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Halogenated Acetonitriles in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A "final task force" meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

Acknowledgements

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The work of the following working group coordinators was crucial in the development of this document and others in the third edition:

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Prof. Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
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The contribution of peer reviewers is greatly appreciated. The draft text was posted on the world wide web for comments from the public. The revised text and the comments were discussed at the Final Task Force Meeting for the third edition of the GDWQ, held on 31 March to 4 April 2003, at which time the present version was finalized. The input of those who provided comments and of participants in the meeting is gratefully reflected in the final text.

The WHO coordinators were as follows:

Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters, and formerly WHO European Centre for Environmental Health
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Ms C. Vickers provided a liaison with the International Chemical Safety Programme, WHO Headquarters.

Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

Acronyms and abbreviations used in the text

CAS	Chemical Abstracts Service
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency (USA)
GAC	granular activated carbon
GST	glutathione-*S*-transferase
IUPAC	International Union of Pure and Applied Chemistry
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program (USA)
PQL	practical quantification level
TDI	tolerable daily intake
TPA	12-*O*-tetradecanoylphorbol-13-acetate
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

Compound	*CAS No.*	*Molecular formula*
Dichloroacetonitrile	3018-12-0	$CHCl_2CN$
Dibromoacetonitrile	3252-43-5	$CHBr_2CN$
Bromochloroacetonitrile	83463-62-1	CHBrClCN
Trichloroacetonitrile	545-06-2	CCl_3CN

The IUPAC name for acetonitrile is ethanenitrile.

1.2 Physicochemical properties (Verschueren, 1977; Budavari et al., 1989; Weast, 1989)

Property	*Dichloro-acetonitrile*[1]	*Dibromo-acetonitrile*[2]	*Bromochloro-acetonitrile*[3]	*Trichloro-acetonitrile*[4]
Boiling point (°C)	112.3	67–69	125–130	84.6
Melting point (°C)	–	–	–	-42
Density at 20 °C (g/cm^3)	1.37	2.30	1.68	1.44

[1] Conversion factor in air: 1 ppm = 4.49 mg/m^3.
[2] Conversion factor in air: 1 ppm = 8.14 mg/m^3.
[3] Conversion factor in air: 1 ppm = 6.31 mg/m^3.
[4] Conversion factor in air: 1 ppm = 5.91 mg/m^3.

1.3 Major uses

Trichloroacetonitrile has reportedly been used as an insecticide (Budavari et al., 1989).

1.4 Environmental fate

Dihalogenated acetonitriles (dichloroacetonitrile, dibromoacetonitrile and bromochloroacetonitrile) undergo hydrolysis in water (Bieber & Trehy, 1983).

Dichloroacetonitrile and dibromoacetonitrile are very mobile in soil and are expected to leach. In moist, alkaline soils, dichloroacetonitrile and dibromoacetonitrile may hydrolyse. In water, dibromoacetonitrile is lost through hydrolysis, which occurs at a faster rate in alkaline waters and in the presence of chlorine (Oliver, 1983; Peters et al., 1990; HSDB, 2001). Roughly 10% and 60% of dichloroacetonitrile and 5% and 20% of dibromoacetonitrile are lost via hydrolysis in 10 days at pH 6 and 8, respectively (Oliver, 1983; HSDB, 2001). Volatilization losses are expected to be minimal, and adsorption to sediment and bioconcentration in aquatic organisms are not expected.

In the atmosphere, dichloroacetonitrile and dibromoacetonitrile react extremely slowly with photochemically produced hydroxyl radicals, with resulting half-lives of 434 days for dichloroacetonitrile and 696 days for dibromoacetonitrile (HSDB, 2001).

2. ANALYTICAL METHODS

EPA Method 551.1 can be used for the separation and determination of haloacetonitriles by capillary column gas chromatography using an electron capture detector. Method detection limits are <0.03 µg/litre for dichloro-, dibromo-, bromochloro- and trichloroacetonitrile. The practical quantification level (PQL) is approximately 0.5 µg/litre for the four acetonitriles (US EPA, 1996; Fair et al., 2002).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Water

Halogenated acetonitriles are produced during water chlorination or chloramination from naturally occurring substances, including algae, fulvic acid and proteinaceous material (Bieber & Trehy, 1983; Oliver, 1983). In general, increasing temperature and/or decreasing pH have been associated with increasing concentrations of halogenated acetonitriles (AWWARF, 1991; Siddiqui & Amy, 1993).

Many factors between the source and the tap can influence the disinfection by-products to which consumers are exposed. Halogenated acetonitriles form rapidly but then decay in the distribution system as a result of hydrolysis (IPCS, 2000). Different trends were observed in the halogenated acetonitrile concentrations of different source waters. For two source waters, halogenated acetonitrile levels formed rapidly for the first 8 h and continued to increase slowly or levelled off after 96 h (AWWARF, 1991). Dibromoacetonitrile levels remained relatively stable over the 96 h, as did bromochloroacetonitrile and dichloroacetonitrile levels. For the other sources, levels of halogenated acetonitriles, consisting mostly of dichloroacetonitrile, increased rapidly up to 4–8 h and began to decline by the end of the 96-h period. For these sources, bromochloroacetonitrile appeared to be slightly more stable than dichloroacetonitrile (AWWARF, 1991). Peters et al. (1990) reported that the concentration of dibromoacetonitrile in tap water was generally 20–50% of that at the treatment plants, indicating that hydrolysis occurred during transport.

Ambient bromide levels appear to influence, to some degree, the speciation of halogenated acetonitrile compounds (IPCS, 2000). Dichloroacetonitrile is by far the most predominant halogenated acetonitrile species detected in drinking-water from sources with bromide levels of 20 µg/litre or less. In chlorinated or chloraminated water from sources with higher bromide levels (50–80 µg/litre), bromochloroacetonitrile was the second most prevalent compound. However, none of the treated water from any of these sources had a dibromoacetonitrile concentration exceeding 0.5 µg/litre, including treated water from one source that had a much higher bromide level (170 µg/litre) (IPCS, 2000).

Data for drinking-water supplies in the USA (US EPA, 2002b) indicate that dichloroacetonitrile is present in groundwater and surface water distribution systems at mean concentrations of 0.87 and 2.21 µg/litre, respectively. In a national survey in Canada, concentrations of dichloroacetonitrile ranged from 0.1 to 2.21 µg/litre, respectively (Health Canada, 1995). In the USA, dibromoacetonitrile was detected in groundwater and surface water distribution systems at mean concentrations of 0.82 and 0.75 µg/litre, respectively (US EPA, 2002b). At high bromate levels, dibromoacetonitrile was found at a concentration of 11 µg/litre (Krasner et al., 1989). Bromochloroacetonitrile was detected in groundwater and surface water distribution systems at mean concentrations of 0.73 and 1.14 µg/litre, respectively, and trichloroacetonitrile was detected in groundwater and surface water distribution systems at mean concentrations of 0.14 and 0.03 µg/litre, respectively (US EPA, 2002b).

In the Netherlands, the concentration of halogenated acetonitriles in drinking-water ranged from 0.04 to 1.05 µg/litre (IPCS, 2000).

3.2 Estimated total exposure and relative contribution of drinking-water

For non-carcinogenic chemicals, the portion of the TDI allocated to drinking-water is based, where available, on mean levels of the chemical in air, food and water. The data on the halogenated acetonitriles are not adequate to quantify the contributions of each source for an overall assessment of exposure.

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Only a small fraction of total radioactivity was observed in the faeces of rats and mice following oral dosing with labelled dichloroacetonitrile, indicating that it is well absorbed from the gastrointestinal tract (Roby et al., 1986). Six days after administration of a single oral gavage dose of ^{14}C-labelled dichloroacetonitrile to rats and mice, the radiolabel was found mainly in the liver, muscle, skin and blood, although residual tissue levels represented only a small portion of the administered oral dose (Roby et al., 1986).

Urinary thiocyanate accounted for 2.25–12.8% of a single gavage dose of bromochloroacetonitrile, dibromoacetonitrile, dichloroacetonitrile or trichloroacetonitrile during the 24-h period following dosing of male rats. This suggests that halogenated acetonitriles are metabolized via oxidative dehalogenation and dehydration to carbon dioxide and cyanide, which is then further metabolized to thiocyanate (Pereira et al., 1984). The first step in this reaction is catalysed by a mixed-function oxidase (such as a cytochrome P-450) and results in production of a halocyanomethanol. The identity of the isozyme that carries out the individual reactions has not been determined. It is proposed that the halocyanomethanols then dehydrate to form halocyanoformaldehydes or lose cyanide to form haloformaldehydes, including phosgene. The cyanide carbon group is more readily excreted in the urine, whereas the halomethyl carbon group is excreted nearly equally

in expired air and in urine; excretion in faeces is low (Roby et al., 1986). Glutathione conjugation (mediated by glutathione transferases or non-enzymatic) may also play a role in the metabolism of halogenated acetonitriles (Lin & Guion, 1989).

Halogenated acetonitriles may be formed *in vivo* following the ingestion of chlorinated water. Dichloro- and dibromoacetonitrile were detected in the stomach contents of rats following oral administration of sodium hypochlorite/potassium bromide, presumably formed by reaction with organic material in the stomach (Mink et al., 1983).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

Acute oral LD_{50}s for the halogenated acetonitriles in rodents range from 245 to 361 mg/kg of body weight (Smyth et al., 1962; Meier et al., 1985; Hayes et al., 1986).

5.2 Short-term exposure

5.2.1 Dichloroacetonitrile

Dichloroacetonitrile in corn oil was administered to CD rats (10 per sex per dose) by gavage at doses of 0, 12, 23, 45 or 90 mg/kg of body weight per day for 14 days. In males, decreased body weight gain was observed at the three highest doses, whereas decreased weight gain in females was noted only in the highest dose group. Significantly increased levels of serum glutamate–pyruvate transaminase in females in the highest dose group and of alkaline phosphatase levels in the highest dose group in males and in the two highest dose groups in females were observed. Relative liver weight was statistically significantly increased in males in all dose groups. The relative liver weights in males were 13%, 26%, 42% and 45% greater than controls at doses of 12, 23, 45 and 90 mg/kg of body weight per day, respectively. In female rats, both relative and absolute liver weights were statistically significantly elevated beginning at 23 mg/kg of body weight per day, with relative liver weights 36%, 40% and 31% greater than controls at 23, 45 and 90 mg/kg of body weight per day. No other consistent compound-related effects were observed in any of the haematological, serum chemistry or urinary parameters measured. The LOAEL for this study was identified as 12 mg/kg of body weight per day, the lowest dose tested, based on increased relative liver weight in males (Hayes et al., 1986).

Dichloroacetonitrile in corn oil was administered to CD rats (20 per sex per dose) by gavage at doses of 0, 8, 33 or 65 mg/kg of body weight per day for 90 days. Compound-related deaths occurred in the highest dose group (50% of males and 25% of females). No consistent compound-related effects were observed in any of the haematological, serum chemistry or urinary parameters measured, although alkaline phosphatase levels were significantly increased in males and females at the high dose and in males also at 33 mg/kg of body weight per day. Body weight gain was significantly depressed in males and females at 65 mg/kg of body weight per day (to

73% of controls) and in males beginning at 33 mg/kg of body weight per day (to 81% of controls). Relative liver weight was significantly increased in males, beginning at 33 mg/kg of body weight per day (60% increase), and in females, beginning at 8 mg/kg of body weight per day (17% increase). The relative liver weight was also increased in males (by 12%) at 8 mg/kg of body weight per day, but this increase was not statistically significant. The LOAEL for this study was the lowest dose tested, 8 mg/kg of body weight per day, based on increased relative liver weights (Hayes et al., 1986).

5.2.2 Dibromoacetonitrile

Dibromoacetonitrile in corn oil was administered to CD rats (10 per sex per dose) by gavage at doses of 0, 23, 45, 90 or 180 mg/kg of body weight per day for 14 days. Increased mortality was observed at 90 (40% of males and 20% of females) and 180 (100% of both sexes) mg/kg of body weight per day. In males, a dose-dependent decrease in body weight (>20% in both groups, relative to controls) was observed in the two highest surviving dose groups (doses of 45 and 90 mg/kg of body weight per day), whereas no effect on body weight was noted in females. No consistent treatment-related effects were observed in any of the haematological, serum chemistry or urinary parameters measured. A dose-dependent increase in relative liver weight was reported in females, beginning at 23 mg/kg of body weight per day; however, no changes in serum levels of hepatic enzymes were observed, and it was not clear whether this increase could be considered an adverse effect. The authors stated that the NOAEL was 45 mg/kg of body weight per day (Hayes et al., 1986), but the decreased body weight in males at this dose suggests that the NOAEL for this study was 23 mg/kg of body weight per day.

The short-term toxicity of dibromoacetonitrile has also been evaluated by the NTP (2000a,b,c, 2002a) in B6C3F1 mice and F344 rats as part of initial dose range-finding studies in support of chronic exposure studies that are currently in progress. For the mouse study (NTP, 2000b), dibromoacetonitrile was administered in drinking-water for 14 days to male and female B6C3F1 mice (five per sex per dose) at concentrations of 0, 12.5, 25, 50, 100 or 200 mg/litre. The corresponding doses reported by the study authors were 0, 2.1, 4.3, 8.2, 14.7 and 21.4 mg/kg of body weight per day for males and 0, 2.0, 3.3, 10.0, 13.9 and 21.6 mg/kg of body weight per day for females. Animals were observed for clinical signs of toxicity, as well as body weight, organ weight and organ pathology. In addition, liver glutathione-*S*-transferase (GST) activity was measured. The only treatment-related effect was a decrease in water consumption in both males and females. The decrease in water consumption was concentration related, decreasing to 58% of controls for males and 54% of controls for females in the 200 mg/litre group. Since the only effect observed was a concentration-related decrease in water intake, which could reflect poor water palatability, the high doses of 21.4 mg/kg of body weight per day for males and 21.6 mg/kg of body weight per day for females are considered NOAELs. No LOAEL is identified.

For the rat study (NTP, 2000c), dibromoacetonitrile was administered in drinking-water for 14 days to male and female F344 rats (five per sex per dose) at

concentrations of 0, 12.5, 25, 50, 100 or 200 mg/litre. The corresponding doses reported by the study authors were 0, 2, 3, 7, 12 and 18 mg/kg of body weight per day for males and 0, 2, 4, 7, 12 and 19 mg/kg of body weight per day for females. Animals were observed for clinical signs of toxicity, as well as body weight, organ weight and organ pathology. In addition, liver GST activity was measured. A concentration-related decrease in water consumption was observed for both males and females. Water consumption decreased to 60% of controls for males and 61% of controls for females in the 200 mg/litre group. No effects other than decreased water consumption were noted in females. However, in males, dibromoacetonitrile exposure caused a decrease in body weight gain and terminal body weight that was judged to be toxicologically significant only at the high dose. The reported body weight gains for males were 61.1, 66.3, 66.0, 65.2, 56.4 and 34.0 g for the control and increasing dose groups, respectively. Terminal body weights as a percentage of controls were 100%, 104.5%, 104.3%, 101.3%, 98.7% and 82.7% for the control and increasing dose groups, respectively. Significantly decreased testes weights were observed in the high-dose males. This finding was accompanied by testicular atrophy in two of five males in this dose group. Elevated liver GST activity (126% of controls) was also reported for high-dose males. Based on decreased body weight and decreased testes weight and pathology in males, the NOAEL for this study is 12 mg/kg of body weight per day and the LOAEL is 18 mg/kg of body weight per day.

Dibromoacetonitrile was administered to CD rats (20 animals per sex per dose) by gavage at doses of 0, 6, 23 or 45 mg/kg of body weight per day for 90 days. At the highest dose tested, male body weights were depressed to 79% of controls and relative liver weights were increased, but there was no corresponding effect on serum biochemistry in males. The only finding noted in females was an increase in alkaline phosphatase levels at the highest dose tested. No other consistent compound-related effects were observed in any of the parameters measured. The NOAEL is 23 mg/kg of body weight per day, based on decreased body weight (Hayes et al., 1986).

The subchronic toxicity of dibromoacetonitrile has also been evaluated by the NTP (2001a,b, 2002a,b) in B6C3F1 mice and F344 rats as part of initial dose range-finding studies for chronic exposure studies that are currently in progress. For the mouse study (NTP, 2001a, 2002a,b), dibromoacetonitrile was administered in drinking-water for 13 weeks to male and female B6C3F1 mice (10 per sex per dose) at concentrations of 0, 12.5, 25, 50, 100 or 200 mg/litre. The corresponding doses reported by the study authors were 0, 1.6, 3.2, 5.6, 10.7 and 17.9 mg/kg of body weight per day for males and 0, 1.6, 3.0, 6.1, 11.1 and 17.9 mg/kg of body weight per day for females. Animals were observed for clinical signs of toxicity, as well as body weight, organ weight and pathology, haematology and clinical chemistry. A separate set of animals (10 per sex per dose) was exposed to the same concentrations as the main study groups for 26 days, but was co-exposed to 5-bromo-2-deoxyuridine during the last 5 days of this period. These animals were used to collect tissue samples for analysis of cell proliferation. Decreased water consumption and decreased body weight were the only effects related to dibromoacetonitrile treatment. Decreased water consumption was observed in both males and females at dibromoacetonitrile concentrations of 50 mg/litre and higher. A slight and transient decrease in body weight gain was observed;

terminal body weights were 94% of controls in high-dose males and 96% of controls in high-dose females. These small changes are not judged as toxicologically significant. Based on the minimal effects observed for dibromoacetonitrile in this study, the NOAEL is 17.9 mg/kg of body weight per day for males and females. No LOAEL was identified.

For the rat study (NTP, 2001b, 2002a,b), dibromoacetonitrile was administered in drinking-water for 13 weeks to male and female F344 rats (10 per sex per dose) at concentrations of 0, 12.5, 25, 50, 100 or 200 mg/litre. The corresponding doses reported by the study authors were 0, 0.9, 1.8, 3.3, 6.2 and 11.3 mg/kg of body weight per day for males and 0, 1.0, 1.9, 3.8, 6.8 and 12.6 mg/kg of body weight per day for females. Animals were observed for clinical signs of toxicity, as well as body weight, organ weight and pathology, haematology and clinical chemistry. A separate set of animals (10 per sex per dose) was exposed to the same concentrations as the main study groups for 26 days, but was co-exposed to 5-bromo-2-deoxyuridine during the last 5 days of this period. These animals were used to collect tissue samples for analysis of cell proliferation. Decreased water consumption and decreased body weight were the only effects related to dibromoacetonitrile treatment. Slight changes in clinical chemistry and haematology findings were considered by the study authors to be related to decreased water consumption. Decreased water consumption was observed in males at dibromoacetonitrile concentrations of 50 mg/litre and higher and in females at the two highest concentrations. A slight decrease in body weight gain was observed for high-dose males and females. Terminal body weights were 94% of controls in high-dose males and 95% of controls in high-dose females. These small changes are not judged as toxicologically significant. Based on the minimal effects observed for dibromoacetonitrile in this study, the NOAEL is 11.3 mg/kg of body weight per day for males and 12.6 mg/kg of body weight per day for females. No LOAEL was identified.

5.3 Reproductive and developmental toxicity

The majority of reproductive and developmental toxicity studies of the halogenated acetonitriles were conducted using tricaprylin as a vehicle for gavage administration of the compound under study. Tricaprylin was subsequently demonstrated to be a developmental toxicant that potentiated the effects of trichloroacetonitrile (Christ et al., 1995) and, presumably, other halogenated acetonitriles. Thus, the results reported in this section, using tricaprylin as the gavage vehicle, are likely to overestimate the developmental toxicity of these halogenated acetonitriles.

5.3.1 Dichloroacetonitrile

Dichloroacetonitrile was administered to pregnant Long-Evans rats by gavage in a tricaprylin vehicle on gestation days 6–18 at doses of 0, 5, 15, 25 or 45 mg/kg of body weight per day. Two high-dose dams died. Maternal body weight gain was significantly depressed in the highest dose group, and liver weight was significantly increased at 25 mg/kg of body weight per day, but not at the high dose. At 45 mg/kg of body weight per day, the number of viable litters was decreased, and fetal weight

and length were decreased. At 25 mg/kg of body weight per day and greater, post-implantation losses and fetal resorptions were elevated, and an increase in the incidence of soft tissue malformations of the cardiovascular, digestive and urogenital systems was observed. No effects were noted at lower doses. In this study, the maternal NOAEL was 15 mg/kg of body weight per day, based on increased maternal liver weight. The NOAEL for developmental toxicity was also 15 mg/kg of body weight per day, based on decreased fetal weight and length and an increase in soft tissue malformations (Smith et al., 1989).

In a developmental toxicity screening study, pregnant Long-Evans rats were given dichloroacetonitrile in a tricaprylin vehicle on gestation days 7–21 at 0 or 55 mg/kg of body weight per day. Maternal weight gain was decreased in treated females. Dichloroacetonitrile significantly reduced the percentage of females delivering litters and increased the percentage of fetal resorptions ($P \leq 0.05$). Fetal birth weights were reduced, and postnatal pup survival was significantly decreased. In this study, the LOAEL for both maternal and developmental toxicity was the only dose tested, 55 mg/kg of body weight per day (Smith et al., 1987; also briefly summarized in Smith et al., 1986).

The sperm of male B6C3F1 mice (10 per dose) given dichloroacetonitrile by gavage at 0, 12.5, 25 or 50 mg/kg of body weight per day for 5 days did not exhibit any treatment-related effects on sperm head morphology (Meier et al., 1985).

5.3.2 Dibromoacetonitrile

In an initial developmental toxicity screening study, pregnant Long-Evans rats were given dibromoacetonitrile in a tricaprylin vehicle on gestation days 7–21 at 0 or 50 mg/kg of body weight per day. Treatment-related increases in maternal deaths were observed. Dibromoacetonitrile also caused a decrease in maternal weight gain during pregnancy and a decrease in mean birth weights. Maternal weight gains were measured prior to delivery, and the authors noted that the observed decrease in maternal weight gain may have been due to increased litter resorptions or decreased fetal weights, or both. In this study, the LOAEL for developmental toxicity was the only dose tested, 50 mg/kg of body weight per day. This dose also represented a LOAEL for maternal toxicity, based on increased mortality (Smith et al., 1987; also briefly summarized in Smith et al., 1986).

In a reproductive and developmental toxicity screening assay, young male Sprague-Dawley rats (10 per dose group, beginning at 11 weeks of age) were given dibromoacetonitrile in drinking-water at concentrations of 0, 0.015, 0.050 or 0.15 g/litre (0, 1.4, 3.3 or 8.2 mg/kg of body weight per day) on study days 6–34. No treatment-related reproductive tract toxicity or altered sperm morphology was observed. In this screening assay, one group of Sprague-Dawley female rats (10 per dose group) was administered dibromoacetonitrile in drinking-water at the same concentrations as the males (daily doses equivalent to 0, 1.8, 5.1 or 10.9 mg/kg of body weight per day) on study days 1–34, which included a 5-day period of cohabitation with treated males (study days 13–17) and gestation. No treatment-

related changes were observed in any of the mating, fertility, pregnancy or developmental end-points examined. A second group of females (13 per dose group) was cohabited with treated males beginning on study day 1 for up to 5 days. These females were then exposed on gestation day 6 through postnatal day 1 to the same dibromoacetonitrile concentrations in drinking-water as the other groups (average daily doses were 0, 1.9, 5.3 or 10.8 mg/kg of body weight per day). No treatment-related effects were observed for maternal body weights, gross necropsy or the numbers of resorptions and implantation sites. Treated pups did not differ from controls in body weight, litter sex ratios or the number of live and dead pups per litter when these parameters were measured on postnatal days 1, 3 and 5; there was no difference from controls in anogenital distance measured on postnatal day 1. The only treatment-related effect was a decrease in water consumption in the two highest dose groups. In this study, the NOAEL for systemic parental toxicity is the highest dose tested in males (8.2 mg/kg of body weight per day), and the NOAEL for female reproductive and developmental effects is 10.8 mg/kg of body weight per day (R.O.W. Sciences, 1997).

The sperm of male B6C3F1 mice (10 per dose) given dibromoacetonitrile by gavage at 0, 12.5, 25 or 50 mg/kg of body weight per day for 5 days did not exhibit any treatment-related effects on sperm head morphology (Meier et al., 1985).

5.3.3 Bromochloroacetonitrile

In a developmental toxicity screening study, the pups of Long-Evans rats given bromochloroacetonitrile in a tricaprylin vehicle on gestation days 7–21 at 55 mg/kg of body weight per day had significantly reduced mean birth weights. A reduction in pup body weight gain was also noted on postnatal day 4 and continued to be observed from weaning until puberty (Smith et al., 1987; also briefly summarized in Smith et al., 1986).

Pregnant Long-Evans rats were given bromochloroacetonitrile by gavage in tricaprylin vehicle on gestation days 6–18 at doses of 0, 5, 25, 45 or 65 mg/kg of body weight per day. Dam mortality was increased in the highest dose group. Significantly decreased maternal body weight gain (adjusted for gravid uterine weight) and increased liver and spleen weights were also noted in the highest dose group; maternal kidney weights were significantly increased at 25 mg/kg of body weight per day and greater. At 45 mg/kg of body weight per day and higher, an increase in full-litter resorptions and the percentage of resorbed fetuses per litter and a decrease in the number of viable litters were observed, compared with controls. A decrease in fetal crown–rump length and an increase in the incidence of fetal cardiovascular malformations were noted in all dose groups. Total soft tissue malformations were significantly increased at 25 mg/kg of body weight per day and above, and skeletal malformations were significantly increased at 45 mg/kg of body weight per day and above, compared with controls. Because the tricaprylin vehicle alone had significant effects on embryotoxicity and teratogenicity compared with a water vehicle, the effects observed with bromochloroacetonitrile cannot be fully attributed to the test material. In this study, the NOAEL for maternal toxicity was 45 mg/kg of body

weight per day, based on adverse maternal effects; the high dose of 65 mg/kg of body weight per day was a LOAEL, based on decreased maternal weight (after adjusting for gravid uterine weight) and increased dam mortality. The LOAEL for developmental and teratogenic effects was the lowest dose tested, 5 mg/kg of body weight per day, based on decreased fetal growth and teratogenicity (Christ et al., 1995).

There were no treatment-related effects on sperm head morphology in groups of male B6C3F1 mice (10 per dose group) given bromochloroacetonitrile by gavage at doses of 0, 12.5, 25 or 50 mg/kg of body weight per day for 5 days (Meier et al., 1985).

5.3.4 Trichloroacetonitrile

Trichloroacetonitrile was administered to pregnant Long-Evans rats (19–21 per dose group) by gavage in a tricaprylin vehicle on gestation days 6–18 at doses of 0, 1, 7.5, 15, 35 or 55 mg/kg of body weight per day. The highest dose was lethal to 4 of 19 dams, and there was 100% fetal resorption in 67% of the surviving dams that became pregnant. Maternal body weight gain (adjusted for fetal weight and excluding females with full-litter resorptions) was significantly depressed in the highest dose group. Dose-related increases in full-litter resorptions were observed at 7.5 mg/kg of body weight per day and greater. At 15 mg/kg of body weight per day and higher, post-implantation losses were significantly increased; fetal weight was significantly depressed only at 35 mg/kg of body weight per day. The frequency of soft tissue malformations (primarily cardiovascular and urogenital malformations) was dose dependent, ranging from 18% at 7.5 mg/kg of body weight per day to 35% at 35 mg/kg of body weight per day. Although the incidence of soft tissue malformations at 1 mg/kg of body weight per day (8.4%) was not significantly different from that in controls (3.8%), the authors expressed concern that this incidence of malformations might be of biological significance. However, evaluation of these data in terms of the percentage of litters affected (4/20 litters at 1 mg/kg of body weight per day compared with 6/30 litters in tricaprylin controls) did not show evidence of teratogenic effects at this dose level. The incidence of pups with cardiovascular malformations was increased at 15 mg/kg of body weight per day, and urogenital malformations were significantly increased at both 15 and 35 mg/kg of body weight per day ($P \leq 0.05$); the percentage of litters with cardiovascular malformations was increased beginning at 7.5 mg/kg of body weight per day (8/18 litters affected versus 6/30 litters in controls). Therefore, the NOAEL for teratogenic effects was set at 1 mg/kg of body weight per day. The highest dose tested, 55 mg/kg of body weight per day, was a maternal LOAEL, and the maternal NOAEL was 35 mg/kg of body weight per day, based on decreased body weight gain (Smith et al., 1988).

In a developmental toxicity screening study, pregnant Long-Evans rats were given trichloroacetonitrile in a tricaprylin vehicle on gestation days 7–21 at 0 or 55 mg/kg of body weight per day. Treatment-related increases in maternal deaths were observed. Trichloroacetonitrile also caused a decrease in maternal weight gain during pregnancy, a reduction in the percentage of females becoming pregnant or delivering viable litters and an increase in the percentage of full-litter resorptions. Fetal mean

birth weight and pup survival on postnatal day 4 were also significantly reduced, and decreased body weight gain was noted in surviving male and female pups at weaning and from weaning until puberty. The authors noted that maternal weight gains were measured prior to delivery and that the observed decrease may have been due to increased litter resorptions or decreased fetal weights, or both. In this study, the LOAEL for developmental toxicity was the only dose tested, 55 mg/kg of body weight per day. This dose also represents a LOAEL for maternal toxicity, based on increased dam mortality (Smith et al., 1987; also briefly summarized in Smith et al., 1986).

Trichloroacetonitrile was administered to pregnant Long-Evans rats (20 per dose group) by gavage in corn oil vehicle on gestation days 6–18 at doses of 0, 15, 35, 55 or 75 mg/kg of body weight per day. To investigate the effects of tricaprylin vehicle on the developmental toxicity of trichloroacetonitrile, an additional group of pregnant rats was given 15 mg/kg of body weight per day of trichloroacetonitrile in tricaprylin vehicle on gestation days 6–18. At the highest dose of trichloroacetonitrile in corn oil, mortality, full-litter resorptions and a decreased pregnancy rate resulted in the production of only one viable litter; other data for this dose group were not reported. At 35 and 55 mg of trichloroacetonitrile in corn oil vehicle per kg of body weight per day, maternal weight gain (adjusted for gravid uterine weight) was significantly depressed (to 40% and 63% of corn oil controls, respectively). In animals given trichloroacetonitrile in corn oil, maternal relative liver weight was increased at ≥35 mg/kg of body weight per day; at 55 mg/kg of body weight per day, maternal spleen and kidney weights were significantly increased compared with corn oil vehicle controls. Other effects at 55 mg of trichloroacetonitrile in corn oil per kg of body weight per day included an increase in post-implantation losses, a decrease in the number of live fetuses per litter, fetal body weight and fetal crown–rump length and an increase in the percentage of fetuses per litter with external malformations, skeletal malformations and soft tissue malformations. In the group given 15 mg of trichloroacetonitrile in tricaprylin vehicle per kg of body weight per day, maternal relative liver weights were increased compared with corn oil vehicle controls. Other effects in this group included decreased fetal weights, decreased fetal crown–rump lengths and an increase in total soft tissue and cardiovascular malformations. None of these effects was observed in animals given trichloroacetonitrile in corn oil at a dose of 15 or 35 mg/kg of body weight per day. The authors also noted a shift in the spectrum of fetal malformations with vehicle, from primarily external cranio-facial malformations and positional cardiovascular malformations when trichloroacetonitrile was administered in corn oil at 55 mg/kg of body weight per day to structural cardiovascular defects and urogenital effects induced by trichloroacetonitrile in tricaprylin at 15 mg/kg of body weight per day. In this study, the NOAEL for maternal toxicity is 15 mg of trichloroacetonitrile in corn oil per kg of body weight per day, based on decreased maternal weight gain of ≥40%; the NOAEL for developmental toxicity and teratogenicity is 35 mg/kg of body weight per day (Christ et al., 1996).

The sperm of male B6C3F1 mice (10 per dose) given trichloroacetonitrile by gavage at 0, 12.5, 25 or 50 mg/kg of body weight per day for 5 days did not exhibit any treatment-related effects on sperm head morphology (Meier et al., 1985).

5.4 Mutagenicity and related end-points

Dichloroacetonitrile and bromochloroacetonitrile were direct-acting mutagens, and dibromoacetonitrile and trichloroacetonitrile were non-mutagenic in *Salmonella typhimurium* (Bull et al., 1985). All of the halogenated acetonitriles except for dibromoacetonitrile were positive in the Ames fluctuation assay with *S. typhimurium*, in the presence and absence of metabolic activation (Le Curieux et al., 1995). All of the halogenated acetonitriles increased micronuclei formation in erythrocytes of *Pleurodeles waltl* (newt) larvae (Le Curieux et al., 1995). Dichloroacetonitrile, but not dibromoacetonitrile, induced aneuploidy in the offspring of female *Drosophila melanogaster* (fruit fly) exposed via inhalation (Osgood & Sterling, 1991). Dichloroacetonitrile also induced genetic damage in *Saccharomyces cerevisiae* (yeast) (Zimmermann et al., 1984).

Studies that have evaluated DNA damage have produced equivocal results. In the SOS chromotest using *Escherichia coli*, dibromoacetonitrile and bromochloroacetonitrile were weakly positive without metabolic activation and negative with it; dichloroacetonitrile was positive in the presence of metabolic activation, but negative in its absence; and trichloroacetonitrile was negative, with and without metabolic activation (Le Curieux et al., 1995). All four halogenated acetonitriles induced sister chromatid exchanges in Chinese hamster ovary cells, with and without exogenous metabolic activation. Comparison of potencies showed the following order: dibromoacetonitrile > bromochloroacetonitrile > trichloroacetonitrile > dichloroacetonitrile (Bull et al., 1985). Halogenated acetonitriles induced DNA strand breaks in cultured human lymphoblastic cells; the order of potency was trichloroacetonitrile > bromochloroacetonitrile ≈ dibromoacetonitrile > dichloroacetonitrile. Highly variable alkylation activity was observed among the halogenated acetonitriles, with the order of potency being dibromoacetonitrile > bromochloroacetonitrile >> dichloroacetonitrile > trichloroacetonitrile (Daniel et al., 1986).

No significant increase in the frequency of micronuclei was observed for any of the four halogenated acetonitriles in an *in vivo* assay in CD-1 mice, using gavage dosing (Bull et al., 1985). Oral administration of halogenated acetonitriles in rats resulted in the formation of DNA adducts by trichloroacetonitrile, but not by dichloroacetonitrile or dibromoacetonitrile (Lin et al., 1986, 1992).

5.5 Carcinogenicity

No 2-year carcinogenicity bioassays have been conducted for any of the halogenated acetonitriles by any route of exposure. No alternative carcinogenicity studies were identified for any of the halogenated acetonitriles by the inhalation route. There are,

however, several short-term assays that can aid in hazard identification. In addition, dibromoacetonitrile is currently under test in a full cancer bioassay by the NTP.

Groups of 40 A/J female mice were given a single oral dose of dichloro-, dibromo-, bromochloro- or trichloroacetonitrile of 10 mg/kg (4.3 mg/kg of body weight per day) 3 times per week for 8 weeks. The incidence of lung tumours (adenomas) was significantly increased in the groups given trichloro- and bromochloroacetonitrile, while dichloro- and dibromoacetonitrile produced marginal and non-significant increases in these tumours. The authors stated that these results should be interpreted with caution, as there is a relatively large variation in the background incidence of lung tumours in this strain of mice, and the dose level tested was considerably below the maximum tolerated dose (Bull & Robinson, 1985).

The ability of the four halogenated acetonitriles to act as skin tumour initiators was studied in mouse skin. For each compound, six topical doses of 0, 200, 400 or 800 mg/kg of body weight were applied to the shaved backs of female Sencar mice (40 per dose) over a 2-week period, to give total applied doses of 0, 1200, 2400 or 4800 mg/kg of body weight. Two weeks after the last dose, a tumour promotion schedule involving the application of 1 µg of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) 3 times per week was begun and continued for 20 weeks. After 1 year, the incidence of application site squamous cell carcinomas was significantly increased relative to the control group in mice treated with dibromo- and bromochloroacetonitrile. An increase in squamous cell tumours in mice given trichloroacetonitrile at 2400 mg/kg of body weight was not reproducible in a second experiment. No significant increases in squamous cell tumours were observed with dichloroacetonitrile (Bull et al., 1985). In another similar study designed to assess the ability of dermally applied halogenated acetonitriles to act as complete carcinogens, dermal doses of 800 mg of bromochloroacetonitrile, dichloroacetonitrile or trichloroacetonitrile per kg of body weight or 400 mg of dibromoacetonitrile per kg of body weight were applied to the skin of female Sencar mice 3 times per week for 24 weeks. No skin tumours were induced by any of these halogenated acetonitriles (Bull et al., 1985).

In a similar study designed to assess the ability of orally administered halogenated acetonitriles to act as skin tumour initiators, female Sencar mice were given total oral doses of 50 mg of each compound per kg of body weight, administered 6 times over a 2-week period. The tumour promotion phase of the study was conducted using dermal application of TPA, following the same protocol as in the dermal tumour initiation study described in the previous paragraph. No significant increases in skin tumour yield or decreases in tumour latency were observed for any of the halogenated acetonitriles (Bull et al., 1985).

Dichloro-, dibromo- and trichloroacetonitrile were inactive as initiators in the rat liver γ-glutamyl transpeptidase foci assay (Herren-Freund & Pereira, 1986).

6. GUIDELINE VALUES

IARC (1991, 1999) has concluded that dichloro-, dibromo-, bromochloro- and trichloroacetonitrile are not classifiable as to their carcinogenicity in humans (Group 3).

6.1 Dichloroacetonitrile

The previous TDI of 15 µg/kg of body weight was based on a developmental toxicity study in which dichloroacetonitrile was administered by gavage in tricaprylin vehicle (Smith et al., 1989). However, US EPA (2002a) judged this study to be unreliable because the results of a more recent study indicate that tricaprylin potentiates the developmental and teratogenic effects of halogenated acetonitriles and alters the spectrum of malformations in the fetuses of treated dams (Christ et al., 1996). Thus, the developmental toxicity study on which the previous TDI was based does not accurately reflect the toxicity of dichloroacetonitrile in drinking-water.

A TDI of 2.7 µg/kg of body weight was calculated based on a LOAEL of 8 mg/kg of body weight per day for increased relative liver weight in male and female rats in a 90-day study (Hayes et al., 1986). A composite uncertainty factor of 3000 was used, based on a factor of 10 each for intra- and interspecies variation, a factor of 3 for the short duration of the study, a factor of 3 for the use of a minimal LOAEL and a factor of 10 for database deficiencies. Due to the overlap of uncertainty factors, the product of three factors of 10 and two partial factors of 3 (actually the square root of 10) is 3000 (US EPA, 2002a).

Using the TDI of 2.7 µg/kg of body weight, a guideline value of 20 µg/litre (rounded figure) can be calculated, allocating 20% of the TDI to drinking-water and assuming a body weight of 60 kg and a daily drinking-water intake of 2 litres. Due to the large size of the uncertainty factors used, this guideline value is provisional.

The PQL for EPA Method 551.1 used to analyse drinking-water concentrations of halogenated acetonitriles is approximately 0.5 µg/litre. The provisional guideline value of 20 µg/litre for dichloroacetonitrile is therefore well above the achievability of the analytical method. The guideline value concentration can also be achieved by currently available treatment technology. Removals of about 95% of 3.1 µg of total halogenated acetonitriles per litre by GAC over 1 year's operation was reported from a pilot plant study (Lykins et al., 1991). Other studies confirm the efficiency of GAC for halogenated acetonitrile removal (Dixon & Lee, 1991; Hartman et al., 1991).

6.2 Dibromoacetonitrile

The previous TDI of 23 µg/kg of body weight was calculated based on a NOAEL of 23 mg/kg of body weight per day for decreased body weight in male CD rats in a 90-day corn oil gavage study (Hayes et al., 1986), incorporating an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the short duration of the study).

No chronic studies of dibromoacetonitrile toxicity were located, although dibromoacetonitrile is currently under test for chronic toxicity in mice and rats (NTP, 2000a). Both the NTP (2001b, 2002a,b) subchronic drinking-water study in male rats and the subchronic gavage study by Hayes et al. (1986) were considered in the selection of the critical study for derivation of the TDI. The NOAEL of 11.3 mg/kg of body weight per day for male rats in the 13-week NTP study was selected as the most appropriate basis for derivation of the TDI. This value was judged to be more appropriate for deriving the TDI than the NOAEL of 23 mg/kg of body weight per day for decreased body weight observed in male rats reported in Hayes et al. (1986) for several reasons. First, in the NTP study, dibromoacetonitrile was administered in drinking-water, a dose route more relevant to environmental exposure than the corn oil gavage dosing employed by Hayes et al. (1986). Second, although the NTP 13-week study did not identify a LOAEL, the NOAELs for decreased body weight were the same for the 14-day and 13-week NTP studies, and the LOAEL was 18 mg/kg of body weight per day in the 14-day study. Since slight body weight decreases were also observed in the 13-week study at 11.3 mg/kg of body weight per day, this suggests that the LOAEL for the 13-week study might approximate the LOAEL of 18 mg/kg of body weight per day for the 14-day study, which is significantly lower than the LOAEL of 45 mg/kg of body weight per day reported in Hayes et al. (1986). This argues that the NOAEL/LOAEL boundary would be lower in the NTP (2001b) study than in Hayes et al. (1986). Third, since the NTP (2001b) and Hayes et al. (1986) studies are not directly comparable, due to differences in the methods of dose administration and rat strains employed, and since both studies were of adequate quality to derive the TDI, selection of the lower study NOAEL would be most appropriate.

In the derivation of a TDI, uncertainty factors of 10 each are used to account for extrapolation from an animal study and for inter-individual variability in human sensitivity, in the absence of sufficient data to allow a departure from these defaults. An additional uncertainty factor of 3 was chosen to account for less-than-lifetime exposure, based on the absence of progression of toxicological effects from 14 days to 90 days (NTP, 2000c, 2001b, 2002a,b). This factor was chosen to replace the default factor of 10 because the subchronic toxicity of dibromoacetonitrile has been evaluated in two species (Hayes et al., 1986; NTP, 2001a,b). Furthermore, decreased body weight was identified as the most sensitive effect in both studies, even though the NTP (2001b, 2002a,b) study included a thorough examination of tissue histopathology, haematology and clinical chemistry. These results suggest that no new systemic target organs for dibromoacetonitrile are likely to be identified. An uncertainty factor of 3 was also used to account for insufficiencies in the database. The data gap may be particularly relevant since cyanide, a metabolite of dibromoacetonitrile, induces male reproductive system toxicity (US EPA, 2002c) and due to uncertainty regarding the significance of the testes effects observed in the 14-day NTP (2001b) rat study for dibromoacetonitrile. However, none of the available reproductive or developmental toxicity studies was adequate to use in the quantitative dose–response assessment. The reproductive and development toxicity study by R.O.W. Sciences (1997) was limited by the fact that it was a screening study that was

not designed to evaluate the full spectrum of end-points of interest. The developmental toxicity study by Smith et al. (1987) is of limited use, because it was a single-dose study, because an insufficient array of end-points was evaluated and because the observed toxicity was confounded by the use of tricaprylin as the solvent vehicle.

Therefore, based on default factors of 10 each for interspecies extrapolation and inter-individual variability and partial factors of 3 each for subchronic to chronic extrapolation and for database insufficiencies (lack of adequate developmental and reproductive toxicity studies), the composite uncertainty factor used is 1000.

A TDI of 11 µg/kg of body weight was therefore calculated based on the NOAEL of 11.3 mg/kg of body weight per day for decreased body weight in male F344 rats in a 90-day drinking-water study by NTP (2001b, 2002a,b), incorporating an uncertainty factor of 1000. A guideline value of 70 µg/litre (rounded figure) can be calculated by allocating 20% of the TDI to drinking-water and assuming a body weight of 60 kg and a daily drinking-water intake of 2 litres.

The PQL for EPA Method 551.1 used to analyse drinking-water concentrations of halogenated acetonitriles is approximately 0.5 µg/litre. The guideline value of 70 µg/litre for dibromoacetonitrile is therefore well above the achievability of the analytical method. The guideline value concentration can also be achieved by currently available treatment technology. Removals of about 95% of 3.1 µg of total halogenated acetonitriles per litre by GAC over 1 year's operation was reported from a pilot plant study (Lykins et al., 1991). Other studies confirm the efficiency of GAC for halogenated acetonitrile removal (Dixon & Lee, 1991; Hartman et al., 1991).

6.3 Bromochloroacetonitrile

Available data are insufficient to serve as a basis for derivation of a guideline value for bromochloroacetonitrile.

6.4 Trichloroacetonitrile

The available data are insufficient to serve as a basis for derivation of a guideline value for trichloroacetonitrile. The previous TDI of 0.2 µg/kg of body weight was based on a developmental toxicity study in which trichloroacetonitrile was administered by gavage in tricaprylin vehicle (Smith et al., 1988). A recent re-evaluation by IPCS (2000) judged this study to be unreliable in light of the finding in a more recent study that tricaprylin potentiates the developmental and teratogenic effects of halogenated acetonitriles and alters the spectrum of malformations in the fetuses of treated dams (Christ et al., 1996). Thus, the results of Smith et al. (1988) may not accurately reflect the toxicity of trichloroacetonitrile in drinking-water. The Christ et al. (1996) study was not used to derive a TDI, due to the absence of adequate subchronic or chronic toxicity data for trichloroacetonitrile.

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