

16. Disinfectants and disinfectant by-products

Disinfectants

16.1 Introduction

Disinfection is unquestionably the most important step in the treatment of water for public supply. The destruction of microbiological pathogens is essential and almost invariably involves the use of reactive chemical agents such as chlorine, which are not only powerful biocides but also capable of reacting with other water constituents to form new compounds with potentially harmful long-term health effects. Thus, an overall assessment of the impact of disinfection on public health must consider not only the microbiological quality of the treated water, but also the toxicity of the disinfectants and their reaction products.

The paramount importance of microbiological quality requires some flexibility in the derivation of guideline values for these substances. Fortunately this is possible because of the substantial margin of safety incorporated into these values. Guideline values for carcinogenic disinfectant by-products are presented here for an excess lifetime cancer risk of 10^{-5} . The conditions specified for disinfection vary not only according to water composition and temperature but also with available technology and socioeconomic factors in different parts of the world. Where local circumstances require that a choice must be made between meeting either microbiological guidelines or guidelines for disinfectants or disinfectant by-products, the microbiological quality must always take precedence, and where necessary, a chemical guideline value can be adopted corresponding to a higher level of risk. Efficient disinfection must never be compromised.

Although not addressed with respect to the individual parameters presented below, it is noted that, in a number of epidemiological studies, positive associations between the ingestion of chlorinated drinking-water and mortality rates from cancer, particularly of the bladder, have been reported. The degree of evidence for this association is considered inadequate by IARC (1).

The level of disinfection by-products can be reduced by optimizing the treatment process (see Volume 1, section 6.3). Removal of organic substances prior to disinfection reduces the formation of potentially harmful by-products.

The following guidance is provided to help authorities decide which guideline values may be of greater or lesser importance for setting national standards: guideline values for chemicals of greater importance generally include those for chloramines and chlorine (when used as disinfectants); followed by those for bromoform, dibromochloromethane, bromodichloromethane, chloroform, and chloral hydrate; and chlorite, bromate, dichloroacetic acid, and trichloroacetic acid (provisional guideline values have been established for this last group). Guideline values for chemicals of lesser importance generally include those for 2,4,6-trichlorophenol, formaldehyde, dichloroacetonitrile, dibromoacetonitrile, trichloroacetonitrile, and cyanogen chloride. Although given less importance, it may be appropriate to measure their levels at least once. It should also be noted that a number of non-volatile, poorly characterized by-products may be formed as well, including those derived from humic substances. These recommendations are general, and local monitoring and surveillance capabilities must be considered in the setting of national standards.

Reference

1. International Agency for Research on Cancer. *Chlorinated drinking-water; chlorination by-products; some other halogenated compounds; cobalt and cobalt compounds*. Lyon, 1991:45-359 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 52).

16.2 Chhloramines

16.2.1 General description

Identity

CAS no.: 10599-90-3
Molecular formula: NH_2Cl

Mono-, di-, and trichloramines are formed when water containing ammonia is chlorinated. Only monochloramine, the most abundant chloramine, will be considered here, as it has been the most extensively studied.

Physicochemical properties (1-3)¹

¹ Conversion factor in air: 1 ppm = 2.1 mg/m³

Property	Value
Melting point	-66 °C
Water solubility	Soluble

Organoleptic properties

Most individuals are able to taste chlorine and its by-products, including chloramines, at concentrations below 5 mg/litre, and some at levels as low as 0.3 mg/litre (1).

Major uses

The chloramines are used as intermediates in the manufacture of hydrazine; when formed *in situ* from ammonia and chlorine, they are also disinfectants for drinking-water (4).

Environmental fate

Monochloramine is persistent in the environment. Its rate of disappearance is primarily a function of pH and salinity: its half-life increases with increasing pH and decreases with increasing salinity. It decomposes more quickly if discharged into receiving waters containing bromide, presumably as a result of the formation of bromochloramine and the decomposition of the dihalamine. Monochloramine is expected to decompose via chlorine transfer to give organic nitrogen-containing compounds in receiving waters (5).

16.2.2 Analytical methods

Chloramines can be determined by colorimetric methods; the detection limit is about 10 µg/litre (6,7).

16.2.3 Environmental levels and human exposure

Water

Inorganic chloramines are found as by-products of the chlorination of water. In one survey, mono- and dichloramines were found in secondary sewage effluents and cooling water at levels in the range of 0.03-1.0 and 0.002-0.70 mg/litre, respectively (8). Many water companies have begun to use chloramines for disinfection instead of chlorine to prevent the formation of trihalomethanes. Typical chloramine concentrations of 0.5-2 mg/litre are found in drinking-water supplies where chloramine is used as a primary disinfectant or to provide a chlorine residual in the distribution system (9).

16.2.4 Kinetics and metabolism in laboratory animals and humans

Monochloramine administered by the oral route in the rat is readily absorbed from the gastrointestinal tract, the highest concentration 5 days after administration being found in plasma followed by whole blood, skin, testes, packed cells, bone marrow, kidney, lung, stomach, thyroid and thymus, carcass, liver, ileum, and fat. Monochloramine is metabolized to the chloride ion, which is excreted mainly in the urine and to a lesser extent in the faeces (10).

16.2.5 Effects on laboratory animals and *in vitro* test systems

Short-term exposure

Male A/JAX mice (12 per dose) were exposed to monochloramine at concentrations of 0, 2.5, 25, 50, 100, or 200 mg/litre (approximately 0, 0.4, 4, 8, 15, or 30 mg/kg of body weight per day) for 30 days. No significant adverse effects on various haematological parameters, including blood cell counts, haemoglobin, GSH levels, and glucose-6-phosphate dehydrogenase activity, were reported at any dose level tested. The NOAEL in this study was 30 mg/kg of body weight per day (11).

Monochloramine was administered to Fischer 344 rats and B6C3F₁ mice in drinking-water at concentrations of 0, 25, 50, 100, 200, or 400 mg/litre (approximately 0, 2.5, 5, 10, 20, or 40 mg/kg of body weight per day in rats and 0, 4, 8, 15, 30, or 60 mg/kg of body weight per day in mice) for 13 weeks. Decreased body weight gain and liver damage (e.g. cellular hypertrophy) were reported in mice exposed at concentrations of 100, 200, and 400 mg/litre. The authors also reported decreased body weight gain and decreased relative liver weight in male and female rats and increased protein excretion in male rats given 200 and 400 mg/litre. The NOAELs in this study were 50 mg/litre (8 mg/kg of body weight per day) for mice and 100 mg/litre (10 mg/kg of body weight per day) for rats (12).

Monochloramine at 0, 25, 50, 100, or 200 mg/litre was administered in drinking-water to male and female Sprague-Dawley rats for 90 days, corresponding to 0, 1.8, 3.4, 5.8, and 9.0 mg/kg of body weight per day for males and 0, 2.6, 4.3, 7.7, and 12.1 mg/kg of body weight per day for females. The authors considered the highest dose a LOAEL for both sexes, based on the respective reductions in liver and spleen weights. In addition, overall reductions in body weight gain were observed at 50 mg/litre and higher, but significant reductions only at 200 mg/litre. The authors concluded that 100 mg/litre (7.7 and 5.8 mg/kg of body weight per day for female and male rats, respectively) can be considered a NOAEL (13).

Long-term exposure

Monochloramine was administered for 2 years to male and female F344/N rats at 0, 50, 100, or 200 mg/litre in the drinking-water, corresponding to average doses of 2.9, 5.2, and 9.4 mg/kg of body weight per day in males and 3.1, 5.7, and 10.2 mg/kg of body weight per day in females. The authors failed to find any clinical changes attributable to the consumption of chloraminated water. Mean body weights of rats given the highest dose were lower than those of their respective control groups. Significant decreases in liver and kidney weights in high-dose males and increases in brain- and kidney-weight-to-body-weight ratios in high-dose rats of both sexes were related to the lower body weights in these groups. Based on these considerations, the authors considered the NOAELs for this study to be 5.2 and 5.7 mg/kg of body weight per day for male and female rats, respectively. However, it is probable that the observed weight decreases were a direct result of the unpalatability of the drinking-water (14).

In a second bioassay, B6C3F₁ mice were exposed for 2 years to monochloramine in their drinking-water at levels of 0, 50, 100, or 200 mg/litre, corresponding to average doses of 0, 5.4, 9.8, and 17.0 mg/kg of body weight per day for males and 0, 5.8, 10.6, and 19.0 mg/kg of body weight per day for females. The authors reported that there were no clinical changes attributable to the consumption of chloraminated water. Based on changes in body weight at the highest dose, the NOAELs were 9.8 and 10.6 mg/kg of

body weight per day for male and female mice, respectively (14).

Reproductive toxicity, embryotoxicity, and teratogenicity

Chloramine was administered by gavage at doses of 0, 2.5, 5.0, or 10 mg/kg of body weight per day to male and female Long-Evans rats for 66-76 days before and during mating and throughout gestation and lactation. No significant differences were observed between controls and exposed rats in fertility, viability, litter size, mean weight of pups, or day of eye opening. There were no alterations in sperm count, direct progressive sperm movement, percentage motility, or sperm morphological characteristics in adult males. The weights of male and female reproductive organs were not significantly different between the test and control groups, and no significant anatomical changes were seen on tissue examination. A NOAEL of 10 mg/kg of body weight per day was identified (15).

In a study in which monochloramine was administered to female Sprague-Dawley rats (6 per dose) at 0, 1, 10, or 100 mg/litre daily (approximately 0, 0.1, 1, or 10 mg/kg of body weight per day) in drinking-water before mating and throughout gestation, it was found not to be teratogenic or embryotoxic. The reliability of these findings is reduced because of the small number of dams exposed and the lack of data on maternal toxicity (16).

Mutagenicity and related end-points

Monochloramine was reported to be weakly mutagenic at the *trpC* locus of *Bacillus subtilis* (17). It did not increase the number of revertant colonies above the levels in untreated controls in assays employing *Salmonella typhimurium* strains TA97, TA100, and TA102 (18), nor did it significantly increase bone marrow chromosomal aberrations or micronuclei in CD-1 mice, or cause sperm-head abnormalities in B6C3F₁ mice (19).

Carcinogenicity

In 2-year bioassays, mice and rats were exposed to chloramine at 0, 50, 100, or 200 mg/litre in drinking-water, the highest doses being equivalent to 9.4 and 10.2 mg/kg of body weight per day for male and female rats, respectively, and 17.0 and 19.0 mg/kg of body weight per day for male and female mice, respectively. The studies provided equivocal evidence of the carcinogenic activity of chloraminated drinking-water in female F344/N rats, as indicated by an increase in comparison with concurrent controls, in the incidence of mononuclear-cell leukaemia. This increase, however, was within the range observed in historical controls. There was no evidence of carcinogenic activity in male rats or male and female mice (14).

16.2.6 Effects on humans

Chloramine was administered at increasing doses (approximately 0.0001, 0.01, 0.11, 0.26, or 0.34 mg/kg of body weight per day) to five groups of 10 human subjects each, over a 16-day period. There were no adverse effects on clinical signs, urinalysis, haematology, and clinical chemistry in comparison with controls. In a second phase of the study, 10 healthy adult males were given a chloramine solution of concentration 5 mg/litre (0.04 mg/kg of body weight per day). There were no adverse effects on physical condition, urinalysis, or clinical chemistry and no serious objections to the taste of chloramine at the dose tested (20).

Acute haemolytic anaemia, characterized by the denaturation of haemoglobin and the lysis of red blood cells, was reported in haemodialysis patients when tapwater containing chloramines was used for dialysis (21).

In epidemiological studies, no association was found between the ingestion of chloraminated drinking-water and increased mortality rates for bladder cancer (22,23).

16.2.7 Guideline value

IARC has not evaluated the carcinogenic potential of inorganic chloramines. In the National Toxicology Program (NTP) bioassay in two species (14), the incidence of mononuclear cell leukaemias in female F344/N rats was increased, but no other increases in tumour incidence were observed. Although monochloramine has been shown to be mutagenic in some *in vitro* studies, it has not been found to be genotoxic *in vivo*.

The guideline value for monochloramine is 3 mg/litre (rounded figure), based on a TDI of 94 µg/kg of body weight, calculated from a NOAEL of 9.4 mg/kg of body weight per day (the highest dose administered to males in the 2-year NTP rat drinking-water study, chosen because of the probability that the lower body weights were caused by the unpalatability of the drinking-water) (14). An uncertainty factor of 100 (for intra- and interspecies variation) is incorporated, and 100% of the TDI is allocated to drinking-water. An additional uncertainty factor for possible carcinogenicity was not applied because equivocal cancer effects reported in the NTP study in only one species and in only one sex were within the range observed in historical controls.

Available data are insufficient for the establishment of guideline values for dichloramine and trichloramine. The odour thresholds of dichloramine and trichloramine are much lower than that for monochloramine.

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16.3 Chlorine

16.3.1 General description

Identity

Element or compound	CAS no.	Molecular formula
Chlorine	7782-50-5	Cl ₂
Hypochlorous acid	7790-92-3	HOCl
Sodium hypochlorite	7681-52-9	NaOCl

Physicochemical properties of chlorine (1,2)¹

¹ Conversion factor in air: 1 ppm = 2.9 mg/m³

Property	Value
Boiling point	-34.6 °C
Melting point	-101 °C
Density	3.214 g/litre at 0 °C and 101.3 kPa
Vapour pressure	480 Pa at 0 °C
Water solubility	14.6 g/litre at 0 °C

Organoleptic properties

The taste and odour thresholds for chlorine in distilled water are 5 and 2 mg/litre, respectively. In air, chlorine has a pungent and disagreeable odour (2).

Major uses

Large amounts of chlorine are produced for use as disinfectants and bleach for both domestic and industrial purposes, and it is also widely used to disinfect drinking-water and swimming-pool water and to control bacteria and odours in the food industry (3,4).

Environmental fate

In water, chlorine reacts to form hypochlorous acid and hypochlorites. All three species exist in equilibrium with each other, the relative amounts varying with the pH. In dilute solutions and at pH levels above 4.0, very little molecular chlorine exists in solution. The concentrations of hypochlorous acid and the hypochlorite ion are approximately equal at pH 7.5 and 25 °C. Chlorine can react with ammonia or amines in water to form chloramines (4,5).

16.3.2 Analytical methods

A colorimetric method can be used to determine free chlorine in water at concentrations of 0.1-10 mg/litre. Other methods allow for the determination of free chlorine, chloramines, other chlorine species, and total available chlorine, and are suitable for total chlorine concentrations up to 5 mg/litre. The minimum detectable concentration of chlorine is about 0.02 mg/litre (6).

16.3.3 Environmental levels and human exposure

Air

A mean ambient air level of 1 mg/m³ was reported for chlorine (7).

Water

Chlorine is present in most disinfected drinking-water at concentrations of 0.2-1 mg/litre (3).

Food

Cake flour bleached with chlorine contains chloride at levels in the range 1.3-1.9 g/kg. Unbleached flour may contain small amounts of chlorite (400-500 mg/kg) (8).

Estimated total exposure and relative contribution of drinking-water

The major routes of exposure to chlorine are through drinking-water, food, and contact with items either bleached or disinfected with it.

16.3.4 Kinetics and metabolism in laboratory animals and humans

Most studies on the pharmacokinetics of chlorine, hypochlorous acid, or hypochlorites employ reactive ³⁶Cl-labelled compounds and probably reflect the fate of the chloride ion or other reaction products generated from the parent molecules. In rats, hypochlorous acid was readily absorbed through the gastrointestinal tract, distribution being highest in the plasma; smaller amounts were found in bone marrow, kidney, testes, lung, skin, duodenum, spleen, liver, and bone (9,10). *In vivo*, sodium hypochlorite was metabolized to trichloroethanoic acid, dichloroethanoic acid, chloroform, and dichloroacetonitrile (11). Hypochlorous acid administered to rats was excreted primarily in the urine and faeces, mostly in the form of chloride ion (10). None was excreted in expired air (9).

16.3.5 Effects on laboratory animals and *in vitro* test systems

Acute exposure

Calcium hypochlorite has an oral LD₅₀ in the rat of 850 mg/kg of body weight (2).

Short-term exposure

No consistent effects on organ weights or histopathology of tissues were noted in Sprague-Dawley rats (10 per sex per dose) given chlorine in drinking-water at 0, 25, 50, 100, 175, or 200 mg/litre (males: 0, 2, 7.5, 12.8, or 16.7 mg/kg of body weight per day; females: 0, 3.5, 12.6, 19.5, or 24.9 mg/kg of body weight per day) for 90 days (12) or in rats fed flour containing 1257 or 2506 mg of chlorine per kg (62.5 or 125 mg/kg of body weight per day) for 28 days (13).

Enhanced weight gain was observed in all male rats (10 per dose) given drinking-water containing chlorine at 0, 20, 40, or 80 mg/litre (0, 4.1, 8.1, or 15.7 mg/kg of body weight per day) for 6 weeks (14). The results of a 4-week study in which female C57BL/6N mice were given hyperchlorinated tapwater (4.8-5.8 mg/kg of body weight per day) suggested an adverse effect on the macrophage defence mechanisms of mice. The LOAEL in this study was 4.8 mg/kg of body weight per day (15).

In a study in which male CR-1:CD-1 mice (30 per dose) received chlorinated drinking-water (0.02, 0.2, 2.9, or 5.8 mg/kg of body weight per day) for 120 days, none of the mice showed evidence of a statistically significant change in humoral or cell-mediated immune response. A NOAEL of 5.8 mg/kg of body weight per day was identified (16).

Long-term exposure

F344 rats (50 per sex per dose) were administered sodium hypochlorite in drinking-water (males: 0.05% or 0.1%, 75 or 150 mg/kg of body weight per day; females: 0.1% or 0.2%, 150 or 300 mg/kg of body weight per day) for 2 years. Effects included a dose-related depression in body weight gain in all groups, depressed liver, brain, and heart weights in males given a 0.05% dose, decreased salivary gland weights in both female groups, and decreased kidney weights in females given 0.2% (17).

In a 2-year bioassay, F344 rats and B6C3F₁ mice were given chlorine in drinking-water at levels of up to 275 mg/litre (up to 24 mg/kg of body weight per day for male rats and male mice, 15 mg/kg of body weight per day for female rats, and 22 mg/kg of body weight per day for female mice). There was a dose-related decrease in water consumption for both mice and rats. No effects on body weight or survival were observed in any of the treated animals (18).

Wistar rats were fed cake prepared from flour treated with 1250 or 2500 mg of chlorine per kg (males: 12.8 or 25.3 mg/kg of body weight per day; females: 17.0 or 35.0 mg/kg of body weight per day) for 104 weeks. A dose-related reduction in spleen weight was seen in females, and dose-related haematological effects were observed in both sexes. A LOAEL of 12.8 mg/kg of body weight per day was identified in this

study (19).

Reproductive effects, embryotoxicity, and teratogenicity

C3H/HeJ and C57BL/6J mice administered drinking-water containing 10 mg of residual chlorine per litre (1.9 mg/kg of body weight per day) for 6 months showed no adverse reproductive effects (20). In a seven-generation study in which rats were given drinking-water chlorinated at 100 mg/litre (10 mg/kg of body weight per day), no treatment-related effects on fertility were found (21).

Oral administration of hypochlorite ion or hypochlorous acid at 100, 200, or 400 mg of chlorine per litre (1.6, 4.0, or 8.0 mg/kg of body weight per day) resulted, in the case of hypochlorite, in dose-related increases in the amount of sperm-head abnormalities in male B6C3F₁ mice. A NOAEL of 8.0 mg/kg of body weight per day was identified for hypochlorous acid and a LOAEL of 1.6 mg/kg of body weight per day for hypochlorite ion (22).

Mutagenicity and related end-points

Sodium hypochlorite has been found to be mutagenic in *Salmonella typhimurium* TA1530 and TA100 but not TA1538 (23,24). Calcium and sodium hypochlorite both produced chromosomal aberrations in Chinese hamster fibroblast cells without metabolic activation (24). Hypochlorite ion and hypochlorous acid were negative in the *in vivo* erythrocyte micronucleus assay and in bone marrow aberration studies (22).

Carcinogenicity

F344 rats (50 per sex per dose) were given sodium hypochlorite in drinking-water (males: 0.05% or 0.1%, 75 or 150 mg/kg of body weight per day; females: 0.1% or 0.2%, 150 or 300 mg/kg of body weight per day) for 2 years. Experimental groups did not differ from controls with respect to the total tumour incidences or mean survival times, and most of the tumours found were of types that commonly occur spontaneously in F344 rats. The authors concluded that sodium hypochlorite was not carcinogenic in rats (16).

In a seven-generation toxicity study, the incidence of malignant tumours in rats consuming drinking-water with a free chlorine level of 100 mg/litre (10 mg/kg of body weight per day) did not differ from that in controls (21). The incidence of tumours in treated animals was not significantly elevated in F344 rats and B6C3F₁ mice (50 per sex per dose) given solutions of sodium hypochlorite (70 or 140 mg/kg of body weight per day for male rats, 95 or 190 mg/kg of body weight per day for female rats, 84 or 140 mg/kg of body weight per day for male and female mice) in their drinking-water for 103-104 weeks (25).

In a 2-year bioassay, F344 rats and B6C3F₁ mice were given chlorine in drinking-water at levels of 0, 70, 140, or 275 mg/litre (8, 13, or 24 mg/kg of body weight per day for male rats; 5, 7, or 15 mg/kg of body weight per day for female rats; 8, 15, or 24 mg/kg of body weight per day for male mice; and 1, 13, or 22 mg/kg of body weight per day for female mice). Although there was a marginal increase in mononuclear-cell leukaemia in the groups of female rats given 140 and 275 mg/litre, it was considered to be equivocal evidence of carcinogenic activity because the incidence was significantly elevated compared with controls only for the middle dose and the incidence of leukaemia in the concurrent controls was lower than the mean in historical controls (18).

16.3.6 Effects on humans

Exposure to chlorine, hypochlorous acid, and hypochlorite ion through ingestion of household bleach occurs most commonly in children. Intake of a small quantity of bleach generally results in irritation of the oesophagus, a burning sensation in the mouth and throat, and spontaneous vomiting. In these cases, it is not clear whether it is the sodium hypochlorite or the extremely caustic nature of the bleach that causes the tissue injury.

The effects of heavily chlorinated water on human populations exposed for varying periods were summarized in a report that was essentially anecdotal in character and did not describe in detail the health effects observed (26). In a study on the effects of progressively increasing chlorine doses (0, 0.001, 0.014, 0.071, 0.14, 0.26, or 0.34 mg/kg of body weight) on healthy male volunteers (10 per dose), there was an absence of adverse, physiologically significant toxicological effects in all of the study groups (27). It has been reported that asthma can be triggered by exposure to chlorinated water (28). Episodes of dermatitis have also been associated with exposure to chlorine and hypochlorite (29, 30).

In a study of 46 communities in central Wisconsin where chlorine levels in water ranged from 0.2 to 1 mg/litre, serum cholesterol and low-density lipoprotein levels were higher in communities using chlorinated water. Levels of high-density lipoprotein (HDL) and the cholesterol/HDL ratio were significantly elevated in relation to the level of calcium in the drinking-water, but only in communities using chlorinated water. The authors speculated that chlorine and calcium in drinking-water may interact in some way that affects lipid levels (31).

An increased risk of bladder cancer appeared to be associated with the consumption of chlorinated tapwater in a population-based, case-control study of adults consuming chlorinated or non-chlorinated water for half of their lifetimes (32).

16.3.7 Guideline value

In humans and animals exposed to chlorine in drinking-water, specific adverse treatment-related effects have not been observed. IARC has concluded that hypochlorites are not classifiable as to their carcinogenicity to humans (Group 3) (17).

The guideline value for free chlorine in drinking-water is derived from a NOAEL of 15 mg/kg of body weight per day, based on the absence of toxicity in rodents that received chlorine as hypochlorite in drinking-water for up to 2 years (18). Application of an uncertainty factor of 100 (for inter- and intraspecies variation) to this NOAEL gives a TDI of 150 µg/kg of body weight. With an allocation of 100% of the TDI to drinking-water, the guideline value is 5 mg/litre (rounded figure). It should be noted, however, that this value is conservative, as no adverse effect level was identified in this study. Most individuals are able to taste chlorine or its by-products (e.g. chloramines) at concentrations below 5 mg/litre, and some at levels as low as 0.3 mg/litre.

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16.4 Chlorine dioxide, chlorite, and chlorate

16.4.1 General description

Identity

Compound	CAS no.	Molecular formula
Chlorine dioxide	10049-04-4	ClO ₂
Chlorite (sodium salt)	7758-19-2	NaClO ₂
Chlorate (sodium salt)	7775-09-0	NaClO ₃

Physicochemical properties (1-3)

Property	Chlorine dioxide¹	Sodium chlorite	Sodium chlorate
Boiling point (°C)	11	-	>300 (decomposes)
Melting point (°C)	-59	180-200 (decomposes)	248
Density at 0 °C (g/cm ³)	1.64 (liquid)	-	2.5
Vapour pressure at 25 °C	-	Negligible	-
Water solubility (g/litre)	3.01 (25 °C)	390 (17 °C)	-

¹ Conversion factor in air: 1 ppm = 2.8 mg/m³.

Organoleptic properties

The taste and odour threshold for chlorine dioxide in water is 0.4 mg/litre (3).

Major uses

Chlorine dioxide is used for disinfection and odour/taste control of water; as a bleaching agent for cellulose, paper pulp, flour, and oils; and for cleaning and detanning leather. Sodium chlorite is used in on-site production of chlorine dioxide; as a bleaching agent in production of paper, textiles, and straw products; and in the manufacture of waxes, shellacs, and varnishes. Sodium chlorate is used in the preparation of chlorine dioxide; in the manufacture of dyes, matches, and explosives; for tanning and finishing leather; and in herbicides and defoliants (1-3).

Environmental fate

Chlorine dioxide rapidly decomposes into chlorite, chlorate, and chloride ions in treated water, chlorite being the predominant species. This reaction is favoured by alkaline conditions.

16.4.2 Analytical methods

Methods are available for the determination of chlorine dioxide, chlorite, and total available chlorine (4,5). The limits of detection for these methods are 8 µg/litre for chlorine dioxide, 4 µg/litre for total chlorine, and 10 µg/litre for chlorite and chlorate.

16.4.3 Environmental levels and human exposure

Water

Chlorite occurs in drinking-water when chlorine dioxide is used for purification purposes. The levels of chlorite in water reported in one study ranged from 3.2 to 7.0 mg/litre (6).

Food

Chlorine dioxide, chlorite, and chlorate may occur in foodstuffs as a result of their use in flour processing, as a decolorizing agent for carotenoids and other natural pigments (chlorine dioxide), as a bleaching agent in the preparation of modified food starch (sodium chlorite), as an indirect additive in paper and paperboard products used for food packaging (sodium chlorite), and as a defoliant, desiccant, and fungicide in agriculture (sodium chlorate) (7-9).

Estimated total exposure and relative contribution of drinking-water

The major route of environmental exposure to chlorine dioxide, sodium chlorite, and sodium chlorate is through drinking-water.

16.4.4 Kinetics and metabolism in laboratory animals and humans

Chlorine dioxide is rapidly absorbed from the gastrointestinal tract. No particular organ appears to selectively concentrate the dose following exposure (10). Following oral ingestion by monkeys, chlorine dioxide was rapidly converted into chloride ion and, to a lesser extent, chlorite and chlorate (11). Excretion is mainly via the urine, smaller amounts being excreted in faeces (12).

Chlorite was readily absorbed when administered to rats, then randomly distributed throughout the tissues (12). It was transformed mainly into chloride in rats, smaller amounts appearing as unchanged chlorite. Excretion was mainly via the urine, followed by faeces (13).

Chlorate was readily absorbed and randomly distributed throughout the tissues of rats (12). It was excreted mainly in the form of chloride in the urine, smaller amounts appearing as chlorite and chlorate

(13).

16.4.5 Effects on laboratory animals and *in vitro* test systems

Chlorine dioxide

Short-term exposure

Drinking-water containing 0, 10, or 100 mg of chlorine dioxide per litre (equivalent to approximately 0, 1.5, or 15 mg/kg of body weight per day) was administered to mice (10 per dose) for 30 days with no apparent effects on blood parameters. The NOAEL for this study was 15 mg/kg of body weight per day (14).

A total of 12 African green monkeys were exposed to water containing chlorine dioxide at concentrations of 0, 30, 100, or 200 mg/litre (corresponding to measured doses of 0, 3.5, 9.5, or 11 mg/kg of body weight per day) using a rising dose protocol. Each dose was maintained for 30-60 days. A slight suppression of thyroid function (decreased thyroxine) was observed in monkeys receiving the two highest doses. No other effects were noted. The NOAEL was 3.5 mg/kg of body weight per day (11).

Six monkeys were treated for 8 weeks with drinking-water containing chlorine dioxide at 100 mg/litre, corresponding to an average measured dose of about 4.6 mg/kg of body weight per day. Thyroxine level was reduced after 4 weeks of treatment but rebounded after a further 4 weeks. In the same study, drinking-water containing chlorine dioxide at 0, 100, or 200 mg/litre was administered to male rats (12 per dose) (equivalent to 0, 10, or 20 mg/kg of body weight per day). A dose-dependent decrease in thyroxine levels was observed after 8 weeks of treatment; there was no rebound. The exposure level of 100 mg/litre, equivalent to a dose of approximately 10 mg/kg of body weight per day, was the LOAEL in this study (15).

Sprague-Dawley rats (10 per sex per dose) were exposed to 0, 25, 50, 100, or 200 mg of chlorine dioxide per litre in drinking-water for 90 days (approximate dose levels of 0, 2, 4, 6, or 12 mg/kg of body weight per day for males and 0, 2, 5, 8, or 15 mg/kg of body weight per day for females). Water consumption was decreased in both sexes at the three highest dose levels, probably due because of its reduced palatability. Food consumption was decreased in males receiving the highest dose. Goblet-cell hyperplasia was significantly increased in the nasal turbinates of females given 100 or 200 mg/litre and males at all doses. Inflammation of the nasal cavity was observed in males at 25 mg/litre and in both sexes at higher doses. The authors concluded that the lowest dose (2 mg/kg of body weight per day) was a LOAEL (16).

Long-term exposure

In a drinking-water study, chlorine dioxide was administered to rats (7 per sex per dose) at concentrations of 0, 0.5, 1, 5, 10, or 100 mg/litre (highest dose equivalent to about 13 mg/kg of body weight per day) for 2 years. At the highest dose level, survival rate was substantially decreased in both sexes, and mean life span was reduced compared with that for control animals. No correlation was observed between treatment and histopathological findings. In this study, a NOAEL of 10 mg/litre (1.3 mg/kg of body weight per day) was identified (17).

Reproductive toxicity, embryotoxicity, and teratogenicity

Female rats were exposed to 0, 1, 10, or 100 mg of chlorine dioxide per litre in drinking-water (equivalent to 0, 0.1, 1, or 10 mg/kg of body weight per day) for 2.5 months before mating and throughout gestation. At the highest dose, there was a slight reduction in the number of implants and live births per pregnancy. No effects were observed at 1 mg/kg of body weight per day, which was identified as the NOAEL (18).

Female Sprague-Dawley rats (13-16 per dose) were supplied with drinking-water containing 0, 2, 20, or 100 mg of chlorine dioxide per litre from 2 weeks before mating to gestation and lactation until pups were weaned on postnatal day 21. No significant effect on the body weight of either the dams or the pups was

observed at any dose tested. At 100 mg/litre (14 mg/kg of body weight per day for the pregnant dam), a significant depression of serum thyroxine and an increase in serum triiodothyronine were observed in the pups at weaning, but not in the dams. Neurobehavioural exploratory and locomotor activities were decreased in pups born to dams exposed to 100 mg/litre but not to those exposed to 20 mg/litre (3 mg/kg of body weight per day), which was considered a NOAEL (19).

In a second experiment, rat pups were exposed directly (by gavage) to 14 mg of chlorine dioxide per kg of body weight per day (equivalent to the dose received by a pregnant dam drinking water containing 100 mg of chlorine dioxide per litre) on postnatal days 5-20. In this study, serum thyroxine levels were depressed, a somewhat greater and more consistent delay in the development of exploratory and locomotor activity was seen, and pup body weight gain was reduced. The decrease in serum triiodothyronine levels was not statistically significant. Based on decreased pup development and decreased thyroid hormone levels, a LOAEL of 14 mg/kg of body weight per day (the only dose tested) was identified (19).

Cell number was significantly depressed in the cerebellum of 21-day-old rat pups born to dams supplied during gestation and lactation with water containing 100 mg of chlorine dioxide per litre (about 14 mg/kg of body weight per day to the dam). A group of 12 rat pups dosed directly by gavage with 14 mg/kg of body weight per day had depressed cell numbers in both the cerebellum and forebrain at postnatal day 11 and displayed decreased voluntary running-wheel activity at postnatal days 50-60, despite the fact that chlorine dioxide treatments were terminated at 20 days of age. These data suggest that chlorine dioxide is capable of influencing brain development in neonatal rats. In this study, a LOAEL of 14 mg/kg of body weight per day, the only dose tested, was identified (20).

The developmental neurotoxic potential of chlorine dioxide was evaluated in a study in which it was administered to rat pups by oral intubation at 14 mg/kg of body weight per day on postnatal days 1-20. Forebrain cell proliferation was decreased on postnatal day 35, and there were decreases in forebrain weight and protein content on postnatal days 21 and 35. Cell proliferation in the cerebellum and olfactory bulbs was comparable to that in untreated controls, as were migration and aggregation of neuronal cells in the cerebral cortex. Histopathological examination of the forebrain, cerebellum, and brain stem did not reveal any lesions or changes in these tissues. In this study, a LOAEL of 14 mg/kg of body weight per day (the only dose tested) was identified (18).

Mutagenicity and related end-points

Chlorine dioxide was mutagenic in *Salmonella typhimurium* strain TA100 in the absence of a metabolic activation system (21). No sperm-head abnormalities were observed in male mice following chlorine dioxide gavage (22). No chromosomal abnormalities were seen in either the micronucleus test or a cytogenetic assay in mouse bone marrow cells following gavage dosing with chlorine dioxide (22).

Carcinogenicity

Tumours were not observed in rats following 2-year exposures to chlorine dioxide in drinking-water (17).

Chlorite

Acute exposure

An oral LD₅₀ of 105 mg/kg of body weight has been reported in rats (23). Quail were more resistant than rats; the LD₅₀ was 493 mg/kg of body weight (24).

Short-term exposure

Single doses of sodium chlorite administered orally to cats produced methaemoglobinaemia (25). A dose of 20 mg of chlorite per litre (equivalent to approximately 1.5 mg of chlorite per kg of body weight) caused

up to 32% of the haemoglobin to be in the methaemoglobin state and was considered to be the LOAEL. A dose-dependent increase in methaemoglobinaemia and anaemia was observed in 12 African green monkeys treated with sodium chlorite at 0, 25, 50, 100, or 400 mg/litre in drinking-water using a rising dose protocol. Doses of chlorite were approximately 0, 3, 6, 13, and 50 mg/kg of body weight per day, and each dose level was maintained for 30-60 days (11).

Rats were exposed to chlorite ion at 0, 10, 50, 100, 250, or 500 mg/litre in drinking-water (equivalent to 0, 1, 5, 10, 25, or 50 mg/kg of body weight per day) for 30-90 days. Haematological parameters were monitored, and the three highest concentrations produced transient anaemia. At 90 days, red blood cell glutathione levels in the 100 mg/litre group were 40% below those of controls; there was at least a 20% reduction in the rats receiving 50 mg/litre. In this study, a NOAEL of 1 mg/kg of body weight per day was identified (25).

Long-term exposure

The effect of sodium chlorite in drinking-water at 0, 1, 2, 4, 8, 100, or 1000 mg/litre on the survival and postmortem pathology of albino rats (7 per sex per dose) was examined in a 2-year study. The life span of the animals was not significantly affected at any dose. No effects were observed in animals exposed to 8 mg/litre (0.7 mg/kg of body weight per day) or less. Animals exposed to 100 or 1000 mg/litre (9.3 or 81 mg/kg of body weight per day) exhibited treatment-related renal pathology; the author concluded that this was the result of a nonspecific salt effect (17).

Reproductive toxicity, embryotoxicity, and teratogenicity

Female mice (10 per dose) were treated with sodium chlorite at 0 or 100 mg/litre in drinking-water (equivalent to 0 and 72 mg/kg of body weight per day) from day 1 of gestation and throughout lactation. Conception rates were 56% for controls and 39% for treated mice. The body weights of pups at weaning were reduced in treated mice relative to controls, so that 72 mg/kg of body weight per day is the LOAEL for this study (14).

In a series of experiments, sodium chlorite was administered to male rats (12 rats per dose) in drinking-water for 66-76 days at concentrations of 0, 1, 10, 100, or 500 mg/litre (equivalent to 0, 0.1, 1, 10, or 50 mg/kg of body weight per day). No compound-related abnormalities were observed on histopathological examination of the reproductive tract. Abnormal sperm morphology and decreased sperm motility were seen at the two highest dose levels, but no sperm effects were observed at 1 mg/kg of body weight per day, which can be identified as the NOAEL. In another part of the same study, male rats were bred with female rats treated at the same dose levels for 2 weeks before and throughout a 10-day breeding period. Females were exposed to sodium chlorite throughout gestation and lactation until the pups were weaned on day 21. There was no evidence of any adverse effects on conception rates, litter size, day of eye opening, or day of vaginal opening. Based on reproductive effects, a NOAEL of 10 mg/kg of body weight per day, the highest dose tested, was identified (26).

Treatment of maternal mice with 100 mg of sodium chlorite per litre in drinking-water (equivalent to 14 mg of chlorite per kg of body weight per day) throughout gestation and lactation resulted in pups with decreased body weights (14% below those of controls) at weaning. In this study, a LOAEL for developmental effects of 14 mg/kg of body weight per day was identified (14).

Fetuses from maternal rats exposed to chlorite ion via drinking-water at levels of up to 10 mg/litre (about 1 mg/kg of body weight per day) were examined. No compound-related skeletal or soft-tissue anomalies were observed. A NOAEL of 1 mg/kg of body weight per day was identified (27).

Mutagenicity and related end-points

No chromosomal abnormalities were seen in either the micronucleus test or a cytogenetic assay in mouse

bone marrow cells following gavage dosing with chlorite (22).

Carcinogenicity

In a long-term study in which mice received sodium chlorite in drinking-water for 85 weeks, there was no significant increase in tumours as compared with controls at a dose of 250 mg/litre (about 36 mg of chlorite ion per kg of body weight per day). Although treated male mice exhibited an increased incidence of lung and liver tumours, tumour rates were within historical ranges for control mice, increases in the liver tumours did not display a typical dose-response pattern, and significant increases were seen only for benign tumours (28). Tumours were not observed in rats following 2-year exposures to sodium chlorite in drinking-water (17).

Chlorate

Acute exposure

An acute oral dosing study in dogs demonstrated lethality at levels of sodium chlorate as low as 600 mg of chlorate ion per kg (29).

Short-term exposure

Beagle dogs (4 per sex per dose) were exposed by gavage to sodium chlorate at doses of 0, 10, 60, or 360 mg/kg of body weight per day for 3 months. There was no significant effect at any dose level on body weight, food consumption, clinical chemistry, organ weights, ophthalmic effects, gross necropsy, or tissue histopathology. Haematological changes were limited to a slight elevation in methaemoglobin level in highest-dose animals, but this appeared to be within normal limits and was not judged to be treatment-related. In this study, a NOAEL of 360 mg/kg of body weight per day in dogs was identified (30).

Sprague-Dawley rats (14 per sex per dose) were exposed by gavage to sodium chlorate at doses of 0, 10, 100, or 1000 mg/kg of body weight per day for up to 3 months. No treatment-related effects were observed on mortality, physical appearance or behaviour, body weight, food consumption, clinical chemistry, gross necropsy, or organ histopathology. At the highest dose, haematological changes indicative of anaemia included decreases in erythrocyte count, haemoglobin concentration, and erythrocyte volume fraction (haematocrit). In this study, a NOAEL of 100 mg/kg of body weight per day was identified (31).

Reproductive toxicity, embryotoxicity, and teratogenicity

Sodium chlorate was administered to pregnant CD rats by gavage at doses of 0, 10, 100, or 1000 mg/kg of body weight per day on days 6-15 of gestation. There were no maternal deaths in treated animals or treatment-related effects on maternal body weight gain, food consumption, clinical observations, number of implantations, or gross necropsy. Examination of fetuses on day 20 revealed no effects on fetal weight or sex ratio, and no external, visceral, or skeletal abnormalities were detected. In this study, a developmental NOAEL of 1000 mg/kg of body weight per day in rats was identified (32).

Mutagenicity and related end-points

No chromosomal abnormalities were seen in either the micronucleus test or a cytogenetic assay in mouse bone marrow cells following gavage dosing with chlorate (22).

16.4.6 Effects on humans

Chlorine dioxide

Six different doses of chlorine dioxide (0.1, 1, 5, 10, 18, or 24 mg/litre) in drinking-water were administered to each of 10 male volunteers using a rising dose protocol. Serum chemistry, blood count, and urinalysis parameters were monitored. A treatment-related change in group mean values for serum uric acid was observed, which the authors concluded was not physiologically detrimental. The highest dose tested, 24 mg/litre (about 0.34 mg/kg of body weight per day), can be identified as a single-dose NOAEL (33).

The same male volunteers drank 0.5 litres of water containing 5 mg of chlorine dioxide per litre each day for approximately 12 weeks, and were then kept under observation for 8 weeks. Serum chemistry, blood counts, and urinalysis revealed no abnormalities, except for a slight change in blood urea nitrogen, which the authors concluded was of doubtful physiological or toxicological significance. This exposure, equivalent to 36 µg/kg of body weight per day, can be considered a NOAEL (33).

In a prospective study of 197 persons, a portion of the population of a rural village exposed for 12 weeks to a chlorine dioxide-treated water supply (containing 0.25-1.1 mg of chlorine dioxide per litre and 0.45-0.91 mg of free chlorine per litre) experienced no significant changes in haematological parameters, serum creatinine, or total bilirubin (6).

Chlorite

The effects of sodium chlorite on humans were evaluated in 10 male volunteers on a rising dose protocol. Single doses of 0.01, 0.1, 0.5, 1.0, 1.8, and 2.4 mg of chlorite ion per litre in 1 litre of drinking-water were ingested by each subject. Changes in group mean values for serum urea nitrogen, creatinine, and urea nitrogen/creatinine ratio were observed, which the authors concluded were not adverse physiological effects. The highest dose tested, 2.4 mg/litre (0.034 mg/kg of body weight per day), can be identified as a single-dose NOAEL (33).

The same volunteers ingested 0.5 litres of water per day containing 5 mg of sodium chlorite per litre for approximately 12 weeks, and were then kept under observation for 8 weeks. Treatment was associated with a change in group mean corpuscular haemoglobin; however, as there was no trend over time for this change and values were within the normal ranges, the authors were reluctant to attach physiological significance to the observation. The dose tested, equivalent to 36 µg/kg of body weight per day, was identified as the NOAEL (33).

Chlorate

Because of its use as a weed killer, a large number of cases of chlorate poisoning have been reported (3). Symptoms include methaemoglobinaemia, anuria, abdominal pain, and renal failure. For an adult human, the oral lethal dose is estimated to be as low as 20 g of sodium chlorate (230 mg of chlorate per kg of body weight) (34).

Ten male volunteers were given six separate doses of sodium chlorate following a rising dose protocol, single doses of 0.01, 0.1, 0.5, 1.0, 1.8, and 2.4 mg of chlorate ion per litre in 1 litre of drinking-water being ingested by each volunteer. Very slight changes in group mean serum bilirubin, iron, and methaemoglobin were observed, but the authors concluded that they were not adverse physiological effects. The highest dose tested, 2.4 mg/litre (34 µg/kg of body weight per day), can be identified as a single-dose NOAEL (33).

The volunteers also ingested 0.5 litres of water per day containing 5 mg of sodium chlorate per litre (36 µg/kg of body weight per day) for approximately 12 weeks, and were then kept under observation for 8 weeks. Treatment was associated with slight changes in group mean serum urea nitrogen and mean

corpuseular haemoglobin, but the authors concluded that these were not physiologically significant as values remained within the normal range for each parameter. The NOAEL was 36 µg/kg of body weight per day (33).

16.4.7 Guideline values

Chlorine dioxide

Chlorine dioxide has been shown to impair neurobehavioural and neurological development in rats exposed perinatally. Significant depression of thyroid hormones has also been observed in rats and monkeys exposed to it in drinking-water studies.

A guideline value has not been established for chlorine dioxide because of its rapid breakdown and because the chlorite provisional guideline value (see below) is adequately protective for potential toxicity from chlorine dioxide. The taste and odour threshold for this compound is 0.4 mg/litre.

Chlorite

Chlorite affects the red blood cells, resulting in methaemoglobin formation in cats and monkeys. IARC has concluded that chlorite is not classifiable as to its carcinogenicity to humans (Group 3) (35).

The TDI for chlorite is 10 µg/kg of body weight, based on the NOAEL of 1 mg/kg of body weight per day for decreased red blood cell glutathione levels in a 90-day study in rats exposed to chlorite in their drinking-water (25) and applying an uncertainty factor of 100 (to account for inter- and intraspecies variation). Owing to the acute nature of the response and the existence of a 2-year rat study, an additional uncertainty factor of 10 was not incorporated to account for the short duration of the key study. The TDI derived in this manner is consistent with the NOAEL (36 µg/kg of body weight per day) in a 12-week clinical study in a small number of human volunteers (33).

On the assumption that drinking-water contributes 80% of the total exposure, the provisional guideline value is 0.2 mg/litre (rounded figure). This guideline value is designated as provisional because use of chlorine dioxide as a disinfectant may result in the chlorite guideline value being exceeded, and difficulties in meeting the guideline value must never be a reason for compromising adequate disinfection.

Chlorate

Available data on the effects of chlorate in humans and experimental animals are considered insufficient to permit the development of a guideline value. Data on accidental poisonings indicate that the lethal dose to humans is about 230 mg/kg of body weight per day. This is of the same order of magnitude as the NOAELs identified from studies in rats and dogs. Although no effects were observed in a 12-week clinical study in a small number of human volunteers ingesting 36 µg/kg of body weight per day, a guideline value was not derived from these results because no adverse effect level was determined.

Further research is needed to characterize the nonlethal effects of chlorate. Until data become available, it may be prudent to try to minimize chlorate levels. However, adequate disinfection should not be compromised.

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16.5 Iodine

16.5.1 General description

Identity

CAS no.: 7553-56-2

Molecular formula: I₂

Physicochemical properties (1,2)^{1,2}

¹ Also includes data from the Hazardous Substances Data Bank of the National Library of Medicine, Bethesda, MD

² Conversion factor in air: 1 ppm = 10 mg/m³

Property	Value
Boiling point	184.4 °C
Melting point	113.5 °C
Density	4.93 g/cm ³ at 25 °C
Vapour pressure	40 Pa at 25 °C
Water solubility	0.34 g/litre at 25 °C
Log octanol-water partition coefficient	2.49

Organoleptic properties

The taste and odour thresholds for iodine are 0.147-0.204 mg/litre in water and 9 mg/m³ in air (3).

Major uses

Iodine is used as an antiseptic for skin wounds, as a disinfecting agent in hospitals and laboratories, and for the emergency disinfection of drinking-water in the field. Iodide is used in pharmaceuticals and in photographic developing materials.

Environmental fate

Iodine occurs naturally in water in the form of iodide (I⁻), which is largely oxidized to iodine during water treatment.

16.5.2 Analytical methods

Iodide in water is normally determined by a titrimetric procedure which can be used for solutions containing 2-20 mg of iodide per litre. A leuco crystal violet method may be used for the determination of iodide or molecular iodine in water. This photometric method is applicable to iodide concentrations of 50-6000 µg/litre; the detection limit for iodine is 10 µg/litre (4,5).

16.5.3 Environmental levels and human exposure

Water

The mean concentration of total iodine in drinking-water in the USA is 4 µg/litre, and the maximum concentration is 18 µg/litre (2). This is presumably predominantly iodide.

Food

The main natural sources of dietary iodide are seafood (200-1000 µg/kg) and seaweed (0.1-0.2% iodide by weight). Iodide is also found in cow's milk (20-70 µg/litre) and may be added to table salt (100 µg of potassium iodide per gram of sodium chloride) to ensure an adequate intake of iodine (2,6). The estimated dietary iodine requirement for adults ranges from 80 to 150 µg/day (7).

Estimated total exposure

Exposure to iodine may occur through drinking-water, pharmaceuticals, and food. At a concentration of 4 µg/litre in drinking-water, adult human daily intake will be 8 µg of iodine, on the assumption that 2 litres of drinking-water are consumed per day.

16.5.4 Kinetics and metabolism in laboratory animals and humans

Molecular iodine is rapidly converted into iodide following ingestion and this is efficiently absorbed throughout the gastrointestinal tract (8). Molecular iodine vapour is converted into iodide before absorption (2). The highest concentration of iodine in the human body is found in the thyroid, which contains 70-80% of the total iodine content (15-20 mg). Muscle and eyes also contain high iodide concentrations (6,8).

Iodine is an essential element in the synthesis of the thyroid hormones thyroxine (T₄) and triiodothyronine (T₃) through the precursor protein thyroglobulin and the action of the enzyme thyroid peroxidase. Iodide is excreted primarily by the kidneys and is partially reabsorbed from the tubules following glomerular filtration (8). Smaller amounts of iodine are excreted in saliva, sweat, bile, and milk (9).

16.5.5 Effects on laboratory animals and *in vitro* test systems

Acute exposure

The acute oral LD₅₀ for potassium iodide in rats was 4340 mg/kg of body weight (3320 mg of iodide per kg of body weight), and the lowest oral lethal dose in mice was 1862 mg/kg of body weight (1425 mg of iodide per kg of body weight) (9).

Short-term exposure

The effects of iodide on autoimmune thyroiditis were investigated in two strains of chickens (CS and OS) known to be genetically susceptible to this disease. Administration of iodide in drinking-water (20 or 200 mg/litre, as potassium iodide) during the first 10 weeks of life increased the incidence of the disease, as determined by histological examination of the thyroid and measurement of T₃, T₄, and thyroglobulin antibodies. Excessive iodide consumption may increase the incidence of this disease in humans (10).

Reproductive toxicity, embryotoxicity, and teratogenicity

No effects were observed on ovulation rate, implantation rate, or fetal development in female rats given doses of 0, 500, 1000, 1500, or 2000 mg of iodide (as potassium iodide) per kg of diet during gestation and lactation. The dose-related survival rate for pups ranged from 93% (controls) to 16% (2000 mg/kg). Milk secretion was absent or greatly diminished in females exposed to iodide and the high mortality in pups was attributed to the dams' lactational failure (11).

The effects of iodide on brain enzymes in rat pups born to females given 1.1 mg of iodide per day as potassium iodide (about 37 mg/kg of body weight per day) in drinking-water were studied. Transient increases in glutamate dehydrogenase and decreases in succinate dehydrogenase were observed. Increases in phosphofructokinase and malate enzymes were noted, but no changes in hexokinase were reported. Serum T₄ levels did not differ significantly from control values (12).

Metabolism was severely disturbed in foals born to mares receiving excess iodine (48-432 mg of iodine per day) in the diet during pregnancy and lactation. The long bones of the legs of foals showed osteopetrosis (abnormally dense bones); phosphorus and alkaline phosphatase levels in the blood were elevated (13).

Carcinogenicity

In a study on the tumorigenic effects of iodide on the thyroid, groups of 20 rats were fed diets containing 0 or 1000 mg of iodide per kg as potassium iodide (0 or 39 mg of iodide per kg of body weight per day) for 19 weeks. No tumours were found on histopathological examination of the thyroid in either the treated or untreated groups (14). The exposure period may have been too short for a carcinogenic effect to be detected.

16.5.6 Effects on humans

Short-term exposure

Oral doses of 2000-3000 mg of iodine (about 30-40 mg/kg of body weight) are estimated to be lethal to humans, but survival has been reported after ingestion of 10 000 mg. Doses of 30-250 ml of tincture of iodine (about 16-130 mg of total iodine per kg of body weight) have been reported to be fatal. Acute oral toxicity is primarily due to irritation of the gastrointestinal tract, marked fluid loss and shock occurring in severe cases. Exposure to iodine vapour results in lung, eye, and skin irritation, while high concentrations rapidly lead to pulmonary oedema (2).

In rare instances, a hypersensitization reaction may occur immediately after or within several hours of oral or dermal exposure to iodide. The most striking symptoms are angio-oedema (acute, transitory swelling of the face, hands, feet, or viscera) and swelling of the larynx, which may cause suffocation (8). Iodide has been used in the past as an expectorant in the treatment of asthma and related conditions at a typical dose of 3.3 mg/kg of body weight (2).

Long-term exposure

Chronic iodide exposure results in iodism; the symptoms resemble those of a sinus cold but may also include salivary gland swelling, gastrointestinal irritation, acneform skin, metallic or brassy taste, gingivitis, increased salivation, conjunctival irritation, and oedema of eyelids (8). Chronic ingestion of 2 mg of iodide per day (0.03 mg/kg of body weight per day) is considered by some authors to be excessive, but daily doses of 50-80 mg (0.8-1.3 mg/kg of body weight per day) are consumed by some Japanese without ill effect (6).

Chronic consumption of iodinated drinking-water has not been shown to cause adverse health effects in humans, although some changes in thyroid status have been observed. In a 5-year study of prison inmates consuming water containing iodine at a concentration of 1 mg/litre (approximately 0.03 mg/kg of body weight per day), no cases of hyper- or hypothyroidism, urticaria, or iodism were seen. However, a small but statistically significant decrease in radioactive iodine uptake by the thyroid and an increase in protein-bound iodine concentrations were reported (15). No adverse health effects were reported in men who drank water providing iodide at doses of 0.17-0.27 mg/kg of body weight per day for 26 weeks (16).

In one study, the rate of radioactive iodide uptake by the thyroid was measured in 22 individuals with thyroid disease and 10 with normal thyroid function, before and after administration of 2.0 mg of iodide. Radioactive iodine uptake decreased by 54-99% in patients with thyroid disease but only by 8-54% in normal controls. These results suggest that iodide may aggravate certain pre-existing thyroid disease conditions (17).

Eight cases of congenital goitre and hypothyroidism in children were reported to be associated with maternal ingestion of iodide (18). Estimates of maternal iodide exposure ranged from 12 to 1650 mg/day (about 0.02-27 mg/kg of body weight per day) in individuals taking iodide as an expectorant in the treatment of asthma. No direct evidence of a cause-and-effect relationship between iodide exposure and health effects during pregnancy was reported.

Hypothyroidism has also been reported in infants of mothers receiving multiple topical applications of povidone-iodine (about 1% free iodine) during pregnancy and lactation (19).

16.5.7 Conclusions

In 1988, JECFA set a PMTDI for iodine of 1 mg/day (17 µg/kg of body weight per day) from all sources, based mainly on data on the effects of iodide (20). However, recent data from studies in rats indicate that the effects of iodine in drinking-water on thyroid hormone concentrations in the blood differ from those of iodide (21,22).

Available data therefore suggest that derivation of a guideline value for iodine on the basis of information on effects of iodide is inappropriate, and there are few relevant data on the effects of iodine. Because iodine is not recommended for long-term disinfection, lifetime exposure to iodine from water disinfection is unlikely. For these reasons, a guideline value for iodine has not been established at this time.

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Disinfectant by-products

16.6 Bromate

16.6.1 General description

Identity

Compound	CAS no.	Molecular formula
Potassium bromate	7758-01-2	KBrO ₃
Sodium bromate	7789-38-0	NaBrO ₃

The bromate ion (BrO₃⁻) may exist in a variety of salts, the most common of which are potassium and sodium bromate.

Physicochemical properties (1)

Property	Sodium bromate	Potassium bromate
Boiling point (°C)	-	Decomposes at 370 °C
Melting point (°C)	381	350
Density at 20 °C (g/cm ³)	3.34	3.27
Water solubility (g/litre)	275 (8 °C) 909 (100 °C)	133 (40 °C) 498 (100 °C)

Major uses

Bromate is used in home permanent wave neutralizing solutions (2). Small amounts may be added to flour as a maturing agent, to dough as a conditioner, and to improve fish paste. It may also be added to beer or cheese (3).

Environmental fate

Its properties suggest that bromate will not volatilize and will be adsorbed only slightly on to soil or sediment. Because it is a strong oxidant, its commonest fate is probably reaction with organic matter, ultimately leading to the formation of bromide ion.

16.6.2 Analytical methods

Bromate may be determined by several different methods, including iodometric titration and high-performance liquid chromatography. Detection limits range from 0.05 to 1 mg/litre (3). Ion chromatography with conductivity detection has a detection limit of 5 µg/litre (US EPA draft method, available from Environmental Monitoring and Support Laboratory, Cincinnati, OH, USA).

16.6.3 Environmental levels and human exposure

Water

Bromate is not normally present in water but may be formed from bromide during ozonation. Concentrations of 60-90 µg/litre have been reported in ozonated water (4,5).

Food

Small amounts of bromate may be added to flour or dough during the preparation of bread, but this is broken down to bromide during baking (3).

Estimated total exposure and relative contribution of drinking-water

For most people, exposure to bromate is unlikely to be significant. If ozone is used to disinfect drinking-water, intake of bromate might range from 120 to 180 µg/day (5).

16.6.4 Kinetics and metabolism in laboratory animals and humans

Following oral administration, bromate is rapidly absorbed from the gastrointestinal tract (6). It was not detected in rat tissues following a single intragastric dose, but was significantly increased in plasma, red blood cells, pancreas, kidney, stomach, and small intestine (7).

Bromate may be converted into hydrobromic acid by hydrochloric acid in the stomach (6). Liver and kidney tissues may degrade bromate to bromide by a process involving glutathione (8), although only small amounts appear to be reduced in this way (6). Bromate is excreted mainly in the urine as bromate and bromide; some may also be eliminated in the faeces (7).

16.6.5 Effects on laboratory animals and *in vitro* test systems

Acute exposure

Potassium bromate administered orally (9) and intraperitoneally (10) to mice gave LD₅₀s of 223-363 and 136 mg of bromate per kg of body weight, respectively. LD₅₀s of 280-495 mg/kg of body weight were obtained for rats, mice, and hamsters given potassium bromate by gavage (11).

Short-term exposure

Potassium bromate was administered to groups of F344 rats (10 per sex per dose) in water at concentrations of 0, 150, 300, 600, 1250, 2500, 5000, or 10 000 mg/litre (approximately 16, 32, 63, 140, 270, 540, or 1080 mg of bromate per kg of body weight per day) for 13 weeks. All animals exposed to 2500 mg/litre or higher died within 7 weeks. Observed signs of toxicity included significant inhibition of body weight gain in males at 600 mg/litre or above and significant increases in serum parameters in both sexes at 600 mg/litre (11).

Long-term exposure

Male Wistar rats were exposed to 0.04% potassium bromate in drinking-water (approximately 30 mg of bromate per kg of body weight per day) for up to 15 months. Effects included markedly inhibited body weight gain in all exposed animals, karyopyknotic foci in tubules of the inner kidney medulla, increased blood urea nitrogen (BUN), and marked structural abnormalities of the cortical tubules. Based on body weight and renal effects, a LOAEL of 30 mg of bromate per kg of body weight per day was identified in this study (12).

Reproductive toxicity, embryotoxicity, and teratogenicity

The reproductive effects of potassium bromate were evaluated in a study in which rats and mice were fed flour treated with 15 mg of potassium bromate per kg over five and eight generations, respectively. No effects on reproductive performance or survival were observed in either species (11).

Mutagenicity and related end-points

Positive results were obtained for the mutagenicity of potassium bromate in *Salmonella typhimurium* strain TA100 using the Ames test and for chromosomal aberrations in cultured Chinese hamster fibroblast cells (13). Positive results were also obtained in an *in vivo* study of the acute cytogenetic effect of potassium bromate on rat bone marrow cells (14) and in the mouse micronucleus test (9,10). Some evidence of DNA damage in rats given potassium bromate has been observed (15).

Carcinogenicity

F344 rats (50 per sex per dose) were given drinking-water containing 0, 250, or 500 (reduced to 400 at week 60) mg of potassium bromate per litre (average doses 0, 9.6, and 21.3 mg of bromate per kg of body weight per day in males and 0, 9.6 or 19.6 mg of bromate per kg of body weight per day in females) for 110 weeks. The incidence of renal tumours in the three groups was 6%, 60%, and 88% in males and 0, 56%, and 80% in females. The incidence of peritoneal mesotheliomas in dosed males was also significantly elevated (11%, 33%, and 59%). The authors concluded that potassium bromate was carcinogenic in both male and female rats (16).

In a subsequent study, male F344 rats were given water containing potassium bromate at 0, 15, 30, 60, 125, 250, or 500 mg/litre (equivalent to 0, 0.7, 1.3, 2.5, 5.6, 12, or 33 mg of bromate per kg of body weight) for 104 weeks. The incidence of renal cell tumours in these dose groups was 0, 0, 0, 4%, 21%,

25%, and 45% and was significantly elevated at 12 mg/kg of body weight per day and above. The incidence of dysplastic foci (considered to be preneoplastic lesions) was 0, 5%, 25%, 25%, 50%, 95%, and 95% and was significantly elevated at 5.6 mg/kg of body weight per day and above (17).

The carcinogenic potential of potassium bromate was investigated in B6C3F₁ female mice (50 per dose) supplied with water containing 0, 500, or 1000 mg of potassium bromate per litre (average dose 0, 43.5, or 91.6 mg of bromate per kg of body weight per day) for 78 weeks. Based on histological examination of tissues at week 104, no significant difference in tumour incidence between exposed and control animals was apparent (16).

Male F344 rats were supplied with water containing 500 mg of potassium bromate per litre (average dose 32.3 mg of bromate per kg of body weight per day) for up to 104 weeks to assess the time-course of renal cell tumour induction. Dysplastic foci and renal adenomas were first observed following 26 weeks of treatment, but the incidence was not statistically significant. Renal dysplastic foci (62%) and adenomas (52%) were significantly increased as compared with controls by 52 weeks of treatment. After 104 weeks, renal adenocarcinomas were observed in 3 of 20 rats (15%) and adenomas in 6 of 20 (30%). The combined incidence of follicular adenomas and adenocarcinomas of the thyroid (7/35) was significantly increased in rats receiving treatment for 104 weeks. The authors concluded that the minimum induction time for renal adenoma development was 26 weeks (18).

In a related study, the incidence of renal cell tumours was investigated in F344 rats exposed to water containing 500 mg of potassium bromate per litre (29.6-35.5 mg of bromate per kg of body weight per day) for up to 104 weeks. The incidence of renal dysplastic foci was 65% in animals exposed for 1-13 weeks and increased to 100% in animals exposed for 39-52 weeks (0% in controls). The combined incidence of adenomas and adenocarcinomas in rats exposed for 13-52 weeks ranged from 47% to 74%, which is similar to or higher than that in animals exposed continuously for 104 weeks (45%). The authors concluded that the minimum total cumulative dose necessary for the induction of renal adenomas and adenocarcinomas was 4 g of potassium bromate per kg (3.1 g of bromate per kg) and the minimum treatment period for the induction of these tumours was 13 weeks (18).

No significant differences were observed in the incidence of tumours in male or female newborn F344 rats or ICR mice when potassium bromate was administered subcutaneously (19).

16.6.6 Effects on humans

Most cases of human poisoning from bromate are due to the accidental or intentional ingestion of home permanent wave solutions, which can contain 2-10% bromate. In children, serious poisonings have been reported following ingestion of 60-120 ml of 2% potassium bromate (equivalent to 46-92 mg of bromate per kg of body weight per day for a 20-kg child). Lethal oral doses of potassium bromate are estimated to be 200-500 mg/kg of body weight (154-385 mg of bromate per kg of body weight) (2).

Toxic effects of bromate salts include nausea, vomiting, abdominal pain and diarrhoea, varying degrees of central nervous system depression, seizures, respiratory depression, and pulmonary oedema, most of which are reversible. Irreversible effects include renal failure and deafness, both of which have been observed following the ingestion of 240-500 mg of potassium bromate per kg of body weight (185-385 mg of bromate per kg of body weight) (2).

16.6.7 Provisional guideline value

JECFA evaluated bromate and recommended that there should be no residues in food when bromate is used in food processing (20). IARC has concluded that there is sufficient evidence for the carcinogenicity of potassium bromate in animals (3) and has classified it in Group 2B (possible human carcinogen). Bromate is mutagenic both *in vitro* and *in vivo*.

To estimate cancer risks, the linearized multistage model was applied to the incidence of renal tumours in male rats given potassium bromate in drinking-water (16), although it was noted that, if the mechanism of tumour induction is oxidative damage in the kidney, application of the low-dose cancer risk model may not be appropriate. The concentrations in drinking-water associated with excess lifetime cancer risks of 10^{-4} , 10^{-5} , and 10^{-6} are 30, 3, and 0.3 µg/litre, respectively.

Because of limitations in available analytical and treatment methods, a provisional guideline value of 25 µg/litre is recommended. This value is associated with a lifetime excess cancer risk of 7×10^{-5} .

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16.7 Chlorophenols

16.7.1 General description

Identity

Compound	CAS no.	Molecular formula
2-Chlorophenol	95-57-8	ClC ₆ H ₄ OH
2,4-Dichlorophenol	120-83-2	Cl ₂ C ₆ H ₃ OH
2,4,6-Trichlorophenol	88-06-2	Cl ₃ C ₆ H ₂ OH

A total of 19 possible chlorinated phenols exist, but only 2-chlorophenol (2-CP), 2,4-dichlorophenol (2,4-DCP), and 2,4,6-trichlorophenol (2,4,6-TCP) will be evaluated here, as these are the most likely to occur in drinking-water as possible by-products of disinfection.

Physicochemical properties (1-3)

Property	2-CP¹	2,4-DCP²	2,4,6-TCP³
Boiling point (°C)	175-176	210-211	246
Melting point (°C)	8.7	43-44	68
Density (g/cm ³)	1.24	1.38	1.49
Vapour pressure (kPa)	0.133 (12.1 °C)	0.133 (53 °C)	0.133 (76 °C)
Water solubility (mg/litre)	28 000	4500	900
Log octanol-water partition coefficient	2.15	3.06	-

¹ Conversion factors in air: 2-CP, 1 ppm = 5.26 mg/m³.

² Conversion factors in air: 2,4-DCP, 1 ppm = 6.67 mg/m³.

³ Conversion factors in air: 2,4,6-TCP, 1 ppm = 8.08 mg/m³.

Organoleptic properties

Chlorophenols generally have very low organoleptic thresholds. The taste thresholds in water for 2-CP, 2,4-DCP, and 2,4,6-TCP are 0.1, 0.3, and 2 µg/litre, respectively. Odour thresholds are 10, 40, and 300

µg/litre, respectively (2).

Major uses

2-CP is used as a precursor in the production of higher chlorophenols and dyestuffs, and as a preservative. 2,4-DCP is used as a mothproofing agent, germicide and antiseptic, and in the production of the pesticide 2,4-D. 2,4,6-TCP is used in the production of 2,3,4,6-tetrachlorophenol and pentachlorophenol, and as a germicide, glue and wood preservative, and antimildew agent (4,5).

16.7.2 Analytical methods

EPA methods 604 (6,7), 525 (8), and 8270 (9) are used for the determination of chlorophenols. The most sensitive technique involves the formation of the pentafluorobenzyl ether derivatives (an option in method 604); the method has a detection limit of 0.5-5 µg/litre. Chlorophenols can also be determined by gas chromatography with an electron-capture detector. The detection limits are 1-10 µg/litre for monochlorophenols, 0.5 µg/litre for dichlorophenols, and 0.01 µg/litre for trichlorophenols (1).

16.7.3 Environmental levels and human exposure

Water

Chlorophenols are present in drinking-water as a result of the chlorination of phenols during disinfection, as by-products of the reaction of hypochlorite with phenolic acids, as biocides, or as degradation products of phenoxy herbicides. Data from 40 Canadian treatment plants indicate that chlorophenol levels in drinking-water are generally quite low but vary considerably from one location to another (10). Chlorination increased the concentrations of 2-CP (maximum 65 ng/litre), 2,4-DCP (72 ng/litre), and 2,4,6-TCP (719 ng/litre). Drinking-water from the Ruhr area of Germany contained 2,4-DCP at 3B6 ng/litre and 2,4,6-TCP at 1 ng/litre (1). Several chlorophenols were present in Finnish tapwater at levels roughly one order of magnitude higher than those found in Germany (11).

16.7.4 Kinetics and metabolism in laboratory animals and humans

Chlorophenols are well absorbed after oral administration (12), and they readily penetrate the skin (13). Chlorophenols do not appear to accumulate in body tissues in rats but are rapidly metabolized and eliminated from the body (14-16). The major metabolite is the glucuronide conjugate of the parent chlorophenol. Less abundant metabolites include sulfate conjugates and possibly chloromethoxyphenol isomers of the parent compounds (12,14,16,17). Chlorophenols are readily excreted as glucuronide conjugates in urine and, to a lesser extent, faeces (12,16,18).

16.7.5 Effects on laboratory animals and *in vitro* test systems

2-Chlorophenol

Acute exposure

The oral LD₅₀ for 2-CP in mice was reported to be 670 mg/kg of body weight (19).

Long-term exposure

Immunological (e.g. humoral and cell-mediated immunity, macrophage function) and haematological (e.g. red and white blood cell count, haematocrit, haemoglobin) effects were assessed in groups of 12-20 weanling female Sprague-Dawley rats exposed to 0, 5, 50, or 500 mg of 2-CP per litre in drinking-water (0, 0.5, 5, or 50 mg/kg of body weight per day) in a reproductive study. Females were exposed from 3 weeks of age until breeding at 90 days, and throughout gestation to parturition. No treatment-related differences

were found. A NOAEL of 50 mg/kg of body weight per day can be identified (15,20).

Reproductive toxicity, embryotoxicity, and teratogenicity

Groups of 12-20 weanling female Sprague-Dawley rats were exposed to 0, 5, 50, or 500 mg of 2-CP per litre in drinking-water (0, 0.5, 5, or 50 mg/kg of body weight per day) for 10 weeks, then bred. Treatment was continued during breeding, gestation, and weaning. Parameters evaluated included percentage conception, litter size, birth weight, number of stillbirths, weanling weight, and haematology in weanling rats. A treatment-related increase in conception rate, an increase in the number of stillbirths, and a decrease in the size of the litters were observed at the highest dose (15,21).

Carcinogenicity

In a 24-month experiment, female Sprague-Dawley rats (12-22 per dose) were given 2-CP in drinking-water at 0, 5, 50, or 500 mg/litre (0, 0.5, 5, or 50 mg/kg of body weight per day) for 10 weeks, then bred. Ethylurea and nitrite, precursors of the transplacental carcinogen nitrosoethylurea (NEU), were administered to females on days 14-21 of pregnancy. The effects on tumour incidence and latency were most evident in male progeny that received 2-CP with NEU, both pre- and postnatally. The lowest level of 2-CP appeared to exert the greatest effect. The authors suggested that 2-CP is a co-carcinogen (21).

2,4-Dichlorophenol

Acute exposure

The acute oral LD₅₀s for 2,4-DCP in rats ranged from 580 to 4000 mg/kg of body weight (22,23). Acute oral LD₅₀s were 1276 and 1352 mg/kg of body weight for male and female CD-1 mice, respectively (24).

Short-term exposure

CD-1 mice (20 per sex per dose) were exposed to 2,4-DCP in drinking-water for 90 days at concentrations of 0.2, 0.6, or 2.0 g/litre (mean daily doses of 50, 143, and 491 mg/kg of body weight for females and 40, 114, and 383 mg/kg of body weight for males). There were no significant differences in body weight gain and no differences in terminal organ weights or organ weight ratios. Haematological differences, namely an increase in leukocytes (high dose) and in polymorphonuclear leukocytes (low dose), were observed only in males. Changes in clinical chemistry parameters, namely a decrease in creatinine (low dose), an increase in BUN/creatinine ratios (mid-dose), and an increase in alkaline phosphatase (high dose), were significant in females. These changes were not consistently dose-related, and a LOAEL cannot be established (24).

ICR mice of both sexes were fed 2,4-DCP in the diet at 0, 0.05%, 0.1%, or 0.2% (0, 45, 100, or 230 mg/kg of body weight per day) for 6 months. Hyperplasia of hepatic cells was reported in one of seven animals receiving 0.2%. There were no other significant differences in histopathology, organ or body weight gains, red or white blood cell counts, or alanine aminotransferase and aspartate aminotransferase activities at any dose. The authors identified a NOAEL of 100 mg/kg of body weight per day (23).

Pre- and postnatal treatment of rats with 300 mg of 2,4-DCP per litre of drinking-water for 147 days significantly increased liver and spleen weights and enhanced humoral immune responsiveness. Cell-mediated immunity was depressed at 30 and 300 mg/litre. No histopathological changes were reported. Based on these findings, a NOAEL of 3 mg/litre (0.3 mg/kg of body weight per day) and a LOAEL of 30 mg/litre (3 mg/kg of body weight per day) can be identified (25).

Long-term exposure

Investigations of the effects of long-term exposure to 2,4-D have been designed primarily to test its

carcinogenic properties and are described below.

Reproductive toxicity, embryotoxicity, and teratogenicity

Administration of 2,4-DCP (0, 50, 150, or 500 mg/kg of body weight per day) in drinking-water to male CD-1 mice for 90 days had no effect on sperm motility or ability to penetrate ova (26). Exposure of female rats to 0, 3, 30, or 300 mg of 2,4-DCP per litre in drinking-water from 3 weeks of age throughout parturition and lactation had no significant effect on conception, litter size and weight, number of stillborn pups, or survival of weanlings continued on treatment for 5 weeks (25).

Mutagenicity and related end-points

2,4-DCP did not show mutagenic potential in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation (27). In eukaryotic test assays, 2,4-DCP was not mutagenic in primary hepatocyte cultures, as shown by the absence of unscheduled DNA synthesis (28).

Carcinogenicity

F344 rats and B6C3F₁ mice were given 2,4-DCP in feed for 2 years at dietary concentrations of 0, 5000, or 10 000 mg/kg (mice and male rats) and 0, 2500, or 5000 mg/kg (female rats) (male rats: 0, 210, or 440 mg/kg of body weight per day; female rats: 0, 210, or 250 mg/kg of body weight per day; male mice, 0, 800, or 1300 mg/kg of body weight per day; female mice, 0, 430, or 820 mg/kg of body weight per day). There was no evidence of carcinogenicity in either species. The maximum tolerated dose was probably reached, judging from the lower body weight in the treated animals, especially at the high dose. Survival was not affected in either species (29).

2,4,6-Trichlorophenol

Acute exposure

The oral LD₅₀ for 2,4,6-TCP has been reported as 820 mg/kg of body weight in rats (30).

Short-term exposure

2,4,6-TCP was mixed with corn oil and administered daily by gavage to Sprague-Dawley rats (10 per sex per dose) for 90 consecutive days at 0, 80, 240, or 720 mg/kg of body weight per day. At 240 mg/kg of body weight per day, liver weight increased in males and adrenal gland weight increased in females. At the highest dose, treatment-related effects included salivation, increased weights of the kidneys, liver, adrenal glands, and testes, and an increase in serum albumin, total protein, and serum alanine aminotransferase, as well as a decrease in urinary pH. No gross or histopathological changes were seen. In this study, a LOAEL of 240 mg/kg of body weight per day and a NOAEL of 80 mg/kg of body weight per day were identified (Bercz JP et al., unpublished data, 1989).

Long-term exposure

Female Sprague-Dawley rats (12-14 per dose) were exposed to 2,4,6-TCP in drinking-water at 0, 3, 30, or 300 mg/litre from 3 weeks of age and throughout breeding, gestation, parturition, and lactation. Ten pups from each dose group were weaned at 3 weeks and continued on treatment for 12-15 weeks. A dose-related increase in the liver weight of the pups reached statistical significance at 30 and 300 mg/litre. At 300 mg/litre, the spleen weight of the pups also increased significantly. No treatment-related changes in cell-mediated immunity, humoral immunity, or macrophage function were seen in the treated groups. In this study, a LOAEL of 30 mg/litre (3 mg/kg of body weight per day) and a NOAEL of 3 mg/litre (0.3 mg/kg of body weight per day) were identified (21).

F344 rats (50 per sex per dose) were given 2,4,6-TCP in their feed at 0, 5000, or 10 000 mg/kg (0, 250, or 500 mg/kg of body weight per day) for 106-107 weeks. Mean body weights of both dosed groups were lower than those of corresponding controls and were dose-related throughout the study. Other clinical signs were common to both the dosed and the control groups. There was no significant dose-related trend in mortality. In a similar experiment in B6C3F₁ mice, dose-related decreases in mean body weights were seen in male and female mice. Other clinical signs were common to both dosed and control groups. There was no statistically significant dose-related trend in mortality in either sex (30).

Reproductive toxicity, embryotoxicity, and teratogenicity

Sprague-Dawley rats were exposed to 2,4,6-TCP at 0, 30, or 300 mg/litre in drinking-water from 3 weeks of age to parturition. There were no statistically significant treatment-related effects on percentage conception, litter size, percentage stillborn, birth weight, and percentage survival to weaning (21).

Male Long-Evans hooded rats were given 2,4,6-TCP at 0 or 1000 mg/kg of body weight in corn oil by gavage, 5 days per week for 11 weeks (average 0 or 714 mg/kg of body weight per day), then bred with untreated females. No treatment-related effects were seen in copulatory behaviour, semen characteristics, organ weights, fertility, or fetal outcome. Female rats were given 0, 100, 500, or 1000 mg/kg of body weight by gavage, 5 days per week for 2 weeks prior to and during mating and up to day 21 of gestation. No treatment-related effects were reported in litter size or pup survival at the dose levels tested (31).

Mutagenicity and related end-points

Mutagenic activity was not detected in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation (27). 2,4,6-TCP showed weak but significant mutagenic activity in the MP-1 strain of *Saccharomyces cerevisiae* (32). There was no effect on mitotic crossing-over or mitotic gene conversion. Pregnant mice injected with 2,4,6-TCP displayed a slightly increased frequency of spotted coat in the offspring, indicative of weak mutagenic activity (32).

Carcinogenicity

Administration of 2,4,6-TCP to mice at 100 mg/kg of body weight for 72 weeks led to increases in the incidences of hepatomas and reticulum-cell sarcomas. However, the incidences were not statistically significant if males and females are considered separately or if matched controls are considered (33).

F344 rats and B6C3F₁ mice were administered 2,4,6-TCP (96-97% pure) in the feed for over 2 years. Rats and male mice received doses of 0, 5000, or 10 000 mg/kg of body weight and female mice received time-weighted average doses of 0, 5214, or 10 428 mg/kg of body weight. A statistically significant dose-related increase in the incidence of lymphomas or leukaemias was observed in male rats (3/20, 23/50, and 29/50 for control, low-, and high-dose groups, respectively). In addition, the combined incidence of hepatocellular carcinomas and adenomas was significantly increased as compared with controls in both male and female mice (30). The 2,4,6-TCP may have been contaminated with 1,3,6,8-tetrachlorodibenzo-p-dioxin (1,3,6,8-TCDD), which might also be capable of inducing liver tumours in mice but is not expected to induce leukaemias in male rats, as the 2,3,7,8-TCDD isomer does not appear to do so (34).

16.7.6 Guideline values

2-Chlorophenol

Because of the limited database on the toxicity of 2-CP, no health-based guideline value has been derived.

2,4-Dichlorophenol

Because the database for the toxicity of 2,4-DCP is limited, no health-based guideline value has been derived.

2,4,6-Trichlorophenol

2,4,6-TCP has been reported to induce lymphomas and leukemias in male rats and hepatic tumours in male and female mice. IARC has concluded that 2,4,6-TCP is possibly carcinogenic to humans (Group 2B) (35). The compound has not been shown to be mutagenic in the Ames test but has shown weak mutagenic activity in other *in vitro* and *in vivo* assays.

A guideline value can be derived for 2,4,6-TCP by applying the linearized multistage model to leukaemias in male rats observed in a 2-year feeding study (33). The hepatic tumours found in this study were not used for risk estimation, because of the possible role of contaminants in their induction. The concentrations of 2,4,6-TCP in drinking-water (and hence the guideline values) associated with 10^{-4} , 10^{-5} , and 10^{-6} excess lifetime cancer risks are 2000, 200, and 20 µg/litre, respectively.

The lowest reported taste threshold for 2,4,6-TCP is 2 µg/litre. If water containing this chlorophenol is free from taste, it is unlikely to present an undue risk to health.

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16.8 Formaldehyde

16.8.1 General description

Identity

CAS no.: 50-00-00

Molecular formula: CH₂O

The IUPAC name for formaldehyde is methanal.

Physicochemical properties (1-4)¹

¹ Conversion factor in air: 1 ppm = 1.2 mg/m³ at 25 °C

Property	Value
Physical state	Colourless gas
Boiling point	-19.2 °C
Melting point	-118 °C
Relative density	1.04 (air = 1)
Vapour pressure	52.6 kPa at -33 °C
Water solubility	Freely miscible at 25 °C
Log octanol-water partition coefficient	-1

Organoleptic properties

Formaldehyde has a pungent, suffocating, hay- or straw-like odour. Taste and odour thresholds are 50 and 25, respectively (3,4).

Major uses

Formaldehyde's main industrial use is in the production of urea-formaldehyde, phenolic, melamine, pentaerythritol, and polyacetal resins. Its second largest use is in the industrial synthesis of a number of organic compounds. It is also used in cosmetics, fungicides, textiles, and embalming fluids (1).

16.8.2 Analytical methods

Formaldehyde in drinking-water is generally determined by a high-performance liquid chromatographic method following derivatization with 2,4-dinitrophenylhydrazine and liquid-solid extraction. The detection limit is 6.2 µg/litre (5).

16.8.3 Environmental levels and human exposure

Air

Formaldehyde is emitted into air from plastics and resin glues. Low levels in air may also result from the photo-oxidation of hydrocarbons derived from fossil fuel. Typical levels in air are a few µg/m³. Smokers are exposed to high levels of formaldehyde (1,6,7).

Water

Formaldehyde in drinking-water is formed mainly by the oxidation of natural organic (humic) matter during ozonation (8) and chlorination (9). It also enters drinking-water via industrial effluents and leaching from polyacetal plastic fittings. Concentrations of up to 30 µg/litre have been found in ozonated drinking-water (10,11).

Food

Concentrations of formaldehyde ranging from 3 to 23 mg/kg have been reported in a variety of foods (6).

Estimated total exposure and relative contribution of drinking-water

The general population is exposed to formaldehyde mainly by inhalation, smokers receiving about 0.38 mg/day by this route (1,7). People are also exposed by ingesting contaminated drinking-water and food, and from the use of urea-formaldehyde foam in housing insulation, and of cosmetics containing formaldehyde.

16.8.4 Kinetics and metabolism in laboratory animals and humans

Ingested formaldehyde is readily absorbed by the gastrointestinal tract. In dermal studies, it was absorbed less readily in monkeys than in rats or guinea-pigs (12). It appears to be distributed mainly to muscle, lower levels being found in the intestines, liver, and other tissues (13).

Formaldehyde is rapidly oxidized to formic acid; the subsequent oxidation to carbon dioxide and water is slower in monkeys than in rats (14). Other metabolic products, such as *N,N*-bis(hydroxymethyl)urea and *N*-(hydroxymethyl)urea, have been reported in rats (15). Metabolites are eliminated in the urine, faeces, and expired air, the relative amounts depending on the route of administration (1,16,17).

16.8.5 Effects on laboratory animals and *in vitro* test systems

Acute exposure

Oral LD₅₀s of 800 and 260 mg/kg of body weight have been reported for the rat and guinea-pig, respectively (18).

Short-term exposure

In a 4-week study, Wistar rats (10 per sex per dose) received formaldehyde in drinking-water at doses of 0, 5, 25, or 125 mg/kg of body weight per day. Rats receiving the highest dose showed lowered food and liquid intake, histopathological changes in the stomach (i.e., focal hyperkeratosis of the forestomach, moderate papillomatous hyperplasia), and, in males only, lowered total protein and albumin levels in plasma. The NOAEL was 25 mg/kg of body weight per day (1,19).

Oral doses of 0, 50, 100, or 150 mg/kg of body weight per day in rats and 0, 50, 75, or 100 mg/kg of body weight per day in dogs for 91 days had no effect on haematology, clinical chemistry, urinalysis, or gross microscopic pathology. Depression in body weight gain was observed in both species at the highest dose levels and in male rats given 100 mg/kg of body weight per day (20).

Long-term exposure

In a 2-year study, Wistar rats were exposed to formaldehyde in drinking-water at mean doses of 0, 1.2, 15, or 82 mg/kg of body weight per day for males and 0, 1.8, 21, or 109 mg/kg of body weight per day for females. Adverse effects were observed only in animals receiving the highest dose and included lower food and liquid intake, lower body weights, and pathological changes in the stomach, characterized by thickening of the mucosal wall. Relative kidney weights were increased in high-dose females, and an increased incidence of renal papillary necrosis was found in both sexes. Exposure did not appear to affect survival, haematology, or clinical chemistry. The NOAEL was 15 mg/kg of body weight per day (21).

In a similar study, Wistar rats were given formaldehyde in drinking-water at 10, 50, or 300 mg/kg of body weight per day. At the end of 12 months, rats of both sexes in the high-dose group were observed to have gastric erosions, ulcers, squamous cell hyperplasia, hyperkeratosis, and basal cell hyperplasia. Only one male and one female from the mid-dose group showed hyperkeratosis (1,22).

Reproductive toxicity, embryotoxicity, and teratogenicity

No teratogenic effects were reported in mice given formaldehyde at oral doses of 0, 74, 148, or 185 mg/kg of body weight per day on days 6-15 of gestation (23). Growth and viability of neonates from mice given oral doses of 540 mg/kg of body weight per day on days 8-12 of gestation were unaffected (24). No effects on reproductive performance or on the health of offspring were observed in beagle dogs fed 0, 3.1, or 9.4 mg of formaldehyde per kg of body weight per day in their diet on days 4-56 after mating (25). Sperm abnormalities were observed in male rats given single oral doses of 100-200 mg/kg of body weight (26). Intraperitoneal injection of formaldehyde at 8 or 16 mg/kg of body weight per day for 10 days resulted in degeneration of testicular tissue, inhibition of spermatogenesis, and lowered male reproductive organ weights in rats (27).

Mutagenicity and related end-points

Formaldehyde has shown evidence of mutagenicity in prokaryotic and eukaryotic cells *in vitro*. It has also been shown to be genotoxic in *Drosophila melanogaster*. Formaldehyde binds readily to proteins, RNA, and single-stranded DNA to induce DNA-protein cross-links and breaks in single-stranded DNA. It reacts readily with macromolecules in cells, mainly at the point of exposure (28). *In vivo*, formaldehyde increases both DNA synthesis in rats (29) and the number of micronuclei and nuclear anomalies in epithelial cells in

rats (30).

Carcinogenicity

There is little evidence that formaldehyde is carcinogenic by the oral route. In a 2-year study in which Wistar rats were exposed to formaldehyde in drinking-water at mean doses of 0, 1.2, 15, or 82 mg/kg of body weight per day for males and 0, 1.8, 21, or 109 mg/kg of body weight per day for females, exposure did not appear to affect tumour incidence (21). In a 2-year study in which Sprague-Dawley rats were exposed to formaldehyde in drinking-water at dose levels of 0, 1, 5, 10, 50, 100, or 150 mg/kg of body weight per day, a dose-dependent increase in the incidence of leukaemia (mainly lymphoblastic) and lymphosarcoma was reported at dose levels of 5 mg/kg of body weight per day or greater. The increase in the incidence of gastrointestinal neoplasms was not dose-related. Tumours of this type were rare in historical controls and not detected in concurrent controls (31).

In a carcinogenicity study, a group of 10 rats was given drinking-water containing 0.5% formalin (0.2% formaldehyde) for 32 weeks. Histopathological changes were observed in the stomach, as well as neoplastic changes in the forestomach and papillomas. In addition, the authors reported evidence that formaldehyde had tumour-promoting activity. However, because of the presence of high levels of methanol in formalin, the usefulness of this information is limited (32). In another study, formaldehyde induced ornithine decarboxylase activity (an indication of tumour-promoting activity) in rats given a single oral formaldehyde dose of up to 100 mg/kg of body weight (29). There is no evidence that formaldehyde acts as a carcinogen or promoter when applied to mouse skin (33).

There is some evidence that inhalation exposure to formaldehyde causes cancer in rats and mice by irritating the nasal epithelium. Rats exposed to 17 mg of formaldehyde per m³, 6 h per day, 5 days per week for 2 years, exhibited an increased incidence of squamous cell carcinoma of the nasal cavity. Tumours were also noted in mice at the same level of exposure, but this species was less sensitive than the rat (34,35).

16.8.6 Effects on humans

Irritation and allergic contact dermatitis have been associated with exposure of the skin to formaldehyde at levels higher than those encountered in drinking-water (36). Its presence in some types of water filters has been associated with the occurrence of haemolytic anaemia in dialysis patients (1,37).

There is some evidence that formaldehyde is a carcinogen in humans exposed by inhalation. Epidemiological investigations of the mortality of factory workers following prolonged occupational exposure to formaldehyde showed a slight excess of lung cancer that was not related to formaldehyde exposure (2,38). An increase in the incidence of nasopharyngeal cancer was also noted but again did not appear to be related to formaldehyde (39).

16.8.7 Guideline value

Rats and mice exposed to formaldehyde by inhalation exhibited an increased incidence of carcinomas of the nasal cavity at doses that caused irritation of the nasal epithelium (34,35). Ingestion of formaldehyde in drinking-water for 2 years caused stomach irritation in rats (21,22). Papillomas of the stomach associated with severe tissue irritation were observed in one study (32).

On the basis of studies in which humans and experimental animals were exposed to formaldehyde by inhalation, IARC has classified formaldehyde in Group 2A (40). The weight of evidence indicates that formaldehyde is not carcinogenic by the oral route. A guideline value has been derived, therefore, on the basis of a TDI. A TDI of 150 µg/kg of body weight was calculated based on the NOAEL of 15 mg/kg of body weight per day in a 2-year study in rats (21), incorporating an uncertainty factor of 100 (for intra- and interspecies variation). No account was taken of potential carcinogenicity from the inhalation of

formaldehyde from various indoor water uses, such as showering. With an allocation of 20% of the TDI to drinking-water, the guideline value is 900 µg/litre.

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16.9 MX

16.9.1 General description

Identity

CAS no.: 77439-76-0
Molecular formula: $C_5H_3Cl_3O_3$

MX is the common name for 3-chloro-4-dichloromethyl-5-hydroxy-2(5H)-furanone.

Major uses

MX does not have any commercial uses.

Environmental fate

In drinking-water at normal pH, MX exists in the open-ring form, i.e. as (Z)-2-chloro-3-(dichloromethyl)-4-oxobutenoic acid.

16.9.2 Analytical methods

MX in drinking-water can be determined by first concentrating organics using XAD resins, followed by high-pressure liquid chromatography, capillary-column gas chromatography, and mass spectroscopy (1-3).

16.9.3 Environmental levels and human exposure

Water

MX is formed by the reaction of chlorine with complex organic matter in drinking-water and is present in the chlorinated effluents of pulp mills. It has been identified in chlorinated humic acid solutions and drinking-water in Finland, the United Kingdom and the USA, and was found to be present in 37 water sources at levels of 2-67 ng/litre (2,4). Five drinking-water samples from different Japanese cities contained MX at concentrations ranging from <3 to 9 ng/litre (5).

16.9.4 Kinetics and metabolism in laboratory animals and humans

At least 40% of a dose of MX administered by gavage to rats was absorbed, about 5% of it being recovered in the liver, muscle, skin, kidneys, and blood (6). It has been demonstrated that MX is a substrate for direct conjugation with glutathione *in vitro* and that glutathione-S-transferase enhances the reaction (7). Cumulative excretion of label in 48 h by male rats given ¹⁴C-labelled MX by gavage was about 34% in the urine and 47% in faeces (6). No parent compound was excreted in the urine from rats (8).

16.9.5 Effects in laboratory animals and *in vitro* test systems

Acute exposure

An acute oral LD₅₀ of 128 mg/kg of body weight per day has been estimated for mice (9).

Short-term exposure

MX in distilled water was administered to Swiss-Webster mice (5 per sex per dose) by gavage at 10, 20, 42, 88, or 184 mg/kg of body weight per day for 2 days. At 184 mg/kg of body weight per day, all animals died within 1 day following the second dose; enlarged stomachs and haemorrhagic areas of the forestomach were observed. At lower doses, no deaths occurred, no effects on body weight were noted during the 2-week observation period, and gross necropsy results were normal (9).

Mutagenicity and related end-points

MX was reported to be an extremely potent mutagen in *Salmonella typhimurium* strain TA100 without metabolic activation by the S9 fraction of rat liver homogenate. The responses were also positive but not as strong in strains TA92, TA97, TA98, TA102, and TA1535. No mutagenic response was found with TA1537. The addition of the S9 fraction dramatically decreased the responses of TA100, TA98, and TA1535 (9,10).

MX has been examined for genotoxic activity in cultured mammalian cells. In Chinese hamster ovary cells (CHO-K1), it induced significant increases in structural chromosomal aberrations with and without metabolic activation (9). It also induced DNA strand breaks in suspensions of rat hepatocytes, rat testicular cells and V79 Chinese hamster cells (11), but not micronuclei in mouse bone marrow *in vivo*, despite its relatively high clastogenic activity in mammalian cells *in vitro* (9).

Carcinogenicity

A skin tumour initiation-promotion assay was conducted in SENCAR mice (20-40 per dose). A single dose of MX was administered either topically in acetone or orally in distilled water at 5, 16, 28, or 50 mg/kg of body weight. Two weeks after treatment, 12-O-tetradecanoyl-phorbol-13-acetate (TPA) was applied topically three times per week for 30 weeks. At 24 weeks, no tumours were observed in animals receiving MX alone (topically or orally) without TPA promotion; results in topically treated animals with TPA promotion were similar to those in controls. In orally treated mice, both the tumour incidence and number of tumours per mouse were significantly elevated at 16 mg of MX per kg of body weight and above. Because of disparities in the tumour incidences for the topical and oral control groups, the data were

reanalysed at 28 weeks, when tumour incidence was significantly higher than for controls only in the group receiving 16 mg/kg of body weight. The authors concluded that these results require confirmation before MX can be considered to possess tumour-initiating activity when administered orally (4).

16.9.6 Conclusions

There are very limited data on the toxicity of MX. ¹⁴C-labelled MX is rapidly absorbed, and most of the radioactivity is excreted in the urine within 24-48 h. It is unlikely to be absorbed as the parent compound because of its high reactivity. MX is an extremely potent mutagen in some strains of *Salmonella typhimurium*, but the addition of liver extract dramatically reduces the response. It is only weakly active or inactive in short-term tests for genotoxicity *in vivo*. Available data are inadequate to permit a guideline value for MX to be established.

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16.10 Trihalomethanes

16.10.1 General description

Identity

Compound	CAS no.	Molecular formula
Bromoform	75-25-2	CHBr ₃
Dibromochloromethane (DBCM)	124-48-1	CHBr ₂ Cl
Bromodichloromethane (BDCM)	75-27-4	CHBrCl ₂
Chloroform	67-66-3	CHCl ₃

Trihalomethanes are halogen-substituted single-carbon compounds with the general formula CHX₃, where X may be fluorine, chlorine, bromine, or iodine, or a combination thereof. From the point of view of drinking-water contamination, only four members of the group are important, namely bromoform, DBCM, BDCM, and chloroform, the last of these being the one most commonly found. The IUPAC names of bromoform and chloroform are tribromomethane and trichloromethane, respectively.

Physicochemical properties (1-7)

Property	Bromoform¹	DBCM²	BDCM³	Chloroform⁴
Boiling point (°C)	149-150	119	90	61-62
Melting point (°C)	8.3	-	-57.1	-63.5
Density at 20 °C (g/cm ³)	2.90	2.38	1.98	1.48
Vapour pressure (kPa)	0.75 (25 °C)	2.0 (10 °C)	6.67 (20 °C)	26.7 (25 °C)
Water solubility (mg/litre)	3190 (30 °C)	1050 (30 °C)	3320 (30 °C)	7220 (25 °C)
Log octanol - water partition coefficient	2.38	2.08	1.88	1.97

¹ Conversion factor in air: 1 ppm = 10.34 mg/m³.

² Conversion factor in air: 1 ppm = 8.52 mg/m³.

³ Conversion factor in air: 1 ppm = 6.70 mg/m³.

⁴ Conversion factor in air: 1 ppm = 4.96 mg/m³.

Organoleptic properties

The odour threshold for bromoform in water is 0.3 mg/litre. Chloroform has a characteristic odour, with odour threshold values of 2.4 mg/litre in water and 420 mg/m³ in air (2, 7).

Major uses

Brominated trihalomethanes have been used as laboratory reagents, as chemical intermediates for the synthesis of organic compounds, and as fluids for mineral ore separation. They were formerly used as solvents for fats, waxes, and resins and as flame retardants. Bromoform has been used as a sedative and cough suppressant (8).

Chloroform is used mainly as the starting material in the manufacture of the refrigerant fluorocarbon-22. It is an important extraction solvent for resins, gums, and other products. Chloroform was previously used as an anaesthetic, but it has been replaced by safer materials.

Environmental fate

In air, brominated trihalomethanes may be degraded by photo-oxidative interaction with atmospheric

hydroxyl radicals; their typical atmospheric half-life is about 2 months (1, 9). Chloroform can be photo-oxidized in air with a half-life of 26-260 days (10).

Volatilization is a major transport process for trihalomethanes. Estimated volatilization half-lives from rivers and streams are 1 h to 24 days for bromoform, 0.7 h to 16 days for DBCM, and 0.5-24 h for BDCM (11, 12). Volatilization half-lives for chloroform are 1-2 days for ponds and rivers and 9-10 days for lakes (13, 14).

Under anaerobic conditions, brominated trihalomethanes are readily bio-degraded within days in the presence of methane-producing bacteria and under denitrifying and sulfate-reducing conditions (15, 16). Chloroform can be bio-degraded in groundwater with a half-life ranging from weeks to years (13). Hydrolysis of brominated trihalomethanes in aqueous media is very slow; estimated half-lives are 1000, 274, and 686 years for BDCM, DBCM, and bromoform, respectively (17). Based on partition coefficients, bioaccumulation of trihalomethanes in aquatic organisms may occur, but only to a limited degree (8, 13).

Chloroform is not strongly absorbed by soil or sediments (13). Brominated trihalomethanes are expected to be mobile in soil, based on their partition coefficients and data from percolation studies (8). Studies in aqueous media suggest that anaerobic biodegradation could be a major removal process in soil if volatilization is restricted. Chloroform can be biodegraded in soil with a half-life of 4-24 weeks (13).

16.10.2 Analytical methods

The preferred technique for the determination of trihalomethanes is gas chromatography, with detection by flame ionization, electron capture, or mass spectroscopy (18). The purge-and-trap gas chromatographic procedure is well suited to biological and environmental samples that are soluble in water; it has a detection limit of approximately 0.5 µg/litre (19). The detection limit for chloroform in biological materials (e.g. blood, tissue, and food) when the purge-and-trap technique is used is in the range 0.1 - 1 µg/kg (13).

16.10.3 Environmental levels and human exposure

Air

Ambient air concentrations at several urban locations in the USA averaged 37 ng/m³ for bromoform, 32 ng/m³ for DBCM, and 7.4 ng/m³ for BDCM (highest values reported were 0.73, 0.23, and 1.3 µg/m³, respectively). The maximum concentration of bromoform in the air sampled in Toronto (Canada) was 0.1 µg/m³ (54 samples) (20, 21). Typical background levels of chloroform in outdoor air in rural/remote, urban/suburban, and source-dominated areas are 0.02-0.2, 0.2-3.4, and 0.2-13 µg/m³, respectively (13, 22-24). Typical concentrations of chloroform in indoor air range from 0.07 to 3.6 µg/m³ (23, 25, 26).

Water

Trihalomethanes are generated principally as by-products of the chlorination of drinking-water. Hypochlorous acid oxidizes bromide ion to form hypobromous acid, which reacts with endogenous organic materials (e.g. humic or fulvic acids) to form brominated trihalomethanes (1). Chlorine reacts with the same organic substances in water to form chloroform. The amount of each trihalomethane formed depends on the temperature, pH, and chlorine and bromide ion concentrations (27). Trihalomethanes are rarely found in raw water but are often present in finished water (28, 29).

In a Canadian survey of the water supplies of 70 communities, the average concentrations of bromoform, DBCM, BDCM, and chloroform were 0.1, 0.4, 2.9, and 22.7 µg/litre, respectively (30). In a survey of 105 systems in the USA using surface water, bromoform was found in 14 supplies at <1.0 - 5.7 µg/litre (median 1.3 µg/litre), DBCM in 70 supplies at <0.5-45 µg/litre (median 3.2 µg/litre), and BDCM in 99 supplies at <0.5-62 µg/litre (median 8.2 µg/litre). In a survey of 315 systems using groundwater, bromoform was found in 81 supplies at <1.0-110 µg/litre (median 3.0 µg/litre), DBCM in 107 supplies at

<0.5-32 µg/litre (median 4.1 µg/litre), and BDCM in 104 supplies at <0.5-51 µg/litre (median 3.5 µg/litre) (31). Chloroform was found in 99.5% of finished drinking-water samples in two surveys in the USA at concentrations ranging from the detection limit to 311 µg/litre; in most samples, concentrations were between 32 and 68 µg/litre (32, 33).

Trihalomethanes can be found in chlorinated swimming pools, total concentrations ranging from 120 to 660 µg/litre (34). BDCM concentrations were about the same in saltwater as in freshwater pools (13-34 µg/litre) (35).

Food

BDCM is not a common food contaminant but has been found in trace amounts in some samples: 1.2 µg/kg in one dairy composite and 7 µg/kg in butter (36). Chloroform has been found in various foods, including seafood (3-180 µg/kg), dairy products (1-33 µg/kg), meat (1-4 µg/kg), oil and fat (2-10 µg/kg), beverages (0.4-18 µg/kg), fruit and vegetables (2-18 µg/kg), and bread (2 µg/kg) (37). Many drugs contain residual amounts of chloroform as a result of its use as a solvent or formation as a by-product in the manufacturing process (38).

Estimated total exposure and relative contribution of drinking-water

The major routes of exposure to trihalomethanes are via drinking-water and inhalation. If it is assumed that the average human intake of air is 20 m³/day, the average daily intake of chloroform by inhalation in urban areas can be estimated to be 4 - 68 µg. Indoor air contamination from such sources as volatilization from household uses of chlorinated water (e.g. showers, cleaning) probably contributes more to human exposure than outdoor air. It has been estimated that the ingestion of 2 litres of drinking-water per day by the average adult results in an exposure of 4-88 µg of chloroform (13).

16.10.4 Kinetics and metabolism in laboratory animals and humans

Available studies indicate that gastrointestinal absorption is high for all trihalomethanes, while chloroform is also rapidly and extensively absorbed through the lungs (39-42). Because of their high lipophilicity, accumulation is higher in tissues of high lipid content, including body fat, liver, and kidneys (41, 42).

In rats, trihalomethanes are oxidized by the hepatic cytochrome P-450 mixed-function oxidase system to trihalomethanols, which then decompose to yield highly reactive dihalocarbonyls (43, 44). The amount metabolized depends on the species, being higher in mice than in rats (39, 42). Under anaerobic conditions, chloroform is reduced by cytochrome P-450 to yield the dichloromethyl radical (45). As the reactive metabolites of trihalomethanes may be responsible for their toxicity or carcinogenicity (14), interspecies differences in metabolic patterns should be taken into account in the extrapolation of toxicity or carcinogenicity data from experimental animals to humans (46).

Excretion of unchanged compounds and carbon dioxide occurs primarily in exhaled air, only small amounts being excreted in urine (39, 42).

16.10.5 Effects on laboratory animals and *in vitro* test systems

Bromoform

Acute exposure

The oral LD₅₀s for bromoform administered in an aqueous vehicle to male and female mice were 1400 and 1550 mg/kg of body weight, respectively (47). For male and female rats given bromoform in corn oil, LD₅₀s were 1388 and 1147 mg/kg of body weight, respectively (48).

Short-term exposure

Bromoform was administered in drinking-water at levels of 0, 5, 50, 500, or 2500 mg/litre (0, 0.6, 7, 52, or 250 mg/kg of body weight per day) to Sprague-Dawley rats (20 per sex per dose) for 90 days. Mild to moderate histological changes in the liver and thyroid and a significant increase in the severity of hepatic lesions were observed at the highest dose, and lactate dehydrogenase activity was significantly reduced. Based on the observed liver effect, the NOAEL was 52 mg/kg of body weight per day (49).

Young adult rats (10 per sex per dose) were given bromoform by gavage in corn oil at doses of 0, 12, 25, 50, 100, or 200 mg/kg of body weight per day, 5 days per week for 13 weeks. Male and female mice were given doses of 0, 25, 50, 100, 200, or 400 mg/kg of body weight per day. Growth was not affected except at the highest dose in male mice, in which it was slightly suppressed. Male mice at the two highest dose levels showed "minimal to moderate" hepatocellular vacuolation in a few cells. Male rats showed a dose-related increase in hepatocellular vacuolation, which became statistically significant at 50 mg/kg of body weight per day. The NOAELs for hepatocellular vacuolation were 25 and 100 mg/kg of body weight per day in male rats and male mice, respectively (50).

Long-term exposure

The effect of feeding bromoform (microencapsulated and mixed in the diet) was evaluated in Wistar SPF rats (40 per sex) dosed for 2 years at 0.04%, 0.16%, or 0.65% (18, 71, or 480 mg/kg of body weight per day for males and 30, 120, or 870 mg/kg of body weight per day for females). Animals given the highest dose exhibited body weight depression; decreases in serum triglycerides, nonesterified fatty acids, glucose, and cholinesterase activity; elevated γ -glutamyl transpeptidase activity; and yellowing and roughening of the liver surface. Similar but less severe effects were seen in the mid-dose groups. Based on body weight depression and serum enzyme changes, the authors considered the NOAELs to be 18 and 30 mg/kg of body weight per day for male and female rats, respectively (51).

Rats of both sexes and female mice (50 per dose) were given bromoform by gavage in corn oil at doses of 100 or 200 mg/kg of body weight per day, 5 days per week for 2 years. Male mice received 50 or 100 mg/kg of body weight per day. Survival was reduced relative to controls in male rats in the high-dose group.

A dose-related suppression of growth was also noted in male rats, but female rats showed an adverse effect on growth only at the high dose level. Male mice at the lower dose showed no effect on growth, but female mice showed a slight suppression that was not clearly related to dose. Rats of both sexes and female mice showed a dose-related increased incidence of fatty change (or vacuolation) in the liver. An increased incidence of mild fatty changes was noted in both low-dose and high-dose female mice but not in male mice. The LOAEL was 100 mg/kg of body weight per day for hepatocellular vacuolation and suppression of weight gain in rats and female mice (50).

Reproductive toxicity, embryotoxicity, and teratogenicity

The effect of bromoform on fertility and reproduction was investigated in Swiss CD-1 mice (20 pairs per dose) dosed for 105 days at 0, 50, 100, or 200 mg/kg of body weight per day in corn oil by gavage. No apparent effect on fertility or reproduction (e.g. litters per pair, live pups per litter, pup body weights) was reported in either the parental or the F₁ generation, and a reproductive NOAEL of 200 mg/kg of body weight per day was identified (52).

Mutagenicity and related end-points

Bromoform was positive in the Ames test in *Salmonella typhimurium* strain TA100 without activation (53, 54) and negative or equivocal in strains TA1535 or TA1937 with and without activation (50). Bromoform gave positive results in the following assays: chromosomal aberration in CHO cells with activation (54)

and in mouse bone marrow cells *in vivo* (50), sister chromatid exchange in human lymphocytes (55), in CHO cells without activation (50), and in mouse bone marrow cells *in vivo* (50, 55), and gene mutation in mouse lymphoma cells (50). It was negative for sister chromatid exchange in CHO cells with activation (50), and results were equivocal in the micronucleus assay (50, 54).

Carcinogenicity

When bromoform (4, 48, or 100 mg/kg of body weight) was administered intraperitoneally to male strain A mice (20 per dose) 3 times per week for 8 weeks, and they were kept under observation for 16 additional weeks, an increased incidence of lung tumours was seen at the intermediate dose (56).

Groups of 50 male B6C3F₁ mice were given bromoform by gavage in corn oil at doses of 0, 50, or 100 mg/kg of body weight per day, 5 days per week for 105 weeks. Females received doses of 0, 100, or 200 mg/kg of body weight per day. No increase in tumours was reported in any tissue in any group. In a similar study, Fischer 344/N rats (50 per sex per dose) were also exposed to bromoform by gavage in corn oil at doses of 0, 100, or 200 mg/kg of body weight per day, 5 days per week for 105 weeks. Adenomatous polyps or adenocarcinoma (combined) of the large intestine (colon or rectum) were induced in three male rats given the highest dose and in eight female rats given the highest dose. The increase was considered to be significant, as these tumours are rare in control animals. On the basis of these data, it was concluded that there was "some evidence" of carcinogenic activity in male rats and "clear evidence" in female rats. There were no tumours in the control rats and one in a mid-dose female rat (50).

Dibromochloromethane

Acute exposure

The oral LD₅₀s for DBCM administered in an aqueous vehicle to male and female mice were 800 and 1200 mg/kg of body weight, respectively (47). LD₅₀s for male and female rats given the compound in corn oil were 1186 and 848 mg/kg of body weight, respectively (48).

Short-term exposure

DBCM was administered in drinking-water at levels of 0, 5, 50, 500, or 2500 mg/litre (0, 0.6, 7, 52, or 250 mg/kg of body weight per day) to Sprague-Dawley rats (20 per sex per dose) for 90 days. Mild to moderate histological changes in the liver and thyroid and a significant increase in the severity of hepatic lesions were observed at the highest dose. Based on the observed liver effect, the NOAEL was 52 mg/kg of body weight per day (49).

Fischer 344/N rats and B6C3F₁ mice (10 per sex per dose) were given DBCM by gavage in corn oil at dose levels of 0, 15, 30, 60, 125, or 250 mg/kg of body weight per day, 5 days per week for 13 weeks. The final body weights of rats that received 250 mg/kg of body weight were depressed. A dose-dependent increase in hepatic vacuolation was observed in male rats. Based on this hepatic effect, the NOAEL in rats was 30 mg/kg of body weight per day. Kidney and liver toxicity were observed in male and female rats and male mice at 250 mg/kg of body weight per day. Survival rates for treated animals and corresponding controls were comparable except in high-dose rats. Clinical signs in the treated animals and controls were comparable. Based on the renal and hepatic lesions, a NOAEL of 125 mg/kg of body weight per day was identified in mice (57).

Long-term exposure

The effect of feeding DBCM (microencapsulated and mixed in the diet) was evaluated in Wistar SPF rats (40 per sex) dosed for 2 years at 0.022%, 0.088%, or 0.35% (10, 39, or 210 mg/kg of body weight per day for males and 17, 66, or 350 mg/kg of body weight per day for females). Animals receiving the highest dose exhibited depressed body weight; decreases in serum triglycerides, nonesterified fatty acids,

glucose, and cholinesterase activity; elevated γ -glutamyl transpeptidase activity; and yellowing and roughening of the liver surface. Similar but less severe findings were present in the mid-dose groups. Based on the body weight depression and serum enzyme changes, the authors considered the NOAELs to be 10 and 17 mg/kg of body weight per day for male and female rats, respectively (51).

Rats (50 per sex per dose) were given DBCM by gavage in corn oil at 0, 40, or 80 mg/kg of body weight, 5 days per week for 104 weeks, and mice (50 per sex per dose) received 0, 50, or 100 mg/kg of body weight by gavage for 105 weeks. Survival in rats and female mice was comparable in all dose groups, whereas it was decreased in high-dose male mice. An overdosing accident at week 58 killed 35 male mice in the low-dose group, so this group was not evaluated further. Mean body weights of high-dose male rats and high-dose mice of both sexes were lower than those of the vehicle controls. The incidence of fatty metamorphosis of the liver was increased in male and female rats and female mice at both low- and high-dose levels. Male mice showed liver effects at the high dose. There was an increased incidence of kidney nephrosis in female rats and in male mice but not in male rats or female mice. Follicular cell hyperplasia of the thyroid occurred at increased incidence in female mice but not in males. Based on the hepatic lesions, LOAELs of 50 and 40 mg/kg of body weight per day for mice and rats, respectively, were identified (57).

Reproductive toxicity, embryotoxicity, and teratogenicity

In a multigeneration reproductive study, groups of 10 male and 30 female ICR mice were treated with DBCM in emulphor at 0, 0.1, 1.0, or 4.0 g/litre (0, 17, 171, or 685 mg/kg of body weight per day) in drinking-water for 35 days, then mated; subsequent re-matings occurred 2 weeks after weaning. The F₁ mice were treated with the same test solution for 11 weeks after weaning and then mated; re-mating occurred 2 weeks after weaning. At 17 mg/kg of body weight per day, there was only a slight depression in the body weight of the newborn pups in the F_{2b} generation. At 171 mg/kg of body weight per day, there was a significant decrease in female body weight and an increase in the occurrence of gross liver pathology of F₀ and F_{1b} mice; the lesions varied in severity from fat accumulation to distinct masses on the liver surface. Although not occurring in every generation, there were significant decreases in litter size, pup viability, postnatal body weight, and lactation index. At 685 mg/kg of body weight per day, the effects were of the same types but more severe. Body weight gain was significantly reduced in both males and females at the highest dose (685 mg/kg of body weight per day) and in females at the middle dose (171 mg/kg of body weight per day). Animals in both these groups exhibited enlarged livers with gross morphological changes. In addition, the gestation index, fertility, and survival of the F₁ generation were significantly reduced. Based on maternal toxicity and fetotoxicity, a NOAEL of 17 mg/kg of body weight per day was identified (58).

Mutagenicity and related end-points

DBCM was positive in the Ames test with *S. typhimurium* strain TA100 without activation (53, 54) but negative in strains TA98, TA1535, and TA1537 with or without activation (58). It gave positive results for chromosomal aberration in CHO cells with activation (54) and for sister chromatid exchange in human lymphocytes and mouse bone marrow cells *in vivo* (55); it was negative in the micro-nucleus assay (54).

Carcinogenicity

DBCM was administered to rats and mice (50 per sex per dose) in corn oil by gavage at doses of 0, 40, or 80 mg/kg of body weight per day for rats and 0, 50, or 100 mg/kg of body weight per day for mice, 5 days per week for 104-105 weeks. An overdose killed 35 of the 50 low-dose male mice, so that this group could not be used for the study of carcinogenicity. DBCM significantly increased the incidence of hepatocellular adenomas and the combined incidence of hepatocellular adenomas and carcinomas in high-dose female mice. The incidence of hepatocellular carcinomas was significantly increased in high-dose male mice; the combined incidence of hepatocellular adenomas and carcinomas was marginally significant by the life-table test but not by the incidental tumour test. DBCM did not produce an increased incidence of tumours in treated rats. There was "no evidence" of carcinogenic activity in male or female rats, "equivocal

evidence” of carcinogenicity in male mice, and “some evidence” of carcinogenicity in female mice under the conditions of this study (57).

Bromodichloromethane

Acute exposure

Oral LD₅₀s for BDCM administered in an aqueous vehicle to mice were 450 and 900 mg/kg of body weight for males and females, respectively (47). Male and female rats given the compound in corn oil had LD₅₀s of 916 and 969 mg/kg of body weight, respectively (48).

Short-term exposure

BDCM was administered in drinking-water at levels of 0, 5, 50, 500, or 2500 mg/litre (0, 0.6, 7, 52, or 250 mg/kg of body weight per day) to Sprague-Dawley rats (20 per sex per dose) for 90 days. Mild to moderate histological changes in the liver and thyroid and a significant increase in the severity of hepatic lesions were observed at the highest dose. Based on the observed liver effect, the NOAEL was 52 mg/kg of body weight per day (49).

Fischer 344/N rats and B6C3F₁ mice were given BDCM by gavage in corn oil 5 days per week for 13 weeks. Rats (10 per sex per dose) were given 0, 19, 38, 75, 150, or 300 mg/kg of body weight per day. Male mice (10 per dose) were given 0, 6.3, 12.5, 50, or 100 mg/kg of body weight per day, and female mice were given 0, 25, 50, 100, 200, or 400 mg/kg of body weight per day. Of the male and female rats that received the highest dose, 50% and 20% respectively died before the end of the study. None of the mice died. Body weights decreased significantly in male and female rats given BDCM at 150 and 300 mg/kg of body weight per day. Centrilobular degeneration of the liver was observed at 300 mg/kg of body weight per day in male and female rats and at 200 and 400 mg/kg of body weight per day in female mice. Degeneration and necrosis of the kidney were observed at 300 mg/kg of body weight per day in male rats and at 100 mg/kg of body weight per day in male mice. The NOAELs in rats were 75 and 150 mg/kg of body weight per day for body weight reduction and for hepatic and renal lesions, respectively. The NOAEL for renal lesions in mice was 50 mg/kg of body weight per day (59).

Long-term exposure

The effect of feeding BDCM (microencapsulated and mixed in the diet) was evaluated in Wistar SPF rats (40 per sex) dosed for 2 years at 0.014%, 0.055%, or 0.22% (6, 24, or 130 mg/kg of body weight per day for males and 11, 41, or 220 mg/kg of body weight per day for females). Animals receiving the highest dose exhibited depressed body weight; decreases in serum triglycerides, nonesterified fatty acids, glucose, and cholinesterase activity; elevated γ -glutamyl transpeptidase activity; and yellowing and roughening of the liver surface. Similar but less severe findings were present in the mid-dose groups. Based on the body weight depression and serum enzyme changes, the authors considered the NOAELs to be 6 and 11 mg/kg of body weight per day for male and female rats, respectively (51).

Groups of Fischer 344/N rats (50 per sex per dose) were given 0, 50, or 100 mg of BDCM per kg of body weight per day in corn oil by gavage 5 days per week for 102 weeks. Male B6C3F₁ mice (50 per dose) were given 0, 25, or 50 mg/kg of body weight per day, and female mice received 0, 75, or 150 mg/kg of body weight per day by gavage for 102 weeks. Renal cytomegaly was observed in male rats at 50 mg/kg of body weight per day and above and in male mice at 25 mg/kg of body weight per day and above. Fatty metamorphosis of the liver was observed in male and female rats at 50 mg/kg of body weight per day and above and in male mice at 25 mg/kg of body weight per day and above. Compound-related follicular cell hyperplasia of the thyroid was also observed in male and female mice. Survival was decreased in female mice only. Mean body weights were decreased at 100 mg/kg of body weight per day in rats and at 50 and 150 mg/kg of body weight per day in male and female mice, respectively. Based on the observed renal and liver effects, a LOAEL of 50 mg/kg of body weight per day was identified for rats. Based on the

observed renal, liver, and thyroid effects in male mice and thyroid effects in female mice, a LOAEL of 25 mg/kg of body weight per day was identified for mice (59).

Reproductive toxicity, embryotoxicity, and teratogenicity

A dose-related increased incidence in sternebral anomalies was reported in fetuses from groups of 9-15 pregnant rats exposed to BDCM in corn oil by gavage at doses of 0, 50, 100, or 200 mg/kg of body weight per day on days 6-15 of gestation. The authors interpreted the sternebral anomalies as evidence of a fetotoxic (rather than a teratogenic) effect. The LOAEL based on this fetotoxic effect was 50 mg/kg of body weight per day (60).

Mutagenicity and related end-points

BDCM was positive in the Ames test with *S. typhimurium* strain TA100 without activation (53, 54) but negative in strains TA98, TA1535, and TA1537 with or without activation (59). It induced gene mutations in mouse lymphoma cells with, but not without, activation (59). BDCM gave conflicting results for chromosomal aberration in CHO cells with and without activation (54, 59), positive results for sister chromatid exchange in human lymphocytes and in mouse bone marrow cells *in vivo* (55), and negative results for the micronucleus assay (54) and sister chromatid exchange in CHO cells (59).

Carcinogenicity

When BDCM (20, 40, or 100 mg/kg of body weight) was administered intra-peritoneally to male strain A mice (20 per dose) 3 times per week for 8 weeks, and they were kept under observation for 16 additional weeks, an increased incidence of lung tumours was seen at the highest dose (56).

Fischer 344/N rats (50 per sex per dose) were given BDCM in corn oil by gavage at 0, 50, or 100 mg/kg of body weight, 5 days per week for 102 weeks. Male B6C3F₁ mice (50 per dose) were given 0, 25, or 50 mg/kg of body weight per day by gavage, and females received 0, 75, or 150 mg/kg of body weight per day. BDCM caused a significant increase in tumours of the kidney in male mice, the liver in female mice, and the kidney and large intestine in male and female rats. In male mice, the incidences of tubular cell adenomas and the combined incidences of tubular-cell adenomas and adenocarcinomas of the kidneys were significantly increased at 50 mg/kg of body weight per day. In female mice, significant increases in hepatocellular adenomas occurred at 75 and 150 mg/kg of body weight per day, whereas hepatocellular carcinomas were significantly increased at 150 mg/kg of body weight per day. In male and female rats, the incidence of tubular cell adenomas, adenocarcinomas, and the combined incidence of adenomas and adenocarcinomas of the kidneys were significantly increased only at 100 mg/kg of body weight per day. Adenosarcomas of the large intestine were increased in male rats at both doses and in high-dose female rats. Adenomatous polyps were significantly increased in male rats in a dose-dependent manner but were present in females at the high dose only. Based on the data, it was concluded that, under the conditions of this study, there was "clear evidence" of carcinogenic activity for male and female mice and rats (59).

Chloroform

Acute exposure

Oral LD₅₀s in rats and mice for chloroform range from 908 to 2000 mg/kg of body weight (14).

Short-term exposure

Six-week-old male Osborne-Mendel rats (30 per dose) were given chloroform in drinking-water at 0, 20, 38, 58, 81, or 160 mg/kg of body weight per day (based on average weight and water intake) for 36, 60, or 90 days (61). A decrease in body weight was observed at the highest dose. No effects on percentage of kidney fat or serum biochemistry were observed, and gross and microscopic pathology findings were mild

and not dose-related.

A similar study was conducted on B6C3F₁ female mice (30 per dose) given chloroform in drinking-water at approximately 0, 32, 64, 97, 145, 290, or 436 mg/kg of body weight per day (61). Histologically, centrilobular fatty changes in the liver appeared to be treatment-related. There was a statistically significant increase in the percentage of liver fat at the highest dose. Based on fatty changes in the liver, a NOAEL of 290 mg/kg of body weight per day and a LOAEL of 436 mg/kg of body weight per day were identified.

Chloroform was administered to weanling SD rats (20 per dose) in drinking-water at approximately 0, 0.7, 6, 50, or 180 mg/kg of body weight per day (based on average body weight and water intake) (62). Increased mortality, decreased growth rate, and decreased food intake were reported at the highest dose. Mild to moderate liver and thyroid lesions were observed in all groups. However, after a 90-day recovery period, these effects were not significantly different from controls, except for the thyroid lesions in the highest-dose males. No significant changes were observed in the serum biochemical or haematological parameters. A NOAEL of 50 mg/kg of body weight per day was established, based on thyroid lesions and decreased growth.

Chloroform was administered by gavage to B6C3F₁ mice (10 per sex per dose) at doses of 60, 130, or 270 mg/kg of body weight per day for 90 days, either in corn oil or in 2% emulphor (63). When chloroform was given in corn oil, there was a significant increase in aspartate aminotransferase levels in both male and female mice at 270 mg/kg of body weight per day, as well as a significant degree of diffuse parenchymal degeneration and mild to moderate early cirrhosis. Significant pathological lesions were not observed in the mice receiving chloroform in 2% emulphor. The data suggest that administration of chloroform by gavage in corn oil results in more marked hepatotoxicity than administration of chloroform in an aqueous suspension. The study identified 270 mg/kg of body weight per day as a LOAEL for serum enzyme elevation and diffuse liver pathology when chloroform is given in corn oil and the same level as a NOAEL when chloroform is given in an aqueous vehicle.

Long-term exposure

Male and female SD rats (50 per dose) were dosed by gavage with chloroform in a toothpaste-based vehicle at 0 or 60 mg/kg of body weight per day, 6 days per week for 80 weeks. There was a marginal but consistent and progressive retardation of weight gain in both sexes. A decrease in plasma cholinesterase activity and a significant decrease in relative liver weight were seen in treated female rats. No other significant effects on the liver or kidney were observed. In this study, a LOAEL of 60 mg/kg of body weight per day, based on decreases in body weight, liver weight, and plasma cholinesterase activity, was identified (64).

Drinking-water containing chloroform at 600 or 1800 mg/litre (86 or 258 mg/kg of body weight per day) was administered to B6C3F₁ mice (35 per dose) for 24 or 52 weeks. The animals in the high-dose group showed a statistically significant decrease in mean body weight. Focal areas of cellular necrosis were found in the kidneys and liver of treated mice, and focal areas of hepatic lipid accumulation were seen in the high-dose mice. A NOAEL was not identified (65).

Chloroform was administered to Osborne-Mendel rats (50-330 per dose) and B6C3F₁ mice (50-430 per dose) at concentrations of 0, 200, 400, 900, or 1800 mg/litre in drinking-water for 23 months. The time-weighted average doses were 0, 19, 38, 81, and 160 mg/kg of body weight per day for rats and 0, 34, 65, 130, and 263 mg/kg of body weight per day for mice. Although various blood chemistry and haematological parameters differed significantly from the control values at some time points, these parameters were not significantly different from those of matched controls with identical water consumption, and the authors concluded that the effects of chloroform were probably secondary to those of reduced water and food consumption. There was increased mortality in the two highest dose groups for mice. The percentage of fat in the mouse liver was significantly increased in the two highest dose groups

at 6 months. A NOAEL was not established (66).

Chloroform was administered to beagle dogs (12-15 per dose) in a toothpaste base in gelatin capsules at dose levels of 15 or 30 mg/kg of body weight per day for 7.5 years. The most significant effect was the formation of hepatic "fatty cysts" and nodules of altered hepatocytes at both doses. There was also a moderate rise in serum enzyme (e.g. alanine aminotransferase) levels, which reached a peak in the sixth year of the study. Based on the increased alanine aminotransferase levels and increased frequency of fatty cysts, a LOAEL of 15 mg/kg of body weight per day was identified in this study (67).

Reproductive toxicity, embryotoxicity, and teratogenicity

Rats were given chloroform at doses of 0, 20, 50, or 126 mg/kg of body weight per day by gavage in corn oil on days 6-15 of gestation. Dams (25 per dose) receiving 50 or 126 mg/kg of body weight per day displayed signs of maternal toxicity (decreased weight gain, mild fatty changes in the liver). Reduced body weights were seen in the fetuses from dams dosed at the highest level. There was, however, no evidence of teratogenicity. The maternal and fetal NOAELs were 20 and 50 mg/kg of body weight per day, respectively (68).

In a similar study in rabbits, dams were dosed by gavage with chloroform at 0, 20, 35, or 50 mg/kg of body weight per day on days 6-18 of gestation. Maternal toxicity (decreased weight gain) was observed in dams given 50 mg/kg of body weight per day. Fetuses from dams (15 per dose) given 20 or 50 mg/kg of body weight per day had slightly reduced body weights. An increased incidence of incompletely ossified skull bones (usually parietals) was observed at 20 and 35 mg/kg of body weight per day. The authors did not consider these effects to be evidence of teratogenicity or fetotoxicity. The maternal NOAEL identified in this study was 35 mg/kg of body weight per day (68).

Mutagenicity and related end-points

Chloroform was not mutagenic in several Ames bacterial test systems with or without microsomal activation (53, 69, 72). However, positive responses were observed in a host-mediated assay in male mice (71), a sex-linked recessive lethal test in *Drosophila* (70), an assay utilizing yeast (72), and a sperm-head abnormality assay in mice (73).

Carcinogenicity

Osborne-Mendel rats (50 per sex per dose) were treated with chloroform in corn oil, 5 days per week for 78 weeks. Male rats received 90 or 180 mg/kg of body weight per day; females were treated with 125 or 250 mg/kg of body weight per day for 22 weeks and 90 or 180 mg/kg of body weight per day thereafter. Lower body weight gain and survival were observed in all treated groups. The most significant observation was a dose-related increase in renal epithelial tumours of tubular-cell origin in male rats. There was an increase in thyroid tumours in female rats, but this was not considered biologically significant by the authors (74).

B6C3F₁ mice (50 per sex per dose) were given chloroform in corn oil by gavage, 5 days per week for 78 weeks. For the first 18 weeks, dose levels were 100 or 200 mg/kg of body weight per day for males and 200 or 400 mg/kg of body weight per day for females; they were then raised to 150 or 300 mg/kg of body weight per day for males and 250 or 500 mg/kg of body weight per day for females for the rest of the study. Survival rate and weight gain were similar in all treated groups, except for an increase in lesions (including tumours) that tended to shorten the lives of the high-dose female mice. Statistically significant dose-related increases in hepatocellular carcinomas were observed in all treated groups. Nodular hyperplasia of the liver was observed in many male mice that had not developed hepatocellular carcinomas (74).

Male Osborne-Mendel rats (50 - 330 per dose) and female B6C3F₁ mice (50 - 430 per dose) were given

chloroform in drinking-water at levels of 0, 200, 400, 900, or 1800 mg/litre (average dose 0, 19, 38, 81, or 160 mg/kg of body weight per day in rats and 0, 34, 65, 130, or 263 mg/kg of body weight per day in mice) for 104 weeks. The incidence of renal tubular adenomas and adenocarcinomas in male rats was increased in a dose-related manner (14% in the highest-dose group compared with 2% in the control group). In the female B6C3F₁ mice, there was no statistically significant increase in the incidence of hepatocellular carcinomas (66).

It is important to note that chloroform in corn oil at a dose of 250 mg/kg of body weight per day promoted the development of liver tumours in B6C3F₁ mice (74), whereas in drinking-water at 263 mg/kg of body weight per day it failed to induce such tumours in the same strain of mice (66). This may be due either to the toxicokinetic difference between the administration of chloroform as a bolus dose by gavage in corn oil as compared with continuous dosing in water or, alternatively, a synergistic interaction between chloroform and corn oil (74).

16.10.6 Effects on humans

In the past, orally administered bromoform was used as a sedative for children with whooping cough. Typical doses were around 180 mg, given 3-6 times per day. Deaths as a result of accidental overdose were occasionally reported. The clinical signs in fatal cases were central nervous system depression followed by respiratory failure (75, 76). Based on these clinical observations, the estimated lethal dose for a child weighing 10-20 kg is probably about 300 mg/kg of body weight, and the LOAEL for mild sedation is around 54 mg/kg of body weight per day.

Chloroform is a central nervous system depressant and can also affect liver and kidney function. Based on case reports, the mean lethal oral dose for humans was estimated at approximately 44 g (77), but a fatal dose may be as small as 211 mg/kg of body weight, death being caused by respiratory or cardiac arrest (14). Workers exposed to chloroform by inhalation at levels of 112-1158 mg/m³ for one or more years complained of nausea, lassitude, dry mouth, flatulence, thirst, depression, irritability, and scalding urination (78). Workers inhaling chloroform at levels of 10-1000 mg/m³ for 1-4 years had an increased incidence of viral hepatitis and enlarged liver (79).

In several epidemiological studies (80, 81), associations between the ingestion of chlorinated drinking-water (which typically contains trihalomethanes) and increased cancer mortality rates have been reported. In one study (82), there was an apparent association between bladder cancer and trihalomethanes, and a higher degree of correlation was noted with the brominated trihalomethanes than with chloroform. However, as chlorinated water contains many by-products, it is not possible from these epidemiological studies to conclude that brominated trihalomethanes are human carcinogens. In another study, no apparent association was found between chloroform ingested in drinking-water and risk of colorectal cancer (83).

16.10.7 Guideline values

The trihalomethanes may act as an indicator for the presence of other chlorination by-products. Control of the four most commonly occurring trihalomethanes in drinking-water should help to reduce levels of other uncharacterized chlorination by-products.

Because these four compounds usually occur together, it has been the practice to consider total trihalomethanes as a group, and a number of countries have set guidelines or standards on this basis. In the first edition of the *Guidelines for drinking-water quality*, a guideline value was established for chloroform only; few data existed for the remaining trihalomethanes and, for most water supplies, chloroform was the most commonly encountered member of the group. In this edition, no guideline value has been set for total trihalomethanes; however, guideline values have been established separately for all four trihalomethanes.

For authorities wishing to establish a total trihalomethane standard to account for additive toxicity, the following fractionation approach could be taken:

$$\frac{C_{\text{bromoform}}}{GV_{\text{bromoform}}} + \frac{C_{\text{DBCM}}}{GV_{\text{DBCM}}} + \frac{C_{\text{BDCM}}}{GV_{\text{BDCM}}} + \frac{C_{\text{chloroform}}}{GV_{\text{chloroform}}} \leq 1$$

where C = concentration and GV = guideline value.

Authorities wishing to use a guideline value for total trihalomethanes should not simply add up the guideline values for the individual compounds in order to arrive at a standard, because the four compounds are basically similar in toxicological action.

In controlling trihalomethanes, a multistep treatment system should be used to reduce organic trihalomethane precursors, and primary consideration should be given to ensuring that disinfection is never compromised.

Bromoform

In a bioassay carried out by the National Toxicology Program (NTP) in the USA, bromoform induced a small increase in relatively rare tumours of the large intestine in rats of both sexes but did not induce tumours in mice. Data from a variety of assays on the genotoxicity of bromoform are equivocal. IARC has classified bromoform in Group 3.

A TDI was derived on the basis of a NOAEL of 25 mg/kg of body weight per day for the absence of histopathological lesions in the liver in a well-conducted and well-documented 90-day study in rats (50). This NOAEL is supported by the results of two long-term studies. The TDI is 17.9 µg/kg of body weight, correcting for exposure on 5 days per week and using an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for possible carcinogenicity and the short duration of the study). With an allocation of 20% of the TDI to drinking-water, the guideline value is 100 µg/litre (rounded figure).

Dibromochloromethane

In an NTP bioassay, DBCM induced hepatic tumours in female and possibly in male mice but not in rats. The genotoxicity of DBCM has been studied in a number of assays, but the available data are considered inconclusive. IARC has classified DBCM in Group 3.

A TDI was derived on the basis of a NOAEL of 30 mg/kg of body weight per day for the absence of histopathological effects in the liver in a well-conducted and well-documented 90-day study in rats (57). This NOAEL is supported by the results of long-term studies. The TDI is 21.4 µg/kg of body weight, correcting for exposure on 5 days per week and using an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the short duration of the study). An additional uncertainty factor for potential carcinogenicity was not applied because of the questions regarding mouse liver tumours from corn oil vehicles and inconclusive evidence of genotoxicity. With an allocation of 20% of the TDI to drinking-water, the guideline value is 100 µg/litre (rounded figure).

Bromodichloromethane

In an NTP bioassay, BDCM induced renal adenomas and adenocarcinomas in both sexes of rats and male mice, rare tumours of the large intestine (adenomatous polyps and adenocarcinomas) in both sexes of rats, and hepatocellular adenomas and adenocarcinomas in female mice. BDCM has given both positive and negative results in a variety of *in vitro* and *in vivo* genotoxicity assays. IARC has classified bromodichloromethane in Group 2B (84).

Cancer risks have been estimated on the basis of increases in incidence of kidney tumours in male mice observed in the NTP bioassay (59), as these tumours yield the most protective value. Hepatic tumours in female mice were not considered owing to the possible role of the corn oil vehicle in their induction, although the estimated risks are within the same range. Using the linearized multistage model, the range of concentrations of BDCM in drinking-water associated with excess lifetime cancer risks of 10^{-4} , 10^{-5} , and 10^{-6} for kidney tumours are 600, 60, and 6 µg/litre, respectively. These values are supported by a recently published feeding study in rats that was not available for full evaluation.

Chloroform

IARC has classified chloroform in Group 2B as a possible human carcinogen (85). In long-term studies, chloroform has been shown to induce hepatocellular carcinomas in mice when administered by gavage in oil-based vehicles but not in drinking-water; it has been reported to induce renal tubular adenomas and adenocarcinomas in male rats regardless of the carrier vehicle. Chloroform has been studied in a wide variety of genotoxicity assays and has been found to give both positive and negative results.

The guideline value is based on extrapolation of the observed increase in kidney tumours in male rats exposed to chloroform in drinking-water for 2 years (66), although it is recognized that chloroform may induce tumours through a non-genotoxic mechanism. Using the linearized multistage model, concentrations of chloroform in drinking-water of 2000, 200, and 20 µg/litre were calculated to correspond to excess lifetime cancer risks of 10^{-4} , 10^{-5} , and 10^{-6} , respectively. The guideline value associated with an excess lifetime cancer risk of 10^{-5} is also supported by a 7.5-year study in dogs, in which a LOAEL of 15 mg/kg of body weight per day was observed for liver effects (applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for the use of a LOAEL) and allocating 50% of the TDI to drinking-water).

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Other chlorination by-products

A number of oxidation by-products are formed when chlorine reacts with organic materials, such as humic or fulvic acids, present in water as a result of the degradation of animal or plant matter. The following chlorination by-products are dealt with in this section: chlorinated acetic acids, trichloroacetaldehyde, chloroacetones, halogenated acetonitriles, cyanogen chloride, and chloropicrin.

16.11 Chlorinated acetic acids

16.11.1 General description

Identity

<i>Compound</i>	<i>CAS no.</i>	<i>Molecular formula</i>
Monochloroacetic acid	79-11-8	ClCH ₂ COOH
Dichloroacetic acid	79-43-6	Cl ₂ CHCOOH
Trichloroacetic acid	76-03-9	Cl ₃ CCOOH

The IUPAC names for these compounds are mono-, di- and trichloroethanoic acid, respectively.

Physicochemical properties (1-3)

Property	Monochloroacetic acid¹	Dichloroacetic acid²	Trichloroacetic acid³
Boiling point (°C)	187.8	194	197.5
Melting point (°C)	52.5	13.5	-
Density (g/cm ³)	1.58 at 20 °C	1.56 at 20 °C	1.63 at 61 °C
Vapour pressure (kPa)	0.133 at 40 °C	0.133 at 44 °C	0.133 at 51 °C
Water solubility (g/litre)	Very soluble	86.3	13
Log octanol-water partition coefficient	-	0.14	0.10

¹ Conversion factor in air: 1 ppm = 3.87 mg/m³.

² Conversion factor in air: 1 ppm = 5.27 mg/m³.

³ Conversion factor in air: 1 ppm = 6.68 mg/m³.

Organoleptic properties

No information is available on the odour thresholds of chlorinated acetic acids in water.

Major uses

Monochloroacetic acid is used as an intermediate or reagent in the synthesis of a variety of chemicals and as a pre-emergence herbicide. Dichloroacetic acid is used as a chemical intermediate in the synthesis of organic materials, as an ingredient in pharmaceuticals and medicines, as a topical astringent, and as a fungicide. Trichloroacetic acid is used as an intermediate in the synthesis of organic chemicals, and as a laboratory reagent, herbicide, soil sterilizer, and antiseptic (2-5).

16.11.2 Analytical methods

The chloroacetic acids can be determined by either EPA Method 515.1 or draft EPA Method 552, which was developed for non-pesticidal haloacids and phenols, i.e. by capillary column/electron capture/gas chromatography. Data from a monitoring study of water supplies indicate that detection levels of 1 µg/litre are achievable.

16.11.3 Environmental levels and human exposure

Water

Chlorinated acetic acids are formed from organic material during water chlorination (6); typical levels in finished drinking-water supplies range from 30 to 160 µg/litre (7). Limited data for drinking-water supplies in the USA indicate that monochloroacetic acid is generally present at concentrations of less than 1.2 µg/litre (8); it was detected in the finished water at six of 10 sites at levels below 10 µg/litre. Dichloroacetic acid was found in the distribution systems of six water-supply companies at concentrations ranging from 8 to 79 µg/litre; it was detected in the finished water of 10 of 10 companies surveyed and at levels of 10 µg/litre or higher at eight of them. Trichloroacetic acid was found in the distribution systems of six companies at concentrations ranging from 15 to 103 µg/litre; it was detected in finished water at six of 10 companies at concentrations of 10-100 µg/litre (four sites) and less than 10 µg/litre (two sites) (9).

16.11.4 Kinetics and metabolism in laboratory animals and humans

Monochloroacetic acid

In rats given monochloroacetate subcutaneously, levels in liver and kidney were approximately the same and 4-5 times higher than those in plasma, brain, and heart. Approximately 50% of the dose was excreted

in the urine within 17 h. Monochloroacetic acid is metabolized to oxalate and glycine. It can also be conjugated with glutathione, phospholipids, and cholesterol. The glutathione conjugate degrades to thiodiacetic acid (10,11).

Dichloroacetic acid

Plasma dichloroacetic acid concentrations peaked in rats 30 min after dosing by gavage, suggesting rapid intestinal absorption (12). Levels in liver and muscle increased following administration (13). In rats, dogs, and humans given sodium dichloroacetate intravenously, average half-lives of the parent compound in the plasma were 2.97, 20.8, and 0.43 h, respectively; the apparent dose dependence of plasma clearance suggests that metabolic transformation becomes rate-limiting at high doses (14). In the rat, dichloroacetate is rapidly metabolized by dechlorination to glyoxalate, which in turn is metabolized to oxalate (15). In humans, urinary excretion of unchanged dichloroacetate was negligible after 8 h, and cumulative excretion was less than 1% of the total dose in all subjects (14).

Trichloroacetic acid

Trichloroacetic acid appears to be rapidly absorbed from the intestinal tract, metabolism occurring mainly in the liver. It can be converted into carbon dioxide and chloride ion or reduced to the aldehyde. A comparatively small proportion of trichloroacetic acid is metabolized, much of this compound being excreted unchanged in the urine (16,17).

16.11.5 Effects on laboratory animals and *in vitro* test systems

Monochloroacetic acid

Acute exposure

The acute oral LD₅₀s for monochloroacetic acid in mice, male rats, and male guinea-pigs were estimated to be 255, 76, and 80 mg/kg of body weight, respectively (18). In other studies, oral LD₅₀s in mice were found to be 165 mg/kg of body weight (19) and 260 mg/kg of body weight (20). In rats, an oral LD₅₀ of 2820 mg/kg of body weight in males and a dermal LD₅₀ of 8068 mg/kg of body weight were reported (21).

Short-term exposure

Mice (20 per sex per dose) received monochloroacetic acid by gavage at 0, 25, 50, 100, 150, or 200 mg/kg of body weight per day for 13 weeks. Mortality was increased at the highest dose, and females in this group experienced decreased weight gain and increased absolute and relative liver weights. Cholinesterase levels were decreased in females at 150 and 200 mg/kg of body weight per day. The NOAEL was 100 mg/kg of body weight per day for decreased cholinesterase levels (22).

In rats (20 per sex per dose) that received monochloroacetic acid by gavage at 0, 30, 60, 90, 120, or 150 mg/kg of body weight per day for 13 weeks, effects were seen at every dose level. At 90 mg/kg of body weight per day and above, they included accumulations of mononuclear inflammatory cells and myofibre degeneration, elevated blood levels of thyroxin and segmented neutrophils, and increased blood urea nitrogen levels in males. At 60 mg/kg of body weight per day and above, effects included decreased survival, decreased absolute and relative heart weights, degenerative and inflammatory changes (cardiomyopathy), elevated alanine and aspartate aminotransferases, increased actual liver weight and relative kidney weight in males, and increased blood urea nitrogen levels in females. At 30 mg/kg of body weight per day and above, effects included decreased lymphocyte counts and decreased relative heart weight in females. The LOAEL for this study was the lowest dose tested, 30 mg/kg of body weight per day (22).

Long-term exposure

F344/N rats (70 per sex per dose) received monochloroacetic acid by gavage at doses of 0, 15, or 30 mg/kg of body weight per day, 5 days per week for 2 years. No effects on body weight or clinical findings were observed. However, survival was significantly decreased in male rats at 30 mg/kg of body weight per day and in female rats in both dose groups. The incidence of uterine polyps was marginally (nonsignificantly) increased in females at both doses. The LOAEL for this study was 15 mg/kg of body weight per day for reduced survival (22).

In the same study, B6C3F₁ mice (60 per sex per dose) were dosed with monochloroacetic acid at 0, 50, or 100 mg/kg of body weight per day, 5 days per week for 2 years. Effects were seen only at the highest dose and included decreased survival in males, decreased mean body weight and metaplasia of the olfactory epithelium in females, and inflammation of the nasal mucosa and squamous hyperplasia of the forestomach in both sexes. The NOAEL for this study was 50 mg/kg of body weight per day (22).

Mutagenicity and related end-points

Monochloroacetic acid was positive in the mouse lymphoma cell forward mutation assay without metabolic activation (23). It was positive without, and negative with metabolic activation in the sister chromatid exchange assay in Chinese hamster ovary (CHO) cells. In the in vitro chromosomal aberration assay in CHO cells, monochloroacetic acid was negative both with and without metabolic activation (24).

Carcinogenicity

There was no evidence of carcinogenic activity in 2-year bioassays using F344/N rats and B6C3F₁ mice. Rats (70 per sex per dose) received monochloroacetic acid by gavage at 0, 15, or 30 mg/kg of body weight per day, and mice (60 per sex per dose) received 0, 50, or 100 mg/kg of body weight per day (22).

Dichloroacetic acid

Acute exposure

LD₅₀s of 4480 and 5520 mg of dichloroacetic acid per kg of body weight have been reported in rats and mice, respectively (18).

Short-term exposure

In a study in which Sprague-Dawley rats (5 per sex per group) were given water containing 0, 30, 125, 500, or 1875 mg of dichloroacetate per litre (0, 2.4, 10, 40, or 150 mg/kg of body weight per day) for 14 days, none of the parameters monitored (e.g. body weight, lactate and pyruvate levels, blood glucose levels) was significantly altered. In this study, a NOAEL of 150 mg/kg of body weight per day was identified (25).

In a study in which sodium dichloroacetate was administered to Sprague-Dawley rats (10 per sex per dose) by gavage at dose levels of 0, 125, 500, or 2000 mg/kg of body weight per day for 3 months, body weight gain was significantly depressed in a dose-dependent manner at all dose levels. Minimal effects on haematological parameters were observed at the two highest doses. Mean relative weights of liver, kidneys, and adrenals were significantly increased in a dose-dependent fashion. Brain and testes were the principal target organs; brain lesions characterized by vacuolation of the myelinated white tracts resembling oedema were observed in the cerebrum and cerebellum of treated rats of both sexes in all dose groups. Based on effects on organ weights and brain lesions, a LOAEL of 125 mg/kg of body weight per day, the lowest dose tested, was identified in this study (26,27).

Beagle dogs were given sodium dichloroacetate by capsule at 50, 75, or 100 mg/kg of body weight per

day for 13 weeks. Both sexes exhibited dose-dependent weight losses. All dose levels were associated with a progressive depression in erythrocyte counts, erythrocyte volume fraction (haematocrit), and haemoglobin levels. Mean blood glucose, lactate, and pyruvate levels were significantly reduced in all treated animals. There was an increased incidence of lung consolidation among treated dogs. Histopathological examination indicated that all treated dogs suffered slight to moderate vacuolation of white myelinated tracts in the cerebrum and to a lesser extent in the cerebellum. There was an increased incidence of haemosiderin-laden Kupffer's cells in the liver and cystic mucosal hyperplasia in the gallbladder at all dose levels. A LOAEL of 50 mg/kg of body weight per day can be identified from this study (26,27).

Long-term exposure

Male B6C3F₁ mice (50 per dose) received dichloroacetate in their drinking-water at 0, 0.05, 0.5, 3.5, or 5.0 g/litre (0, 7.6, 77, 410, or 486 mg/kg of body weight per day) for 60 weeks. Other groups of mice received dichloroacetate at 7.6 or 77 mg/kg of body weight per day for 75 weeks. In the highest-dose mice, water consumption was reduced to 60% of that of controls. Body weight was decreased at the two highest dose levels, and relative liver weight was increased at the three highest dose levels. An increase in kidney weight was seen only at 410 mg/kg of body weight per day. No effects were seen on testes or spleen weight. The NOAEL for the 60- and 75-week studies was 7.6 mg/kg of body weight per day (28).

Mutagenicity and related end-points

Dichloroacetic acid was reported to cause strand breaks in DNA when administered in vivo to rats and mice in one study (29) but not in a second study at higher doses (30).

Carcinogenicity

The carcinogenic potential of dichloroacetate was investigated in B6C3F₁ mice (50 males per dose) that received this compound in their drinking-water for 60 weeks at concentrations of 0, 0.05, 0.5, 3.5, or 5.0 g/litre (0, 7.6, 77, 410, and 486 mg/kg of body weight per day). Other groups of mice received dichloroacetate at 7.6 or 77 mg/kg of body weight per day for 75 weeks. Hyperplastic nodules were seen in 58% of the mice that received 410 mg/kg of body weight per day and in 83% of the mice that received 486 mg/kg of body weight per day. The incidences of hepatocellular adenomas were 100% and 80%, and those of hepatocellular carcinomas 67% and 83%, respectively. Incidences in the other dose groups were similar to those in controls (28).

The carcinogenic potential of dichloroacetic acid in mice was investigated in a complex regimen that included pretreatment with nitrosoethylurea (NEU) at various doses. Male B6C3F₁ mice were supplied with drinking-water containing 0, 2000, or 5000 mg of dichloroacetate per litre (0, 400, or 1000 mg/kg of body weight per day). Non-initiation protocols (without NEU) were used only at the high-dose level. The incidence of hepatocellular carcinomas was 0% in the control group (no NEU or dichloroacetic acid) and 81% at 1000 mg/kg of body weight per day (no NEU). With dichloroacetic acid and a low dose of NEU, the tumour incidences were 66-72% for the high and low doses. The authors concluded that dichloroacetic acid was carcinogenic at a dose of 1000 mg/kg of body weight per day without prior initiation (31).

Dichloroacetic acid exposure via drinking-water resulted in the induction of liver tumours in male B6C3F₁ mice. Groups of mice received dichloroacetic acid at 0, 1, or 2 g/litre (approximately 0, 137, or 295 mg/kg of body weight per day, based on the authors' calculations of total dose for each group) for 37 or 52 weeks. Hepatocellular carcinomas were seen only in 5 of 24 males (21%) that received the highest dose for 52 weeks (32).

Trichloroacetic acid

Acute exposure

The LD₅₀ for trichloroacetic acid was 3320 mg/kg of body weight in rats and 4970 mg/kg of body weight in mice (18).

Short-term exposure

Groups of male Sprague-Dawley rats were exposed to trichloroacetate in drinking-water at a concentration of 5000 mg/litre (about 312 mg/kg of body weight per day) for 10, 20, or 30 days. No treatment-related changes in body weight, organ weight, gross necropsy, or histopathology were found, and a short-term NOAEL of 312 mg/kg of body weight per day can be identified (33).

Six male Fischer 344 [CDF (F-344)/CrIBR] rats and eight male B6C3F₁ mice were given trichloroacetic acid by gavage at 500 mg/kg of body weight per day for 10 days. The mean liver-to-body-weight ratios were significantly increased in both species, but there was no effect on the mean kidney-to-body-weight ratio. Cyanide-insensitive palmitoyl coenzyme (CoA) oxidation was increased in both species. The LOAEL for liver effects identified in this study was 500 mg/kg of body weight per day for both rats and mice (34).

Male Sprague-Dawley rats (10 per dose) received trichloroacetic acid in their drinking-water at 0, 50, 500, or 5000 mg/litre (0, 4.1, 36.5, or 355 mg/kg of body weight per day) for 90 days. No effects were seen on body weight or actual weight of liver or kidneys. At the highest dose level, actual spleen weight was reduced and relative liver and kidney weights were increased. Liver effects seen at the high dose included increased hepatic peroxisomal beta-oxidation activity, focal hepatocellular enlargement, intracellular swelling, and glycogen accumulation. The NOAEL for this study was 36.5 mg/kg of body weight per day (35).

Dose-related increases in hepatic weight were associated with the administration of trichloroacetic acid in drinking-water at 0, 300, 1000, or 2000 mg/litre to male B6C3F₁ mice for 14 days. The effect was statistically significant at 1000 and 2000 mg/litre. The NOAEL was therefore 300 mg/litre or approximately 55 mg/kg of body weight per day (36).

Long-term exposure

Male Sprague-Dawley rats were exposed to trichloroacetate in drinking-water at concentrations of 0, 50, 500, or 5000 mg/litre (0, 2.89, 29.6, and 277 mg/kg of body weight per day at 6 months) for up to 12 months. No significant changes were detected in body weight, organ weight, gross necropsy, or histopathology during the experiment. A NOAEL of 277 mg/kg of body weight per day was identified in this study (33).

In a study in which B6C3F₁ mice received trichloroacetate at 0, 1, or 2 g/litre in drinking-water for 37 or 52 weeks, both absolute liver weights and liver-to-body-weight ratios in male and female mice were significantly increased in a dose-related manner relative to controls. The LOAEL in this study was 1 g/litre, or 178 mg/kg of body weight per day, based on the authors' calculations of total dose for each group (32).

Mutagenicity and related end-points

Trichloroacetic acid was not mutagenic in *Salmonella typhimurium* strain TA100 without metabolic activation (37). It gave positive results in three in vivo chromosomal aberration assays in mice: the bone marrow assay, the micronucleus test, and the sperm-head abnormality assay (38).

Carcinogenicity

Male B6C3F₁ mice received trichloroacetic acid at 0, 1, or 2 g/litre (approximately 0, 178, or 319 mg/kg of body weight per day, based on the authors' calculations of total dose for each group) in drinking-water for 37 or 52 weeks. An increase in the incidence of hepatocellular carcinomas was seen in males in both treated groups, but none was seen in any of the females (32).

The carcinogenic potential of trichloroacetic acid in mice was investigated in a complex regimen that included pretreatment with NEU at various doses for 61 weeks. Male B6C3F₁ mice were supplied with drinking-water containing trichloroacetate at 0, 2000, or 5000 mg/litre (0, 400, or 1000 mg/kg of body weight per day). Non-initiation protocols (without NEU) were used at the high-dose level only. The incidence of hepatocellular carcinomas was 0% in the controls (no NEU or trichloroacetic acid) and 32% at the highest dose level (no NEU). In both groups given trichloroacetic acid with a low dose of NEU, the tumour incidence was 48%. The authors concluded that trichloroacetic acid was carcinogenic at a dose of 1000 mg/kg of body weight per day without prior initiation (31).

The results of two short-term tests conducted in rats—the hepatic enzyme-altered foci bioassay and stimulation of peroxisomal-dependent palmitoyl-CoA oxidation in liver—suggest that trichloroacetic acid may possess weak promoting activity in the rat liver (33,39).

16.11.6 Effects on humans

Diabetic or hyperlipoproteinaemic patients received a daily oral dose of 3-4 g of dichloroacetate for 6-7 days. Some patients experienced mild sedation, but no other laboratory or clinical evidence of adverse effects was noted during or immediately after the treatment phase. Biochemical effects included significantly reduced fasting blood glucose levels, marked decreases in plasma lactate and alanine, significantly decreased plasma cholesterol levels, decreased triglyceride levels, elevated plasma ketone bodies, and elevated serum uric acid levels (40).

Daily oral doses of 50 mg of dichloroacetate per kg were administered to two young males to treat severe familial hypercholesterolaemia (41). In both patients, total serum cholesterol levels decreased significantly. No adverse clinical or laboratory signs were detected in one patient, but the second complained of tingling in his fingers and toes after 16 weeks. Physical examination revealed slight decreases in the strength of facial and finger muscles, diminished to absent deep tendon reflexes, and decreased strength in all muscle groups of the lower extremities. Electromyographic studies revealed denervation changes in foot and distal leg muscles. Mild slowing of conduction velocity was noted in both posterior tibial nerves, and no measurable response was obtained in the peroneal or sural nerves. Six months after discontinuation of the treatment the neuropathic effects had improved, although serum cholesterol levels returned to high levels (42).

16.11.7 Guideline values

Monochloroacetic acid

No evidence of carcinogenicity was found in a recent 2-year bioassay in rats and mice (22). Available toxicity data are considered insufficient for deriving a guideline value.

Dichloroacetic acid

In several bioassays, dichloroacetate has been shown to induce hepatic tumours in mice. No adequate data on genotoxicity are available. Because the evidence for the carcinogenicity of dichloroacetate is insufficient, a TDI of 7.6 µg/kg of body weight was calculated based on a study in which no effects were seen on the livers of mice exposed to dichloroacetate at 7.6 mg/kg of body weight per day for 75 weeks (28) and incorporating an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for

possible carcinogenicity). With an allocation of 20% of the TDI to drinking-water, the provisional guideline value is 50 µg/litre (rounded figure).

The guideline value is designated as provisional because the data are insufficient to ensure that the value is technically achievable. Difficulties in meeting a guideline value must never be a reason to compromise adequate disinfection.

Trichloroacetic acid

Trichloroacetate has been shown to induce tumours in the liver of mice. It has not been found to be mutagenic in in vitro assays, but has been reported to cause chromosomal aberrations.

Because the evidence for the carcinogenicity of trichloroacetate is restricted to one species, a TDI of 17.8 µg/kg of body weight was calculated based on a LOAEL of 178 mg/kg of body weight per day from a study in which increased liver weight was seen in mice exposed to trichloroacetate in drinking-water for 52 weeks (32) and incorporating an uncertainty factor of 10 000 (100 for intra- and interspecies variation and 100 for the use of a slightly less-than-lifetime study, use of a LOAEL rather than a NOAEL, and possible carcinogenicity). The NOAEL in a 14-day study for the same effect was one-third of the LOAEL in the 52-week study (36). Based on a 20% allocation of the TDI to drinking-water, the provisional guideline value is 100 µg/litre (rounded figure).

The guideline value is designated as provisional because of the limitations of the available toxicological database and because there are inadequate data to judge whether the guideline value is technically achievable. Difficulties in meeting the guideline value must never be a reason for compromising adequate disinfection.

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16.12 Chloral hydrate (trichloroacetaldehyde)

16.12.1 General description

Identity

Compound	CAS no.	Molecular formula
Trichloroacetaldehyde	75-87-6	Cl ₃ CCHO
Chloral hydrate	302-17-0	Cl ₃ CCH(OH) ₂

The IUPAC name for trichloroacetaldehyde is trichloroethanal.

Physicochemical properties (1-3)

Property	Trichloroacetaldehyde¹	Chloral hydrate²
Boiling point (°C)	97.8	96.3
Melting point (°C)	-57.5	57
Density at 20 °C (g/cm ³)	1.512	1.908
Water solubility (g/litre)	Freely soluble	8300 (25 °C)

¹ Conversion factor in air: 1 ppm = 6.03 mg/m³.

² Conversion factor in air: 1 ppm = 6.77 mg/m³.

Major uses

Hydrated trichloroacetaldehyde (chloral hydrate) is used as a sedative and hypnotic in human and veterinary medicine (3,4).

16.12.2 Analytical methods

Trichloroacetaldehyde and chloral hydrate are determined by draft EPA Method 551, i.e. by capillary column/electron-capture/gas chromatography. Monitoring data indicate that a quantitation limit of 0.4 µg/litre is achievable for chloral hydrate.

16.12.3 Environmental levels and human exposure

Water

Trichloroacetaldehyde may enter water from industrial discharges or be formed as a by-product during the chlorination of water containing organic precursor molecules. Chloral hydrate is formed when trichloroacetaldehyde is dissolved in water; it was detected in six of 10 drinking-water supplies sampled, at concentrations ranging from 0.01 to 5 µg/litre (5). In another survey, chloral hydrate was detected in each of 10 drinking-water systems at concentrations ranging from 10 to 100 µg/litre (6).

16.12.4 Kinetics and metabolism in laboratory animals and humans

Chloral hydrate was rapidly absorbed in dogs and humans, most, if not all, being either oxidized to trichloroacetic acid or reduced to trichloroethanol. Most of the dose was excreted in the urine as trichloroethanol glucuronide, together with small amounts of free trichloroethanol. The remainder was excreted as trichloroacetate (7,8).

16.12.5 Effects on laboratory animals and *in vitro* test systems

Acute exposure

The acute oral LD₅₀ for chloral hydrate in mice was 1265-1442 mg/kg of body weight (9). Rats are more sensitive than mice, acute oral LD₅₀s ranging from 285 mg/kg of body weight in newborn pups to 479 mg/kg of body weight in adults (10).

Short-term exposure

Groups of male CD-1 mice were dosed with chloral hydrate by gavage at 14.4 or 144 mg/kg of body weight per day for 14 days. No significant effect on body weight was observed, but a dose-dependent increase in liver weight and decrease in spleen weight were observed. These changes were statistically significant at the higher dose. No effects on haematological or serum biochemical parameters were noted, except for an unusual decrease in lactate dehydrogenase at the higher dose. A NOAEL of 14.4 mg/kg of body weight per day was identified in this study (9).

Male and female CD-1 mice were supplied with chloral hydrate in drinking-water at 70 or 700 mg/litre (time-weighted average doses of approximately 16 or 160 mg/kg of body weight per day) for 90 days. The liver appeared to be the tissue most seriously affected. In males, dose-related hepatomegaly and microsomal proliferation were seen, accompanied by small changes in serum chemistry values for potassium, cholesterol, and glutathione, but no significant changes in serum enzyme levels. Females did not show hepatomegaly but did display changed hepatic microsomal parameters. No other significant toxicological changes were observed in either sex. Based on hepatomegaly, a LOAEL of 16 mg/kg of body weight per day (the lowest dose tested) was identified for chloral hydrate in this study (9).

Long-term exposure

A chronic 2-year drinking-water study of chloral hydrate was conducted on groups of 40 male B6C3F₁ mice for 104 weeks at dose levels of 0 or 1 g/litre (0 and 166 mg/kg of body weight per day). Lesions were primarily confined to the liver and included hepatocellular necrosis, inflammation, and cytomegaly. Organ weight changes were also evident, with increases in absolute and relative liver weights throughout the treatment period. Spleen, kidney, and testicular weights as well as pathological changes in these organs were comparable to those in controls (11).

Reproductive toxicity, embryotoxicity, and teratogenicity

Female mice were exposed to chloral hydrate in drinking-water at concentrations corresponding to doses of 21.3 or 204.8 mg/kg of body weight per day from before breeding until weaning (females only). No gross malformations were noted, and no significant effects were observed in gestational duration, number of pups delivered, pup weight, or number of stillborn pups. All pups showed the same rate of development and degree of performance on several neurobehavioural tests, except that pups from the high-dose group showed impaired retention in a passive avoidance learning task. A NOAEL of 21.3 mg/kg of body weight per day for developmental effects was identified in this study (12).

Mutagenicity and related end-points

Chloral hydrate was reported to be mutagenic in *Salmonella typhimurium* strain TA98. Both chloral hydrate and trichloroacetaldehyde were reported to be mutagenic in *S. typhimurium* strain TA100, with and without metabolic activation. Mutagenic activity was also observed for chloral hydrate in *Streptomyces coelicolor* and *Aspergillus nidulans*. Neither chloral hydrate nor trichloroacetaldehyde was mutagenic in *S. typhimurium* strain TA1535 (13,14).

Chloral hydrate administered to mice caused significant increases in the number of hyperhaploid cells,

probably due to chromosome nondisjunction resulting from a disruptive effect of chloral hydrate on the mitotic spindle (15). Similar disruptive effects of chloral hydrate on chromosomal segregation have been observed in *A. nidulans* (16) and *Saccharomyces cerevisiae* (17). Chloral hydrate did not bind to DNA in mouse liver *in vivo* or form DNA-protein cross-links when incubated with rat liver nuclei *in vitro*, which suggests that it may have low genotoxic potential in animals (18).

Carcinogenicity

The carcinogenic potential of chloral hydrate was investigated in male B6C3F₁ mice (40 per dose) that received the compound in their drinking-water at dose levels of 0 or 1 g/litre (0 or 166 mg/kg of body weight per day) for up to 104 weeks. The most prevalent lesions observed were hepatocellular carcinomas (46%) and hepatocellular adenomas (29%). Proliferative lesions were also observed in the untreated controls but at a lower incidence (2% and 1%, respectively). Hyperplastic nodules (4%) were observed in the treated group but not in untreated controls (11).

A single oral dose of chloral hydrate (10 mg/kg of body weight) administered to 15-day-old male mice resulted in a significant increase in liver tumours after 48-92 weeks (19).

16.12.6 Effects on humans

Chloral hydrate has been widely used as a sedative or hypnotic drug in humans at recommended oral doses of 0.25-1.0 g. Concentrated solutions are irritating to the gastrointestinal tract, and the ingestion of undiluted preparations causes nausea and vomiting. The acute oral toxic dose in humans is usually about 10 g, which causes severe respiratory depression and hypotension (20).

Adverse effects in patients given either 0.5 or 1.0 g of chloral hydrate included central nervous system depression, minor sensitivity reactions, gastrointestinal disturbances, and central nervous system excitement (21). Cardiac arrhythmias induced by chloral hydrate have been described (22).

The chronic use of chloral hydrate may result in the development of tolerance and physical dependence. Those physically dependent on it reportedly take as much as 12 g per day (23).

16.12.7 Provisional guideline value

Chloral hydrate causes liver tumours in mice. It has been shown to be mutagenic in short-term tests *in vitro*, but it does not bind to DNA. It has been shown to disrupt chromosome segregation in cell division. Because of the lack of adequate long-term studies, the guideline value for chloral hydrate is based on the LOAEL from a study in which liver effects were seen in mice that received chloral hydrate in drinking-water at 16 mg/kg of body weight per day for 90 days (9). A TDI of 1.6 µg/kg of body weight was calculated using this LOAEL and incorporating an uncertainty factor of 10 000 (100 for intra- and interspecies variation, 10 for the short duration of the study, and 10 for the use of a LOAEL instead of a NOAEL). With an allocation of 20% of the TDI to drinking-water, the provisional guideline value is 10 µg/litre (rounded figure). This guideline value is designated as provisional because of the limitations of the available database.

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16.13 Chloroacetones

16.13.1 General description

Identity

Compound	CAS no.	Molecular formula
1,1-Dichloroacetone	513-88-2	Cl ₂ CHCOCH ₃
1,3-Dichloroacetone	534-07-6	ClCH ₂ COCH ₂ Cl

The IUPAC name for chloroacetone is chloropropanone.

Physicochemical properties (1-3)

Property	1,1-Dichloroacetone¹	1,3-Dichloroacetone²
Boiling point (°C)	120	173
Melting point (°C)	-	45
Density at 20 °C (g/cm ³)	1.3	1.4
Water solubility at 20 °C	Slightly soluble	Soluble

¹ Conversion factor in air: 1 ppm = 5.19 mg/m³.

² Conversion factor in air: 1 ppm = 5.19 mg/m³.

Major uses

Chlorinated acetones have been proposed for use in tear gas because they are lachrymators. Chloroacetone is used as a reagent in the synthesis of drugs, perfumes, insecticides, and vinyl compounds (3).

16.13.2 Analytical methods

Chloroacetones in water are usually determined by liquid-liquid extraction and gas chromatography with electron-capture detection. A detection limit of 13 ng/litre for 1,1,1-trichloroacetone has been achieved (4).

16.13.3 Environmental levels and human exposure

Water

Dichloroacetones may be formed in water by the oxidation reaction between chlorine and large organic molecules. Concentrations in finished drinking-water are estimated at less than 10 µg/litre (5). Quarterly mean concentrations of 1,1-dichloroacetone ranged from 0.46 to 0.55 µg/litre in grab samples from 35 drinking-water treatment plants in the USA (6).

16.13.4 Effects on laboratory animals and *in vitro* test systems

Acute exposure

Oral LD₅₀s of 250 mg/kg of body weight for 1,1-dichloroacetone and 25 mg/kg of body weight for 1,3-dichloroacetone have been reported in the mouse (7).

Short-term exposure

The hepatotoxicity of 1,1- and 1,3-dichloroacetone was investigated in mice. Single oral doses of each compound were administered to CD-1 mice (5-12 per dose). A dose of 0.25 ml/kg of body weight (325 mg/kg of body weight) of 1,1-dichloroacetone caused significant increases in liver enzymes in serum, and histological examination showed evidence of periportal necrosis. These effects were not observed at doses of 130 mg/kg of body weight or lower. Liver glutathione levels were decreased at doses of 0.1 and 0.25 ml/kg but not at 0.05 ml/kg (65 mg/kg of body weight). Based on measurements of serum enzymes, liver glutathione, and histopathological examination, 1,3-dichloroacetone did not cause liver toxicity at doses of up to 20 mg/kg of body weight. NOAELs of 65 and 20 mg/kg of body weight for 1,1-dichloroacetone and 1,3-dichloroacetone, respectively, were identified in this study (7).

Mutagenicity and related end-points

A number of chlorinated acetones, including 1,1-, 1,3-, 1,1,1-, 1,1,3,3-, and pentachloroacetone, were direct-acting mutagens in one or both of *Salmonella typhimurium* strains TA98 and TA100. Mutagenic activity decreased with increased chlorine substitutions at the C-1 and C-3 positions, although 1,1,1-trichloroacetone was 25 times as potent as 1,1-dichloroacetone (8).

Carcinogenicity

The carcinogenic activity of 1,1-dichloroacetone and 1,1,1-trichloroacetone was studied in female SENCAR mice (60 per dose) that received a single oral (200 mg/kg) or topical (400 mg/kg) dose of 1,1-dichloroacetone or a single oral (50 mg/kg) or topical (400 mg/kg) dose of 1,1,1-trichloroacetone. The vehicle was 0.2 ml of dimethyl sulfoxide for oral exposure and 0.2 ml of ethanol for topical exposure. Two weeks after dosing, a tumour promotion schedule was begun with 1 µg of 12-O-tetradecanoyl-phorbol-13-acetate (TPA) three times per week for 20 weeks. However, 24 weeks after the start of the promotion schedule, there was no evidence of an increase in skin tumours attributable to either chemical (9).

The results of carcinogenicity studies with chlorinated acetones using the mouse skin assay have also been reported. Groups of 40 SENCAR mice received topical doses of 1,1-dichloroacetone at 400, 600, or 800 mg/kg; 1,3-dichloroacetone at 50, 75, or 100 mg/kg; or 1,1,3-trichloroacetone or 1,1,1-trichloroacetone at 50 mg/kg. Doses were applied six times over a 2-week period using 0.2 ml of ethanol as the vehicle. After 2 weeks, 1.0 µg of TPA in 0.2 ml of acetone was applied three times per week for 20 weeks. After 24 weeks, the percentages of animals with tumours in the respective dose groups were: 5% in controls; 0, 5%, and 5% for 1,1-dichloroacetone; 48%, 45%, and 30% for 1,3-dichloroacetone; 10%, 5%, and 0% for 1,1,1-trichloroacetone; and 10% for 1,1,3-trichloroacetone. The authors concluded that 1,3-dichloroacetone is a tumour initiator in mouse skin (10).

16.13.5 Conclusions

The toxicological data on the chloroacetones are very limited, although studies with single doses of 1,1-dichloroacetone indicate that it affects the liver. There are insufficient data at present to permit the proposal of guideline values for any of the chloroacetones.

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16.14 Halogenated acetonitriles

16.14.1 General description

Identity

Compound	CAS no.	Molecular formula
Dichloroacetonitrile	3018-12-0	CHCl ₂ CN
Dibromoacetonitrile	3252-43-5	CHBr ₂ CN
Bromochloroacetonitrile	83463-62-1	CHBrClCN
Trichloroacetonitrile	545-06-2	CCl ₃ CN

The IUPAC name for acetonitrile is ethanenitrile.

Physicochemical properties (1-3)

Property	Dichloro- acetonitrile¹	Dibromo- acetonitrile²	Bromochloro- acetonitrile³	Trichloro- acetonitrile⁴
Boiling point (°C)	112.3	67-69	125-130	84.6

Density at 20 °C (g/cm³) 1.37 2.30 1.68 1.44

¹ Conversion factor in air: 1 ppm = 4.49 mg/m³.

² Conversion factor in air: 1 ppm = 8.14 mg/m³.

³ Conversion factor in air: 1 ppm = 6.31 mg/m³.

⁴ Conversion factor in air: 1 ppm = 5.91 mg/m³.

Major uses

Trichloroacetonitrile has been used as an insecticide (3).

Environmental fate

Halogenated acetonitriles are reported to undergo hydrolysis in water, yielding nonvolatile products (4).

16.14.2 Analytical methods

Draft EPA Method 551 can be used for the determination of haloacetonitriles, by capillary-column/electron-capture/gas chromatography. Extremely low detection limits are achievable. Monitoring data indicate quantitation limits of 0.4 µg/litre for dichloro-, dibromo-, bromochloro-, and trichloroacetonitrile.

16.14.3 Environmental levels and human exposure

Water

Halogenated acetonitriles are formed from organic precursors during the chlorination of drinking-water. Dihalogenated acetonitriles are present in chlorinated water at concentrations ranging from 0.3 to 40 µg/litre (5,6); trichloroacetonitrile has been detected at a concentration of 0.1 µg/litre (6).

16.14.4 Kinetics and metabolism in laboratory animals and humans

Dichloroacetonitrile is well absorbed from the gastrointestinal tract. Most is excreted in urine, with smaller amounts being eliminated in expired air and faeces. Its metabolites are detected in highest concentrations in liver, blood, muscle, and skin. Differences in the pattern of label distribution in tissues and of label excretion indicate that a substantial portion of dichloroacetonitrile is split into two one-carbon fragments that undergo different metabolic reactions (7).

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 the oral administration of sodium hypochlorite/potassium bromide, presumably formed by reaction with organic material in the stomach (8).

16.14.5 Effects on laboratory animals and *in vitro* test systems

Acute exposure

Acute oral LD₅₀s for the halogenated acetonitriles in rodents range from 245 to 361 mg/kg of body weight (9-11).

Short-term exposure

Dichloroacetoneitrile

In a 14-day toxicity study, doses of 0, 12, 23, 45, or 90 mg/kg of body weight per day were administered to rats (10 per sex per dose). In males, a slight, nonsignificant depression in body weight gain was observed at the three highest doses, whereas decreased weight gain was noted only at the highest dose in females. No consistent treatment-related effects were observed in any of the haematological, serum chemistry, or urinary parameters measured. Absolute thymus weights in males given 23, 45, or 90 mg/kg of body weight per day were significantly decreased, but the thymus-to-body-weight ratio was decreased only at the highest dose. Based on decreased body weight as the most sensitive end-point, the NOAEL in this study was 45 mg/kg of body weight per day (11).

In a 90-day study, doses of 0, 8, 33, or 65 mg/kg of body weight per day were administered to groups of rats (20 per sex per dose). No consistent compound-related effects were observed in any of the haematological, urinary, or serum chemistry parameters measured. Body weight gain was significantly depressed in females at 65 mg/kg of body weight per day and in males at 33 mg/kg of body weight per day. The NOAEL in this study was 8 mg/kg of body weight per day (11).

Dibromoacetoneitrile

The 14-day toxicity of dibromoacetoneitrile was investigated in adult rats (10 per sex per dose) that received this compound by gavage at doses of 0, 23, 45, 90, or 180 mg/kg of body weight per day. There was increased mortality at 90 and 180 mg/kg of body weight per day (30% and 100%, respectively). No consistent compound-related effects were apparent in any of the serum chemistry, haematological, or urinary parameters measured. The authors concluded that decreased body weight was the most sensitive indicator of toxicity. In males, dose-dependent decreases occurred at 45 and 90 mg/kg of body weight per day. No effect on body weight was noted in females. The authors concluded that the NOAEL was 45 mg/kg of body weight per day, but the body weight decrease in male rats exposed at this dose suggests that the NOAEL should be 23 mg/kg of body weight per day (11).

In a 90-day study, dibromoacetoneitrile doses of 0, 6, 23, or 45 mg/kg of body weight per day in corn oil were administered by gavage to rats (20 per sex per dose). Body weight gain was significantly depressed only in males at the highest dose tested. No compound-related deaths occurred, no consistent compound-related adverse effects were observed in the haematological, urinary, or serum chemistry parameters measured, and no remarkable findings were apparent at gross necropsy. The authors concluded that decreased body weight is the most sensitive end-point and identified a NOAEL of 23 mg/kg of body weight per day (11).

Reproductive toxicity, embryotoxicity, and teratogenicity

Dichloroacetoneitrile

Dichloroacetoneitrile was administered to pregnant Long-Evans rats by gavage at doses of 0, 5, 15, 25, or 45 mg/kg of body weight per day on gestation days 6-18. At the two highest dose levels, fetal resorptions were significantly increased and fetal weight and size were decreased. Malformations of the cardiovascular, digestive, and urogenital systems were observed in fetuses from dams at the two highest dose levels. No effects were described at lower doses. This study indicated that 15 mg/kg of body weight per day is a developmental and teratogenic NOAEL for dichloroacetoneitrile (12).

Pregnant Long-Evans rats were exposed via gavage to dichloroacetoneitrile at 55 mg/kg of body weight per day on days 7-21 of gestation. Dichloroacetoneitrile decreased the percentage of females delivering litters and increased the percentage of fetal resorptions. Mean birth weights were reduced, and postnatal survival was significantly reduced. A LOAEL of 55 mg/kg of body weight per day was identified in this

study (13,14).

Groups of 10 male B6C3F₁ mice were dosed with dichloroacetonitrile at 0, 12.5, 25, or 50 mg/kg of body weight by gavage for 5 consecutive days. No treatment-related effects were found on examination of sperm for abnormal sperm-head morphology (9).

Dibromoacetonitrile

Pregnant Long-Evans rats were exposed via gavage to dibromoacetonitrile at 50 mg/kg of body weight per day on gestation days 7-21. Maternal weight gain decreased during gestation, and mean birth weights were reduced. A LOAEL of 50 mg/kg of body weight per day was identified in this study (13,14).

Groups of 10 male B6C3F₁ mice were dosed with dibromoacetonitrile at 0, 12.5, 25, or 50 mg/kg of body weight by gavage for 5 days. There were no treatment-related effects on sperm-head morphology. (9)

Bromochloroacetonitrile

In a study in which pregnant Long-Evans rats were exposed via gavage to bromochloroacetonitrile at 55 mg/kg of body weight per day on days 7-21 of gestation, mean birth weights were reduced (13,14). There were no treatment-related effects on sperm-head morphology when groups of 10 male B6C3F₁ mice were dosed with bromochloroacetonitrile at 0, 12.5, 25, or 50 mg/kg of body weight by gavage for 5 days (9).

Trichloroacetonitrile

Trichloroacetonitrile was administered to pregnant Long-Evans rats by gavage at doses of 0, 1, 7.5, 15, 35, or 55 mg/kg of body weight per day on gestation days 6-18. The highest dose was lethal in four of 19 dams, and there was 100% resorption in most survivors. Dose-related decreases in fetal weight and fetal viability were observed in animals exposed at all but the lowest dose. Numerous cardiovascular and urogenital malformations were seen in surviving fetuses. The frequency of soft-tissue 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. The malformation frequency at 1 mg/kg of body weight per day (8.4%) was not statistically different from that in controls (3.8%), but the authors expressed concern that this level of malformation could be of biological significance and suggested that a dose of 1 mg/kg of body weight per day might be the NOAEL or close to the LOAEL for teratogenic effects. (15)

Pregnant Long-Evans rats were exposed via gavage to trichloroacetonitrile at 55 mg/kg of body weight per day on gestation days 7-21. Trichloroacetonitrile decreased the percentage of females delivering litters and increased the percentage of fetal resorptions, while mean birth weights were reduced, and postnatal survival was significantly reduced. A LOAEL of 55 mg/kg of body weight per day was identified in this study (13,14).

Groups of 10 male B6C3F₁ mice were dosed with trichloroacetonitrile at 0, 12.5, 25, or 50 mg/kg of body weight by gavage for 5 days. Examination of sperm for abnormal sperm-head morphology revealed no treatment-related effects (9).

Mutagenicity and related end-points

No significant increase in the frequency of micronuclei was observed for any of the four halogenated acetonitriles in an *in vivo* assay in mice. All the halogenated acetonitriles induced sister chromatid exchanges in Chinese hamster ovary cells with metabolic activation and all except dichloroacetonitrile without it. Comparisons of potencies showed the order to be as follows: dibromoacetonitrile > bromochloroacetonitrile > trichloroacetonitrile > dichloroacetonitrile (16).

Results of the *Salmonella*/microsome assay, with and without metabolic activation by the S9 fraction of rat

liver homogenate, suggested that dichloro- and bromochloroacetonitrile were direct-acting mutagens and that dibromo- and trichloroacetonitrile were nonmutagenic (16). Halogenated acetonitriles reportedly produced DNA strand breaks in cultured human lymphoblastic cells (17). The most potent initiator was trichloroacetonitrile, followed by bromochloro-, dibromo-, and dichloroacetonitrile. It was reported that dichloroacetonitrile formed a covalent adduct when incubated with calf thymus DNA (18).

Carcinogenicity

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) three times per week for 8 weeks. The incidence of lung tumours (adenomas) was significantly increased in groups given trichloro- and bromochloroacetonitrile, while dichloro- and dibromoacetonitrile produced marginal and nonsignificant increases in such tumours. The authors stated that the results should be interpreted with caution, as there is a relatively large variation in background incidence of lung tumours in this strain of mice, and as the dose level tested was considerably below the maximum tolerated dose (19).

The ability of the four halogenated acetonitriles to act as tumour initiators was studied in mouse skin. Six topical doses of 200, 400, or 800 mg/kg were applied to the shaved backs of female SENCAR mice (40 per dose) over a 2-week period to give total doses of 1200, 2400, and 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-tetradecanoyl-phorbol-13-acetate (TPA) three times per week was begun and continued for 20 weeks. After 1 year, the incidence of squamous cell carcinomas was significantly increased relative to the control group in mice treated with dibromo- and bromochloroacetonitrile. An increase in incidence with trichloroacetonitrile at 2400 mg/kg was not reproducible. No significant increases in carcinomas were observed with dichloroacetonitrile (16). Dichloro-, dibromo-, and trichloroacetonitrile were inactive as initiators in the rat liver α -glutamyl transpeptidase foci assay (20).

16.14.6 Guideline values

IARC has concluded that dichloro-, dibromo-, bromochloro-, and trichloroacetonitriles are not classifiable as to their carcinogenicity to humans (Group 3) (5).

Dichloroacetonitrile

A TDI of 15 µg/kg of body weight was calculated from the NOAEL of 15 mg/kg of body weight per day for fetal resorptions, decreases in fetal weight and size, and malformations of the cardiovascular, digestive, and urogenital systems in the offspring of rats exposed to this compound on gestation days 6-18 (12), incorporating an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the severity of the effects at doses above the NOAEL). This NOAEL is consistent with that observed for effects on body weight in a 90-day study in rats. The provisional guideline value is 90 µg/litre, allocating 20% of the TDI to drinking-water. This guideline value is designated as provisional because of the limitations of the database (i.e. lack of long-term toxicity and carcinogenicity bioassays).

Dibromoacetonitrile

A TDI of 23 µg/kg of body weight is calculated based on a NOAEL of 23 mg/kg of body weight per day for effects on body weight in a 90-day study in rats (11), incorporating an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the short duration of the study). The provisional guideline value is 100 µg/litre (rounded figure), allocating 20% of the TDI to drinking-water. This guideline value is designated as provisional because of the limitations of the database (i.e. lack of long-term toxicity and carcinogenicity bioassays).

Bromochloroacetonitrile

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

Trichloroacetonitrile

A TDI of 0.2 µg/kg of body weight was calculated from a NOAEL of 1 mg/kg of body weight per day for fetal resorption, decreased fetal weight and viability, and for numerous cardiovascular and urogenital malformations in a study in which rats were dosed on gestation days 6-18 (15), incorporating an uncertainty factor of 5000 (100 for intra- and interspecies variation, 10 for the severity of effects at doses above the NOAEL, and 5 for limitations of the database, i.e. lack of a 90-day study). The provisional guideline value is 1 µg/litre (rounded figure), assuming the allocation of 20% of the TDI to drinking-water. This guideline value is designated as provisional because of the limitations of the database (i.e. lack of long-term studies).

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16.15 Cyanogen chloride

16.15.1 General description

Identity

CAS no.: 506-77-4
Molecular formula: CNCl

Physicochemical properties (1-3)¹

¹ Conversion factor in air: 1 ppm = 2.5 mg/m³

<i>Property</i>	<i>Value</i>
Boiling point	12.7 °C
Melting point	-6 °C
Density	1.186 g/cm ³ at 20 °C
Water solubility	Very soluble

Major uses

Cyanogen chloride is used in tear gas, in fumigant gases, and as a reagent in the synthesis of other compounds (4).

16.15.2 Analytical methods

EPA Method 524.2, in which purge-and-trap gas chromatography is combined with mass spectroscopy, can be used for the determination of cyanogen chloride. This method has a practical quantification limit of 0.3 µg/litre.

16.15.3 Environmental levels and human exposure

Water

Cyanogen chloride may be formed as a by-product of chloramination or chlorination of water. It has been found in finished water supplies at concentrations below 10 µg/litre. The concentration in water when chlorination was used for disinfection was reported to be 0.4 µg/litre. The level was higher (1.6 µg/litre) in chloraminated water (6).

16.15.4 Kinetics and metabolism in laboratory animals and humans

In an *in vitro* study with rat blood, cyanogen chloride was metabolized to cyanide ion by haemoglobin and glutathione (7).

16.15.5 Effects on laboratory animals and *in vitro* test systems

Acute exposure

Estimates of inhalation LC₅₀s range from 100 mg/m³ in cats to 7536 mg/m³ in rabbits (8). In other lethality tests, a concentration of 100 mg/m³ was fatal to cats within 18 min, 120 mg/m³ for 6 h was fatal to dogs, 5 mg/m³ for 2 min was fatal to goats, and a subcutaneous dose of 20 mg/kg of body weight was fatal to rabbits (9). An LD₅₀ of 6 mg/kg of body weight was reported in rats following oral administration (10). Toxic signs included irritation of the respiratory tract, haemorrhagic exudate of the bronchi and trachea, and pulmonary oedema.

16.15.6 Effects on humans

On inhalation, a concentration of 2.5 mg/m³ causes irritation. Cyanogen chloride was used as a war gas in the First World War. A concentration of 120 mg/m³ was lethal (5).

16.15.7 Guideline value

Cyanogen chloride is rapidly metabolized to cyanide in the body. There are few data on the oral toxicity of cyanogen chloride, and the proposed guideline is therefore based on cyanide. A guideline value of 70 µg/litre for cyanide as total cyanogenic compounds is recommended (see Cyanide, p. 226).

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16.16 Chloropicrin

16.16.1 General description

Identity

CAS no.: 76-06-2
Molecular formula: CCl₃NO₂

The IUPAC name for chloropicrin is trichloronitromethane.

Physicochemical properties (1-3)¹

¹ Conversion factor in air: 1 ppm = 6.68 mg/m³

<i>Property</i>	<i>Value</i>
Boiling point	112 °C
Melting point	-64 °C
Density	1.65 g/cm ³ at 20 °C
Vapour pressure	2.27 kPa at 20 °C

Major uses

Chloropicrin is used as a reagent in the synthesis of organic chemicals, in the manufacture of methyl violet, and as a fumigant for stored grain; it has also been used as a chemical warfare agent (3,5).

Environmental fate

Chloropicrin in water is reduced to chloroform when reducing agents are added to remove excess chlorine (6). In the presence of light, it is degraded to carbon dioxide, chloride ion, and nitrate ion (7).

16.16.2 Analytical methods

Draft EPA Method 551 can be used for the determination of chloropicrin, by capillary-column/electron-capture/gas chromatography. Extremely low detection limits can be achieved.

16.16.3 Environmental levels and human exposure

Water

Chloropicrin is formed in water by the reaction of chlorine with humic acids, amino acids, and nitrophenols. The presence of nitrates increases the amount formed (6). Chloropicrin has been detected in drinking-water; however, in the presence of reducing agents, it is converted into chloroform (6). In one study, the mean chloropicrin concentration was 0.6 µg/litre; the highest concentration observed was 5.6 µg/litre in 36 water supplies expected to have high concentrations of chlorination by-products (8).

16.16.4 Effects on laboratory animals and *in vitro* test systems

Acute exposure

An oral LD₅₀ of 250 mg/kg of body weight was reported in rats (9). An LC₅₀ of 66 mg/m³ in mice was reported following a 4-h exposure to chloropicrin aerosol (10).

Short-term exposure

In a 6-week range-finding test, Osborne-Mendel rats (5 per sex per group) were given chloropicrin by gavage at doses of 0, 16, 25, 40, 63, or 100 mg/kg of body weight per day, 5 days per week. Groups of B6C3F₁ mice were treated in the same manner with doses of 10, 16, 25, 40, or 63 mg/kg of body weight per day. In rats, chloropicrin produced no mortality at 40 mg/kg of body weight per day or less, except for one female at 25 mg/kg of body weight per day. At 40 and 63 mg/kg of body weight per day, mean body weight was depressed by 11% and 38% in males and by 17% and 30% in females, respectively. In mice, there was no mortality at any dose tested. At 40 and 63 mg/kg of body weight per day, mean body weight was depressed by 12% and 20% in males and by 3% and 6% in females, respectively. In both species, a NOAEL of 25 mg/kg of body weight per day was identified (11).

Long-term exposure

The chronic toxicity of chloropicrin was investigated in a 78-week study on Osborne-Mendel rats and B6C3F₁ mice. Chloropicrin in corn oil was administered 5 days per week by gavage to animals (50 per sex per dose) at initial doses of 23 or 46 mg/kg of body weight per day for rats and 25 or 50 mg/kg of body weight per day for mice in a complex dosing regimen. Survival was decreased in both rats and mice. For rats, survival to the end of the study was 6% for high-dose males, 8% for low-dose males, 20% for high-dose females, and 22% for low-dose females. In both vehicle and untreated control groups, at least 50% of the animals survived past week 89. The associations between chloropicrin dose and accelerated mortality in mice were also significant when compared with the vehicle controls for both males and females (11).

Mutagenicity and related end-points

The mutagenicity of chloropicrin in five strains of *Salmonella typhimurium* and one strain of *Escherichia coli* was studied. Chloropicrin was either negative or weakly positive in the absence of the S9 fraction, but positive in one strain in its presence. Chloropicrin significantly increased the number of sister chromatid exchanges in cultured human lymphocytes *in vitro* in the absence of metabolic activation (13).

Carcinogenicity

Osborne-Mendel rats (50 per sex per dose) and B6C3F₁ mice (50 per sex per dose) were given chloropicrin by gavage in corn oil 5 days per week for 78 weeks. A complex dosing regimen was employed in which varying doses were administered for varying intervals; there were also periods during which no chloropicrin was given. The overall time-weighted average doses for the 78-week period were 25

or 26 mg/kg of body weight per day for male rats, 20 or 22 mg/kg of body weight per day for female rats, 66 mg/kg of body weight per day for male mice, and 33 mg/kg of body weight per day for female mice. Post-dosing observation periods were 32 weeks (rats) or 13 weeks (mice). In rats, the incidence of neoplasms in exposed animals was not higher than that in controls. However, mortality in exposed rats was high, and it is likely that most animals did not survive long enough to be at risk from tumours with long latency period. A rapid decrease in survival after the first year of the study was also observed among the high-dose mice of both sexes. Although the mice did not exhibit any statistically significant incidence of tumours, two carcinomas and a papilloma of the squamous epithelium of the forestomach were reported, which were rare in historical controls. The authors concluded that the results of tests with rats did not permit an evaluation of carcinogenicity because of the short survival time of dosed animals, and that the results in mice did not demonstrate conclusive statistical evidence for carcinogenicity under the conditions of the study (11).

16.16.5 Effects on humans

Inhalation of chloropicrin at 2 mg/m³ caused pulmonary effects following a 1-min exposure (9).

16.16.6 Conclusions

Because of the high mortality in the carcinogenesis bioassay and the limited number of end-points examined in the 78-week study, the available data are considered inadequate to support the establishment of a guideline value for chloropicrin.

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Part 3. Radiological aspects

17. Radiological aspects

17.1 Introduction

The guideline levels for radioactivity in drinking-water recommended in the first edition of *Guidelines for drinking-water quality* in 1984 were based on the data available at that time on the risks of exposure to radiation sources. Since then, additional information has become available on the health consequences of exposure to radiation, risk estimates have been reviewed, and the recommendations of the International Commission on Radiological Protection (ICRP) have been revised. This new information (1) has been taken into account in the preparation of the recommendations in this chapter.

The purpose of these recommendations for radioactive substances in drinking-water is to guide the competent authorities in determining whether the water is of an appropriate quality for human consumption.

17.1.1 Environmental radiation exposure

Environmental radiation originates from a number of naturally occurring and man-made sources. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has estimated that exposure to natural sources contributes more than 98% of the radiation dose to the population (excluding medical exposure) (2). There is only a very small contribution from nuclear power production and nuclear weapons testing. The global average human exposure from natural sources is 2.4 mSv/year. There are large local variations in this exposure depending on a number of factors, such as height above sea level, the amount and type of radionuclides in the soil, and the amount taken into the body in air, food, and water. The contribution of drinking-water to the total exposure is very small and is due largely to naturally occurring radionuclides in the uranium and thorium decay series (2).

Levels of natural radionuclides in drinking-water may be increased by a number of human activities. Radionuclides from the nuclear fuel cycle and from medical and other uses of radioactive materials may enter drinking-water supplies; the contributions from these sources are normally limited by regulatory control of the source or practice, and it is through this regulatory mechanism that remedial action should be taken in the event that such sources cause concern by contaminating drinking-water.

17.1.2 Potential health consequences of radiation exposure

Exposure to ionizing radiation, whether natural or man-made, can cause two kinds of health effects. Effects for which the severity of the damage caused is proportional to the dose, and for which a threshold exists below which the effect does not occur, are called “deterministic” effects. Under normal conditions, the dose received from natural radioactivity and routine exposures from regulated practices is well below the threshold levels, and therefore deterministic effects are not relevant to these recommendations.

Effects for which the probability of the occurrence is proportional to dose are known as “stochastic” effects, and it is assumed that there is no threshold below which they do not occur. The main stochastic effect of concern is cancer.

Because different types of radiation have different biological effectiveness and different organs and tissues in the body have different sensitivities to radiation, the ICRP has introduced radiation and tissue-weighting factors to provide a measure of equal effect. The sum of the doubly weighted dose received by all the tissues and organs of the body gives a measure of the total harm and is referred to as the effective dose. Moreover, radionuclides taken into the body may persist and, in some cases, the resulting exposure may extend over many months or years. The committed effective dose is a measure of the total effective dose incurred over a lifetime following the intake of a radionuclide. It is this measure of exposure that is

relevant to the present discussion; in what follows, the term “dose” refers to the committed effective dose, which is expressed in sieverts (Sv). The risk of adverse health consequences from radiation exposure is a function of the total dose received from all sources. A revised estimate of the risk (i.e., the mathematical expectation) of a lifetime fatal cancer for the general population has been estimated by the ICRP to be 5×10^{-2} per sievert (1). (This does not include a small additional health risk from non-fatal cancers or hereditary effects.)

17.1.3 Recommendations

- The recommended reference level of committed effective dose is 0.1 mSv from 1 year’s consumption of drinking-water. This reference level of dose represents less than 5% of the average effective dose attributable annually to natural background radiation.
- Below this reference level of dose, the drinking-water is acceptable for human consumption and action to reduce the radioactivity is not necessary.
- For practical purposes, the recommended guideline activity concentrations are 0.1 Bq/litre for gross alpha and 1 Bq/litre for gross beta activity.

The recommendations apply to routine operational conditions of existing or new water supplies. They do not apply to a water supply contaminated during an emergency involving the release of radionuclides into the environment. Guidelines covering emergencies are available elsewhere (3).

The recommendations do not differentiate between natural and man-made radionuclides.

17.2 Application of the reference level of dose

For practical purposes, the reference level of dose needs to be expressed as an activity concentration of radionuclides in drinking-water.

The dose to a human from radioactivity in drinking-water is dependent not only on intake but also on metabolic and dosimetric considerations. The guideline activity concentrations assume an intake of total radioactive material from the consumption of 2 litres of water per day for 1 year and are calculated on the basis of the metabolism of an adult. The influence of age on metabolism and variations in consumption of drinking-water do not require modification of the guideline activity concentrations, which are based on a lifetime exposure and provide an appropriate margin of safety. Metabolic and dosimetric considerations have been included in the development of dose conversion factors, expressed as sieverts per becquerel, which relate a dose expressed in sieverts to the quantity (in becquerels) of radioactive material ingested.

Examples of radionuclide concentrations (reference concentrations) corresponding to the reference level of dose, 0.1 mSv/year, are given in Table 17.1. These concentrations have been calculated using the dose conversion factors of the United Kingdom National Radiological Protection Board (4) from the formula:

$$\begin{aligned} & \text{reference concentration (Bq/litre)} \\ &= \frac{1 \times 10^{-4} \text{ (Sv/year)}}{730 \text{ (litre/year)} \times \text{dose conversion factor (Sv/Bq)}} \\ &= \frac{1.4 \times 10^{-7} \text{ (Sv/litre)}}{\text{dose conversion factor (Sv/Bq)}} \end{aligned}$$

The previous guidelines recommended the use of an average gross alpha and gross beta activity

concentration for routine screening. These were set at 0.1 Bq/litre and 1 Bq/litre, respectively. The doses associated with these levels of gross alpha and gross beta activity for selected radionuclides are shown in Table 2. For some radionuclides, such as ^{226}Ra and ^{90}Sr , the associated dose is much lower than 0.1 mSv per year. It can also be seen from this table that, if certain radionuclides, such as ^{232}Th , ^{228}Ra , or ^{210}Pb , are singly responsible for 0.1 Bq/litre for gross alpha activity or 1 Bq/litre for gross beta activity, then the reference level of dose of 0.1 mSv per year would be exceeded. However, these radionuclides usually represent only a small fraction of the gross activity. In addition, an elevated activity concentration of these radionuclides would normally be associated with high activities from other radionuclides. This would elevate the gross alpha or gross beta activity concentration above the investigation level and provoke specific radionuclide analysis. Therefore, the values of 0.1 Bq/litre for gross alpha activity and 1 Bq/litre for gross beta activity continue to be recommended as screening levels for drinking-water, below which no further action is required.

Table 17.1 Activity concentration of various radionuclides in drinkingwater corresponding to a dose of 0.1 mSv from 1 year's intake

Radionuclide ^a	Dose conversion factor (Sv/Bq) ^b	Calculated rounded value (Bq/litre)
^3H	1.8×10^{-11}	7800
^{14}C	5.6×10^{-10}	250
^{60}Co	7.2×10^{-9}	20
^{89}Sr	3.8×10^{-9}	37
^{90}Sr	2.8×10^{-8}	5
^{129}I	1.1×10^{-7}	1
^{131}I	2.2×10^{-8}	6
^{134}CS	1.9×10^{-8}	7
^{137}CS	1.3×10^{-8}	10
^{210}Pb	1.3×10^{-6}	0.1
^{210}Po	6.2×10^{-7}	0.2
^{224}Ra	8.0×10^{-8}	2
^{226}Ra	2.2×10^{-7}	1
^{228}Ra	2.7×10^{-7}	1
^{232}Th	1.8×10^{-6}	0.1
^{238}U	3.6×10^{-8}	4
^{234}U	3.9×10^{-8}	4
^{239}Pu	5.6×10^{-7}	0.3

^a For ^{40}K , see below. For ^{222}Rn , see 17.2.3

^b Values from reference 4.

Radionuclides emitting low-energy beta particles such as ^3H and ^{14}C , and some gaseous or volatile radionuclides, such as ^{222}Rn and ^{131}I , will not be detected by standard methods of measurement. The values for average gross alpha and beta activities do not include such radionuclides, so that if their presence is suspected, special sampling techniques and measurements should be used.

It should not necessarily be assumed that the reference level of dose has been exceeded simply because the gross beta activity concentration approaches or exceeds 1 Bq/litre. This situation may well result from the presence of the naturally occurring radionuclide ^{40}K , which makes up about 0.01% of natural potassium. The absorption of the essential element potassium is under homeostatic control and takes place mainly from ingested food. Thus, the contribution to dose from the ingestion of ^{40}K in drinking-water, with its relatively low dose conversion factor (5×10^{-9} Sv/Bq), will be much less than that of many other beta-emitting radionuclides. This situation will be clarified by the identification of the specific radionuclides

in the sample.

Table 17.2 Examples of the doses arising from 1 year's consumption of drinking-water containing any of the given alpha-emitting radionuclides at an activity concentration of 0.1 Bq/litre or of the given beta-emitting radionuclides at an activity concentration of 1 Bq/litre^a

Radionuclide	Dose (mSv)
Alpha emitters (0.1 Bq/litre)	
²¹⁰ Po	0.045
²²⁴ Ra	0.006
²²⁶ Ra	0.016
²³² Th	0.130
²³⁴ U	0.003
²³⁸ U	0.003
²³⁹ Pu	0.04
Beta emitters (1 Bq/litre)	
⁶⁰ Co	0.005
⁸⁹ Sr	0.003
⁹⁰ Sr	0.020
¹²⁹ I	0.080
¹³¹ I	0.016
¹³⁴ CS	0.014
¹³⁷ CS	0.009
²¹⁰ Pb	0.95
²²⁸ Ra	0.20

^a Appropriate dose conversion factors taken from reference 4.

17.2.1 Analytical methods

The International Organization for Standardization (ISO) has published standard methods for determining gross alpha (5) and gross beta (6) activity concentrations in water. Although the detection limits depend on the radionuclides present, the dissolved solids in the sample, and the counting conditions, the recommended levels for gross alpha and gross beta activity concentrations should be above the limits of detection. The ISO detection limit for gross alpha activity based on ²³⁹Pu is 0.04 Bq/litre, while that for gross beta activity based on ¹³⁷CS is between 0.04 and 0.1 Bq/litre.

For analyses of specific radionuclides in drinking-water, there are general compendium sources in addition to specific methods in the technical literature (7-11).

17.2.2 Strategy for assessing drinking-water

If either the gross alpha activity concentration of 0.1 Bq/litre or the gross beta activity concentration of 1 Bq/litre is exceeded, then the specific radionuclides should be identified and their individual activity concentrations measured. From these data, a dose estimate for each radionuclide should be made and the sum of these doses determined. Where the following additive formula is satisfied, no further action is required:

$$\sum_i \frac{C_i}{RC_i} \leq 1$$

where C_i is the measured activity concentration of radionuclide i and RC_i is the reference activity concentration of radionuclide i that, at an intake of 2 litres per day for 1 year, will result in a committed effective dose of 0.1 mSv (see Table 17.1).

Fig. 17.1. Application of recommendations on radionuclides in drinking-water based on annual reference level of dose of 0.1 mSv

If alpha-emitting radionuclides with high dose conversion factors are suspected, this additive formula may also be invoked when the gross alpha and gross beta activity screening values of 0.1 Bq/litre and 1 Bq/litre are approached. Where the sum exceeds unity for a single sample, the reference level of dose of 0.1 mSv would be exceeded only if the exposure to the same measured concentrations were to continue for a full year. Hence, such a sample does not in itself imply that the water is unsuitable for consumption and should be regarded only as a level at which further investigation, including additional sampling, is needed.

The options available to the competent authority to reduce the dose should then be examined. Where remedial measures are contemplated, any strategy considered should first be justified (in the sense that it achieves a positive net benefit) and then optimized in accordance with the recommendations of ICRP (1, 12) in order to produce the maximum net benefit. The application of these recommendations is summarized in Fig. 1.

17.2.3 Radon

There are difficulties in applying the reference level of dose to derive activity concentrations of ^{222}Rn in drinking-water (2). These difficulties arise from the ease with which radon is released from water during handling and the importance of the inhalation pathway. Stirring and transferring water from one container to another will liberate dissolved radon. Water that has been left to stand will have reduced radon activity, and boiling will remove radon completely. As a result, it is important that the form of water consumed is taken into account in assessing the dose from ingestion. Moreover, the use of water supplies for other domestic uses will increase the levels of radon in the air, thus increasing the dose from inhalation. This dose depends markedly on the form of domestic usage and housing construction (13). The form of water intake, the domestic use of water, and the construction of houses vary widely throughout the world. It is therefore not possible to derive an activity concentration for radon in drinking-water that is universally applicable.

The global average dose from inhalation of radon from all sources is about 1 mSv/year, which is roughly half of the total natural radiation exposure. In comparison, the global dose from ingestion of radon in drinking-water is relatively low. In a local situation, however, the risks from inhalation and from ingestion may be about equal. Because of this and because there may be other sources of radon gas entry to a house, ingestion cannot be considered in isolation from inhalation exposures.

All these factors should be assessed on a regional or national level by the appropriate authorities, in order to determine whether a reference level of dose of 0.1 mSv is appropriate for that region, and to determine an activity concentration that may be used to assess the suitability of the water supply. These judgements should be based not only on the ingestion and inhalation exposures resulting from the supply of water, but also on the inhalation doses from other radon sources in the home. In these circumstances, it would appear necessary to adopt an integrated approach and assess doses from all radon sources, especially to determine the optimum action to be undertaken where some sort of intervention is deemed necessary.

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Annex 2. Tables of guideline values

The following tables present a summary of guideline values for microorganisms and chemicals in drinking-water. Individual values should not be used directly from the tables. The guideline values must be used and interpreted in conjunction with the information contained in the text.

Table A2.1. Bacteriological quality of drinking-water^a

Organisms	Guideline value
All water intended for drinking	
<i>E. coli</i> or thermotolerant coliform bacteria ^{b,c}	Must not be detectable in any 100-ml sample
Treated water entering the distribution system	
<i>E. coli</i> or thermotolerant coliform bacteria ^b	Must not be detectable in any 100-ml sample
Total coliform bacteria	Must not be detectable in any 100-ml sample
Treated water in the distribution system	
<i>E. coli</i> or thermotolerant coliform bacteria ^b	Must not be detectable in any 100-ml sample
Total coliform bacteria	Must not be detectable in any 100-ml sample. In the case of large supplies, where sufficient samples are examined, must not be present in 95% of samples taken throughout any 12-month period

^a Immediate investigative action must be taken if either *E. coli* or total coliform bacteria are detected. The minimal action in the case of total coliform bacteria is repeat sampling; if these bacteria are detected in the repeat sample, the cause must be determined by immediate further investigation.

^b Although *E. coli* is the more precise indicator of faecal pollution, the count of thermotolerant coliform bacteria is an acceptable alternative. If necessary, proper confirmatory tests must be carried out. Total coliform bacteria are not acceptable indicators of the sanitary quality of rural water supplies, particularly in tropical areas where many bacteria of no sanitary significance occur in almost all untreated supplies.

^c It is recognized that, in the great majority of rural water supplies in developing countries, faecal contamination is widespread. Under these conditions, the national surveillance agency should set medium-term targets for the progressive improvement of water supplies, as recommended in Volume 3 of *Guidelines for drinking-water quality*.

Table A2.2. Chemicals of health significance in drinking-water

A. Inorganic constituents

	Guideline value (mg/litre)	Remarks
antimony	0.005 (P) ^a	
arsenic	0.01 ^b (P)	For excess skin cancer risk of 6×10^{-4}
barium	0.7	
beryllium		NAD ^c
boron	0.3	
cadmium	0.003	
chromium	0.05 (P)	
copper	2 (P)	ATO ^d
cyanide	0.07	
fluoride	1.5	Climatic conditions, volume of water consumed,

		and intake from other sources should be considered when setting national standards
lead	0.01	It is recognized that not all water will meet the guideline value immediately; meanwhile, all other recommended measures to reduce the total exposure to lead should be implemented
manganese	0.5 (P)	ATO
mercury (total)	0.001	
molybdenum	0.07	
nickel	0.02	
nitrate (as NO ₃ ⁻)	50	The sum of the ratio of the concentration of each to its respective guideline value should not exceed 1
nitrite (as NO ₂ ⁻)	3 (P)	
selenium	0.01	
uranium		NAD

B. Organic constituents

	Guideline value (µg/litre)	Remarks
<i>Chlorinated alkanes</i>		
carbon tetrachloride	2	
dichloromethane	20	
1,1-dichloroethane		NAD
1,2-dichloroethane	30 ^b	For excess risk of 10 ⁻⁵
1,1,1-trichloroethane	2000 (P)	
<i>Chlorinated ethenes</i>		
vinyl chloride	5 ^b	For excess risk of 10 ⁻⁵
1,1-dichloroethene	30	
1,2-dichloroethene	50	
trichloroethene	70 (P)	
tetrachloroethene	40	
<i>Aromatic hydrocarbons</i>		
benzene	10 ^b	For excess risk of 10 ⁻⁵
toluene	700	ATO
xylenes	500	ATO
ethylbenzene	300	ATO
styrene	20	ATO
benzo[a]pyrene	0.7 ^b	For excess risk of 10 ⁻⁵
<i>Chlorinated benzenes</i>		
monochlorobenzene	300	ATO
1,2-dichlorobenzene	1000	ATO
1,3-dichlorobenzene		NAD
1,4-dichlorobenzene	300	ATO
trichlorobenzenes (total)	20	ATO
<i>Miscellaneous</i>		
di(2-ethylhexyl)adipate	80	
di(2-ethylhexyl)phthalate	8	
acrylamide	0.5 ^b	For excess risk of 10 ⁻⁵
epichlorohydrin	0.4 (P)	

hexachlorobutadiene	0.6	
edetic acid (EDTA)	200 (P)	
nitrilotriacetic acid	200	
dialkyltins		NAD
tributyltin oxide	2	

C. Pesticides

	Guideline value (µg/litre)	Remarks
alachlor	20 ^b	For excess risk of 10 ⁻⁵
aldicarb	10	
aldrin/dieldrin	0.03	
atrazine	2	
bentazone	30	
carbofuran	5	
chlordane	0.2	
chlorotoluron	30	
DDT	2	
1,2-dibromo-3-chloropropane	1 ^b	For excess risk of 10 ⁻⁵
2,4-D	30	
1,2-dichloropropane	20 (P)	
1,3-dichloropropane		NAD
1,3-dichloropropene	20 ^b	For excess risk of 10 ⁻⁵
ethylene dibromide		NAD
heptachlor and heptachlor epoxide	0.03	
hexachlorobenzene	1 ^b	For excess risk of 10 ⁻⁵
isoproturon	9	
lindane	2	
MCPA	2	
methoxychlor	20	
metolachlor	10	
molinate	6	
pendimethalin	20	
pentachlorophenol	9 (P)	
permethrin	20	
propanil	20	
pyridate	100	
simazine	2	
trifluralin	20	
chlorophenoxy herbicides other than 2,4-D and MCPA		
2,4-DB	90	
dichlorprop	100	
fenoprop	9	
MCPB		NAD
mecoprop	10	
2,4,5-T	9	

D. Disinfectants and disinfectant by-products

Disinfectants	Guideline value (mg/litre)	Remarks
monochloramine di- and trichloramine	3	NAD
chlorine	5	ATO. For effective disinfection there should be a residual concentration of free chlorine of ≥ 0.5 mg/litre after at least 30 minutes contact time at pH <8.0
chlorine dioxide		A guideline value has not been established because of the rapid breakdown of chlorine dioxide and because the chlorite guideline value is adequately protective for potential toxicity from chlorine dioxide
iodine		NAD
Disinfectants by-products	Guideline value ($\mu\text{g/litre}$)	Remarks
bromate	25 ^b (P)	For 7×10^{-5} excess risk
chlorate		NAD
chlorite	200 (P)	
chlorophenols		
2-chlorophenol		NAD
2,4-dichlorophenol		NAD
2,4,6-trichlorophenol	200 ^b	For excess risk of 10^{-5} , ATO
formaldehyde	900	
MX		NAD
trihalomethanes		The sum of the ratio of the concentration of each to its respective guideline value should not exceed 1
bromoform	100	
dibromochloromethane	100	
bromodichloromethane	60 ^b	For excess risk of 10^{-5}
chloroform	200 ^b	For excess risk of 10^{-5}
chlorinated acetic acids		
monochloroacetic acid		NAD
dichloroacetic acid	50 (P)	
trichloroacetic acid	100 (P)	
chloral hydrate (trichloroacetaldehyde)	10 (P)	
chloroacetone		NAD
halogenated acetonitriles		
dichloroacetonitrile	90 (P)	
dibromoacetonitrile	100 (P)	
bromochloroacetonitrile		NAD
trichloroacetonitrile	1 (P)	
cyanogen chloride (as CN)	70	
chloropicrin		NAD

^a (P) - Provisional guideline value. This term is used for constituents for which there is some evidence of a potential hazard but where the available information on health effects is limited; or where an

uncertainty factor greater than 1000 has been used in the derivation of the tolerable daily intake (TDI). Provisional guideline values are also recommended: (1) for substances for which the calculated guideline value would be below the practical quantification level, or below the level that can be achieved through practical treatment methods; or (2) where disinfection is likely to result in the guideline value being exceeded.

^b For substances that are considered to be carcinogenic, the guideline value is the concentration in drinking-water associated with an excess lifetime cancer risk of 10^{-5} (one additional cancer per 100 000 of the population ingesting drinking-water containing the substance at the guideline value for 70 years). Concentrations associated with estimated excess lifetime cancer risks of 10^{-4} and 10^{-6} can be calculated by multiplying and dividing, respectively, the guideline value by 10.

In cases in which the concentration associated with an excess lifetime cancer risk of 10^{-5} is not feasible as a result of inadequate analytical or treatment technology, a provisional guideline value is recommended at a practicable level and the estimated associated excess lifetime cancer risk presented.

It should be emphasized that the guideline values for carcinogenic substances have been computed from hypothetical mathematical models that cannot be verified experimentally and that the values should be interpreted differently from TDI-based values because of the lack of precision of the models. At best, these values must be regarded as rough estimates of cancer risk. However, the models used are conservative and probably err on the side of caution. Moderate short-term exposure to levels exceeding the guideline value for carcinogens does not significantly affect the risk.

^c NAD - No adequate data to permit recommendation of a health-based guideline value.

^d ATO - Concentrations of the substance at or below the health-based guideline value may affect the appearance, taste, or odour of the water.

Table A2.3. Chemicals not of health significance at concentrations normally found in drinking-water

Chemical	Remarks
asbestos	U
silver	U
tin	U

U - It is unnecessary to recommend a health-based guideline value for these compounds because they are not hazardous to human health at concentrations normally found in drinking-water.

Table A2.4. Radioactive constituents of drinking-water

	Screening value (Bq/litre)	Remarks
gross alpha activity	0.1	If a screening value is exceeded, more detailed radionuclide analysis is necessary. Higher values do not necessarily imply that the water is unsuitable for human consumption
gross beta activity	1	

Table A2.5. Substances and parameters in drinking-water that may give rise to complaints from consumers

	Levels likely to give rise to consumer complaints ^a	Reasons for consumer complaints
<i>Physical parameters</i>		
colour	15 TCU ^b	appearance
taste and odour	-	should be acceptable
temperature	-	should be acceptable
turbidity	5 NTU ^c	appearance; for effective terminal disinfection, median turbidity ≤ 1 NTU, single sample ≤ 5 NTU
<i>Inorganic constituents</i>		
aluminium	0.2 mg/l	depositions, discoloration
ammonia	1.5 mg/l	odour and taste
chloride	250 mg/l	taste, corrosion
copper	1 mg/l	staining of laundry and sanitary ware (health-based provisional guideline value 2 mg/litre)
hardness	-	high hardness: scale deposition, scum formation low hardness: possible corrosion
hydrogen sulfide	0.05 mg/l	odour and taste
iron	0.3 mg/l	staining of laundry and sanitary ware
manganese	0.1 mg/l	staining of laundry and sanitary ware (health-based guideline value 0.5 mg/litre)
dissolved oxygen	-	indirect effects
pH	-	low pH: corrosion high pH: taste, soapy feel preferably <8.0 for effective disinfection with chlorine
sodium	200 mg/l	taste
sulfate	250 mg/l	taste, corrosion
total dissolved solids	1000 mg/l	taste
zinc	3 mg/l	appearance, taste
<i>Organic constituents</i>		
toluene	24-170 µg/l	odour, taste (health-based guideline value 700 µg/l)
xylene	20-1800 µg/l	odour, taste (health-based guideline value 500 µg/l)
ethylbenzene	2-200 µg/l	odour, taste (health-based guideline value 300 µg/l)
styrene	4-2600 µg/l	odour, taste (health-based guideline value 20 µg/l)
monochlorobenzene	10-120 µg/l	odour, taste (health-based guideline value 300 µg/l)
1,2-dichlorobenzene	1-10 µg/l	odour, taste (health-based guideline value 1000 µg/l)
1,4-dichlorobenzene	0.3-30 µg/l	odour, taste (health-based guideline value 300 µg/l)
trichlorobenzenes (total)	5-50 µg/l	odour, taste (health-based guideline value 20 µg/l)
synthetic detergents	-	foaming, taste, odour
<i>Disinfectants and disinfectant by-products</i>		

chlorine	600-1000 µg/l	taste and odour (health-based guideline value 5 µg/l)
chlorophenols		
2-chlorophenol	0.1-10 µg/l	taste, odour
2,4-dichlorophenol	0.3-40 µg/l	taste, odour
2,4,6-trichlorophenol	2-300 µg/l	taste, odour (health-based guideline value 200 µg/l)

^a The levels indicated are not precise numbers. Problems may occur at lower or higher values according to local circumstances. A range of taste and odour threshold concentrations is given for organic constituents.

^b TCU, true colour unit.

^c NTU, nephelometric turbidity unit.

Back cover

The first edition of *Guidelines for drinking-water quality*, published in 1984-85, was widely used as a basis for setting national standards to ensure the safety of the water supply. It established guideline values for a large number of water constituents and contaminants, covering microbiological, biological, chemical, organoleptic, and radiological aspects. For this new edition, all the recommended guideline values have been reviewed and, where necessary, updated in the light of new scientific information. In addition, many drinking-water contaminants not included in the first edition are evaluated.

Volume 2 explains how guideline values for drinking-water contaminants are to be used, defines the criteria used to select the various chemical, physical, microbiological, and radiological contaminants included in the report, describes the approaches used in deriving guideline values, and presents brief summary statements either supporting the guideline values recommended or explaining why no health-based guideline value is required at the present time.

It is emphasized that the guideline values recommended are not mandatory limits. Such limits should be set by national authorities, using a risk-benefit approach and taking into consideration local environmental, social, economic and cultural conditions.

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