of chemicals used for drinking water disinfection for production of chromosomal damage and sperm-head abnormalities in mice. *Environ. Mutagenesis*, *7*, 201-211

Movsum-Zade, E.M., Mamedov, M.G. & Shikhiev, I.A. (1977) Chlorination of acetonitrile (Russ.). *Khim. Prom-st.*, *9*, 662-663

Oliver, B.G. (1983) Dihaloacetonitriles in drinking water: algae and fulvic acid as precursors. *Environ. Sci. Technol.*, *17*, 80-83

Otson, R. (1987) Purgeable organics in Great Lakes raw and treated water. *Int. J. environ. anal. Chem.*, *31*, 41-53

Pereira, M.A., Daniel, F.B. & Lin, E.L.C. (1984a) *Relationship Between the Metabolism of Haloacetonitriles and Chloroform and Their Carcinogenic Activity* (EPA-600/D-84-203; NTIS PB84-246230), Cincinnati, OH, US Environmental Protection Agency

Pereira, M.A., Lin, L.-H.C. & Mattox, J.K. (1984b) Haloacetonitrile excretion as thiocyanate and inhibition of dimethylnitrosamine demethylase: a proposed metabolic scheme. *J. Toxicol. environ. Health, 13*, 633-641

Pfaltz & Bauer (1988) *Organic and Inorganic Chemicals for Research*, Waterbury, CT, pp. 83, 120, 124

Pouchert, C.J., ed. (1974) *The Aldrich Library of NMR Spectra*, Vol. 3, Milwaukee, WI, Aldrich Chemical Co., pp. 162A, 162C

Pouchert, C.J., ed. (1981) *The Aldrich Library of Infrared Spectra*, 3rd ed., Milwaukee, WI, Aldrich Chemical Co., pp. 506D, 506E, 506G

Pouchert, C.J., ed. (1983) *The Aldrich Library of NMR Spectra*, 2nd ed., Vol. 1, Milwaukee, WI, Aldrich Chemical Co., pp. 705D, 706C

Pouchert, C.J., ed. (1985a) *The Aldrich Library of FT-IR Spectra*, Vol. 1, Milwaukee, WI, Aldrich Chemical Co., pp. 848A, 848C, 849A

Pouchert, C.J., ed. (1985b) *The Aldrich Library of FT-IR Spectra*, Vol. 3, Milwaukee, WI, Aldrich Chemical Co., pp. 806D, 807A, 807B

Reckhow, D.A. & Singer, P.C. (1984) The removal of organic halide precursors by preozonation and alum coagulation. *J. Am. Water Works Assoc., 76*, 151-157

Reding, R., Fair, P.S., Shipp, C.J. & Brass, H.J. (1989) Measurement of dihaloacetonitriles and chloropicrin in US drinking waters. In: *Disinfection By-products: Current Perspectives*, Denver, CO, American Water Works Association, pp. 11-22

Riedel-de Haën (1986) *Laboratory Chemicals 1986*, Seelze 1/Hannover, pp. 243, 1070

Roby, M.R., Carle, S., Pereira, M.A. & Carter, D.E. (1986) Excretion and tissue disposition of dichloroacetonitrile in rats and mice. *Environ. Health Perspect., 69*, 215-220

Sadtler Research Laboratories (1980) *The Sadtler Standard Spectra, 1980 Cumulative Index*, Philadelphia, PA

Sax, N.I. & Lewis, R.J. (1987) *Hawley's Condensed Chemical Dictionary*, 11th ed., New York, NY, Van Nostrand Reinhold, pp. 261, 1175

Simmon, V.F., Kauhanen, K. & Tardiff, R.G. (1977) Mutagenic activity of chemicals identified in drinking water. In: Scott, D., Bridges, B.A. & Sobels, F.H., eds, *Progress in Genetic Toxicology*, Amsterdam, Elsevier/North-Holland Biomedical Press, pp. 249-258

Smith, M.K., George, E.L., Zenick, H., Manson, J.M. & Stober, J.A. (1987) Developmental toxicity of halogenated acetonitriles: drinking water by-products of chlorine disinfection. *Toxicology, 46*, 83-93

Smith, M.K., Randall, J.L., Tocco, D.R., York, R.G., Stober, J.A. & Read, E.J. (1988) Teratogenic effects of trichloroacetonitrile in the Long-Evans rat. *Teratology, 38*, 113-120

Smith, M.K., Randall, J.L., Stober, J.A. & Read, E.J. (1989) Developmental toxicity of dichloroacetonitrile: a by-product of drinking water disinfection. *Fundam. appl. Toxicol., 12*, 765-772

Stevens, A.A., Moore, L.A., Slocum, C.J., Smith, B.L., Seeger, D.R. & Ireland, J.C. (1989) By-products of chlorination at ten operating utilities. In: *Disinfection By-products: Current Perspectives*, Denver, CO, American Water Works Association, pp. 23-61

STN International (1989a) *HODOC (Handbook of Data on Organic Chemicals) Database*, Columbus, OH

STN International (1989b) *Beilstein Database*, Columbus, OH

Suffet, I.H., Brenner, L. & Cairo, P.R. (1980) GC/MS identification of trace organics in Philadelphia drinking waters during a 2-year period. *Water Res.*, *14*, 853-867

Tanii, H. & Hashimoto, K. (1984) Studies on the mechanism of acute toxicity of nitriles in mice. *Arch. Toxicol.*, *55*, 47-54

Trehy, M.L. & Bieber, T.I. (1980) Effects of commonly used water treatment processes on the formation of THMs and DHANs. In: *Proceedings of the American Water Works Association 1980 Annual Conference*, Part 1, Denver, CO, American Water Works Association, pp. 125-138

Trehy, M.L. & Bieber, T.I. (1981) Detection, identification and quantitative analysis of dihaloacetonitriles in chlorinated natural waters. In: Keith, L.H., ed., *Advances in the Identification and Analysis of Organic Pollutants in Water*, Vol. 2, Ann Arbor, MI, Ann Arbor Science, pp. 941-975

Trehy, M.L., Yost, R.A. & Miles, C.J. (1986) Chlorination byproducts of amino acids in natural waters. *Environ. Sci. Technol.*, *20*, 1117-1122

Trehy, M.L., Yost, R.A. & Miles, C.J. (1987) Amino acids as potential precursors for halogenated byproducts formed on chlorination of natural waters. In: *194th American Chemical Society Meeting, New Orleans, LA, August 30-Sept 4, 1987* (Extended Abstracts), Washington DC, American Chemical Society, pp. 582-584

Valencia, R., Mason, J.M., Woodruff, R.C. & Zimmering, S. (1985) Chemical mutagenesis testing in *Drosophila*. III. Results of 48 coded compounds tested for the National Toxicology Program. *Environ. Mutagenesis*, *7*, 325-348

Weast, R.C., ed. (1989) *CRC Handbook of Chemistry and Physics*, 70th ed., Boca Raton, FL, CRC Press, pp. C-52, C-204, C-530

Zoeteman, B.C.J., Hrubec, J., de Greef, E. & Kool, H.J. (1982) Mutagenic activity associated with by-products of drinking water disinfection by chlorine, chlorine dioxide, ozone and UV-irradiation. *Environ. Health Perspect.*, *46*, 197-205